



UNIVERSIDADE FEDERAL DE PELOTAS

Centro de Ciências Químicas Farmacêuticas e de Alimentos

Programa de Pós-Graduação em Bioquímica e Bioprospecção

Tese

**Dor Oncológica em Roedores Induzidos com Vincristina: Impactos do
Envelhecimento, Neurodesenvolvimento, Dimorfismo Sexual e o Papel Protetor do
4-PSQ**

Ketlyn Pereira da Motta

Pelotas, outubro de 2025.

Ketlyn Pereira da Motta

**Dor Oncológica em Roedores Induzidos com Vincristina: Impactos do
Envelhecimento, Neurodesenvolvimento, Dimorfismo Sexual e o Papel Protetor do 4-
PSQ**

Tese apresentada ao Programa de Pós-Graduação em Bioquímica e Bioprospecção da Universidade Federal de Pelotas, como requisito parcial para a obtenção do grau de Doutor em Bioquímica e Bioprospecção.

Orientadora: Prof^a Dra. Ethel Antunes Wilhelm

Pelotas, outubro de 2025.

Universidade Federal de Pelotas / Sistema de Bibliotecas
Catalogação da Publicação

M921d Motta, Ketlyn Pereira da

Dor Oncológica em Roedores Induzidos com Vincristina [recurso eletrônico] : impactos do Envelhecimento, Neurodesenvolvimento, Dimorfismo Sexual e o Papel Protetor do 4-PSQ / Ketlyn Pereira da Motta ; Ethel Antunes Wilhelm, orientadora. — Pelotas, 2025.
455 f. : il.

Tese (Doutorado) — Programa de Pós-Graduação em Bioquímica e Bioprospecção, Centro de Ciências Químicas, Farmacêuticas e de Alimentos, Universidade Federal de Pelotas, 2025.

1. Vincristina. 2. Selênio. 3. Neurodesenvolvimento. 4. Neuropatia. 5. Dor oncológica. I. Wilhelm, Ethel Antunes, orient. II. Título.

CDD 616.994

Elaborada por Gabriela Machado Lopes CRB: 10/1842

UNIVERSIDADE FEDERAL DE PELOTAS
Centro de Ciências Químicas Farmacêuticas e de Alimentos Programa de Pós
Graduação em Bioquímica e Bioprospecção

A Comissão Examinadora, abaixo nomeada, aprova a Tese de Doutorado

**Dor Oncológica em Roedores Induzidos com Vincristina: Impactos do
Envelhecimento, Neurodesenvolvimento, Dimorfismo Sexual e o Papel
Protetor do 4-PSQ.**

Elaborada por
Ketlyn Pereira da Motta

Como requisito parcial para a obtenção do grau de
Doutora em Ciências (Bioquímica e Bioprospecção)

COMISSÃO EXAMINADORA:

Documento assinado digitalmente
 **ETHEL ANTUNES WILHELM**
Data: 03/11/2025 15:44:21-0300
Verifique em <https://validar.iti.gov.br>

Prof^a. Dra. Ethel Antunes Wilhelm (Orientadora)

Doutora em Ciências Biológicas (Bioquímica Toxicológica) pela Universidade Federal
de Santa Maria, UFSM, Brasil.

Documento assinado digitalmente
 **GABRIELA TREVISAN DOS SANTOS**
Data: 06/11/2025 13:37:14-0300
Verifique em <https://validar.iti.gov.br>

Prof^a. Dra. Gabriela Trevisan dos Santos

Doutora em Ciências Biológicas (Bioquímica Toxicológica) pela Universidade Federal
de Santa Maria, UFSM, Brasil.

Documento assinado digitalmente
 **EVELYNE DA SILVA BRUM**
Data: 09/11/2025 15:19:33-0300
Verifique em <https://validar.iti.gov.br>

Prof^a. Dra. Evelyne da Silva Brum

Doutora em Ciências Biológicas (Bioquímica Toxicológica) pela Universidade Federal
de Santa Maria, UFSM, Brasil.

Documento assinado digitalmente
 **ROBERTO FARINA DE ALMEIDA**
Data: 06/11/2025 14:05:15-0300
Verifique em <https://validar.iti.gov.br>

Prof. Dr. Roberto Farina Almeida

Doutor em Ciências Biológicas (Bioquímica) pela Universidade Federal do Rio Grande
do Sul, UFRGS, Brasil.

Pois dEle, por Ele e para Ele são todas as coisas.
A Ele seja a glória para sempre! Amém.
(Romanos 11:36 – NVI)

AGRADECIMENTOS

Em primeiro lugar agradeço a Deus por me conceder força diária e capacidade de chegar até aqui. Sem dúvida, conhecer a Deus transformou minha visão de mundo e me impulsionou a alcançar o propósito que foi escrito pra mim. Obrigada Deus, a Ti dedico essa conquista.

Agradeço à minha família que foram suporte e amor para que eu permanecesse firme até aqui. Obrigado em especial ao meu marido, Wesley. Meu amor, você acompanhou toda esta etapa e abriu mão de um tempo da sua vida e planos pra sonhar os nossos sonhos; você é a pessoa que não mede esforços pra me ver crescer e conquistar ainda que seja necessário abdicar de si mesmo. Obrigada por permanecer e amar quando estive exausta e ser colo pra mim, nunca esquecerei de tudo que fez e faz por nós.

Agradeço à minha mãe, Ângela, e meu pai, Moisés (que não está mais aqui para ver-me alcançar esta conquista, mas a quem agradeço por meio da pessoa da minha mãe). Obrigada por toda renúncia que fizeram para me proporcionar sair de uma cidade pequena e conseguir estudar. Obrigada pelo trabalho duro, pelas noites em claro, pelas orações, pelo amparo que nunca me faltou. Espero sempre honrá-los durante minha vida.

Agradeço às minhas irmãs, Karen e Kamille. Obrigada Karen por ser minha companheira de mudança de cidade para estudarmos, por estar sempre presente na minha vida. Obrigada Kamille por ser minha amiga, torcer por mim de verdade e sempre ouvir meus desabafos.

Agradeço à minha orientadora, Ethel, por me permitir ingressar na pesquisa científica, adquirir conhecimento e acreditar no meu trabalho responsável para somar com o grupo e explorar todas as instigações na pesquisa que surgiram no caminho. Estendo um agradecimento especial à Profa. Elvira que me recebeu no seu grupo *Sensory transduction and nociception* durante 6 meses no doutorado sanduíche, após um correio eletrônico inusitado sem de fato me conhecer. Agradeço também ao Instituto de Neurociencias e Universidade Miguel Hernandez de Elche, Alicante, Espanha pela recepção e oportunidade.

Agradeço ao grupo de pesquisadoras e colegas que estiveram presentes durante o desenvolvimento de todo este trabalho com quem chorei, mas também dei muitas risadas. Dentre elas, um destaque à minha colega e amiga Briana, que conheci graças a graduação (há 10 anos) e permaneceu até quase o final do doutorado comigo. Bri, você se tornou uma pessoa insubstituível na minha vida, com conversas profundas e

uma inteligência sem igual, muito obrigada por ser quem és. Vanessa, você é uma mulher incrível e aprendi contigo a ser mais pacífica e amorosa, com certeza você foi um presente para que eu começasse o doutorado. Meliza, com um coração gigante, nos identificamos tanto após nossas perdas, mas o que mais agradeço é pelo teu coração humano, irmandade e alegria contagiante. Caren, aquela que faz a gente acreditar até o final - com certeza sem ti as esperanças do nosso grupo teriam se esgotado no meio da trajetória. Ana, uma guria de raça, trabalho e foco e ao mesmo tempo trazendo paz, além de uma inteligência rara capaz de absorver conhecimentos longos em instantes. Jaini e Karli, agradeço a vocês por serem uma fonte de inspiração pra mim, por ver em vocês exemplos de que sair para outro país seria possível, inspiração também na excelência de vocês em tudo que fazem. Deixo um agradecimento a todos que dividiram o ambiente laboral comigo e/ou depositaram conhecimento que me formaram enquanto profissional.

Não menos importante, agradeço a Universidade Federal de Pelotas (UFPel) que foi berço de toda a minha formação acadêmica até o presente momento. Também agradeço ao Programa de Pós-Graduação em Bioquímica e Bioprospecção incluindo todos os professores.

Em especial, agradeço à Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) pelo apoio financeiro no Brasil e no exterior por meio do Programa de Doutorado-sanduíche no Exterior (PDSE). Um agradecimento ao Instituto de Neurociências vinculado a *Universidad Miguel Hernández de Elche* que me oportunizaram a realização do doutorado sanduíche.

Agradeço outros parceiros para o desenvolvimento deste estudo: Laboratório de Síntese Orgânica Limpa (LASOL), Laboratório de Genômica Estrutural, Laboratório de Controle de Contaminantes em Biomateriais (LCCBio), o Grupo de Pesquisa em Oncologia Celular e Molecular (GPO), Laboratório de Neuroquímica, Inflamação e Câncer e ao Laboratório Regional de Diagnóstico da Faculdade de Medicina Veterinária. Agradeço ainda ao Instituto de Ciências Básicas da Saúde da Universidade Federal do Rio Grande do Sul pela parceria nos estudos realizados.

Agradeço ao Biotério Central da UFPel pelo apoio para o desenvolvimento dos estudos desta tese. Agradeço à Dra. Anelize Campello, veterinária, que foi uma pessoa chave para a execução desses projetos bem como todos os bioteristas.

RESUMO

MOTTA, Ketlyn Pereira da. **Dor Oncológica em Roedores Induzidos com Vincristina: Impactos do Envelhecimento, Neurodesenvolvimento, Dimorfismo Sexual e o Papel Protetor do 4-PSQ**. Orientadora: Ethel Antunes Wilhelm. 2025. 455f. Tese (Doutorado em Ciências com ênfase em Bioquímica e Bioprospecção) - Centro de Ciências Químicas, Farmacêuticas e de Alimentos, Universidade Federal de Pelotas, Pelotas, 2025.

A vincristina (VCR) é um fármaco quimioterápico amplamente utilizado no tratamento de diversas neoplasias. Apesar de sua reconhecida eficácia antitumoral, a VCR está diretamente associada ao desenvolvimento de neurotoxicidade, manifestada principalmente por neuropatia periférica induzida por VCR (NPIV), uma condição debilitante que pode acometer pacientes de diferentes faixas etárias, inclusive crianças em fase de neurodesenvolvimento. Por outro lado, o 7-cloro-4-(fenilselanil)quinolina (4-PSQ) é um composto sintético promissor, que apresenta propriedades antioxidantes, anti-inflamatórias e neuroprotetoras. Este estudo foi desenvolvido para preencher lacunas experimentais relacionadas à NPIV, investigando tanto a influência de fatores biológicos, como idade e dimorfismo sexual, quanto o potencial terapêutico do 4-PSQ. Inicialmente, avaliou-se a hipótese de que o envelhecimento poderia aumentar a suscetibilidade à NPIV. De fato, ratos idosos demonstraram maior vulnerabilidade, evidenciada por degeneração walleriana, estresse oxidativo e alterações na atividade de ATPases, mecanismos fisiopatológicos centrais para o desenvolvimento da neuropatia. Em seguida, buscou-se investigar se a VCR poderia induzir alterações neurocognitivas e emocionais em camundongos machos e fêmeas. Os resultados revelaram comportamentos tipo-ansioso, tipo-depressivo e déficit cognitivo, associados à ativação da via de sinalização Fator Nuclear kappa B (NFkB)/Na⁺, K⁺-ATPase. Em uma terceira etapa, explorou-se o potencial antitumoral do 4-PSQ *in vitro*, o qual demonstrou ação relevante contra a proliferação de células leucêmicas, além de efeitos antinociceptivos em modelos de NPIV em ambos os sexos. Considerando o uso frequente da VCR em pacientes pediátricos, avaliou-se ainda seu impacto em ratos neonatos. Pela primeira vez, demonstrou-se que a VCR compromete significativamente o neurodesenvolvimento e o crescimento físico, induzindo degeneração medular, estresse oxidativo, disfunção mitocondrial (alterações na mitofagia) e apoptose neuronal. Por fim, investigou-se a eficácia do 4-PSQ no manejo da dor oncológica associada à NPIV e a um modelo de sarcoma (S180). O tratamento combinando VCR e 4-PSQ não apenas potencializou os efeitos antitumorais, como também reduziu sinais de neuropatia periférica, modulando o perfil inflamatório, a resposta de macrófagos peritoneais, a atividade de ATPases e o estresse oxidativo. Conclui-se que o envelhecimento, o neurodesenvolvimento e o dimorfismo sexual são fatores críticos na suscetibilidade à NPIV, e que o 4-PSQ representa uma estratégia promissora por combinar ação antitumoral e neuroprotetora, abrindo novas perspectivas terapêuticas para o manejo de pacientes oncológicos expostos à VCR.

Palavras-chave: vincristina, dor oncológica, selênio, neuropatia, neurodesenvolvimento.

ABSTRACT

MOTTA, Ketlyn Pereira da. **Cancer Pain in Rodents Induced with Vincristine: Impacts of Aging, Neurodevelopment, Sexual Dimorphism, and the Protective Role of 4-PSQ**. Adviser: Ethel Antunes Wilhelm. 2025. 455f. Thesis (Doctorate in Science with an emphasis on Biochemistry and Bioprospecting) - Centro de Ciências Químicas, Farmacêuticas e de Alimentos, Universidade Federal de Pelotas, Pelotas, 2025.

Vincristine (VCR) is a chemotherapeutic agent widely used in the treatment of various malignancies. Despite its well-established antitumor efficacy, VCR is directly associated with the development of neurotoxicity, primarily manifested as VCR-induced peripheral neuropathy (VIPN), a debilitating condition that can affect patients across different age groups, including children during critical neurodevelopmental stages. On the other hand, 7-chloro-4-(phenylselenanyl) quinoline (4-PSQ) is a promising synthetic compound with recognized antioxidant, anti-inflammatory, and neuroprotective properties. This study was designed to address experimental gaps related to VIPN by investigating both the influence of biological factors, such as aging and sexual dimorphism, and the therapeutic potential of 4-PSQ. Initially, the hypothesis that aging could increase susceptibility to VIPN was tested. Indeed, aged rats showed greater vulnerability, evidenced by Wallerian degeneration, oxidative stress, and alterations in ATPase activity, which are key pathophysiological mechanisms associated with neuropathy development. Subsequently, the study evaluated whether VCR could induce neurocognitive and emotional impairments in male and female mice. The results demonstrated anxiety-like and depressive-like behaviors, along with cognitive deficits, associated with the activation of the Nuclear Factor kappa B (NFκB)/Na⁺, K⁺-ATPase signaling pathway. In a third stage, the *in vitro* antitumor potential of 4-PSQ was explored, revealing significant activity against the proliferation of leukemic cells, in addition to antinociceptive effects in VIPN models in both sexes. Considering the frequent use of VCR in pediatric patients, its impact on neonatal rats was also assessed. For the first time, it was demonstrated that VCR significantly impairs neurodevelopment and physical growth, inducing spinal cord degeneration, oxidative stress, mitochondrial dysfunction (altered mitophagy), and neuronal apoptosis. Finally, the efficacy of 4-PSQ in managing oncological pain associated with VIPN and a sarcoma (S180) model was investigated. The combined treatment with VCR and 4-PSQ not only enhanced antitumor effects but also reduced signs of peripheral neuropathy by modulating the inflammatory profile, peritoneal macrophage response, ATPase activity, and oxidative stress. In conclusion, aging, neurodevelopmental stage, and sexual dimorphism are critical factors influencing susceptibility to VIPN. Moreover, 4-PSQ emerges as a promising strategy by combining antitumor and neuroprotective actions, opening new therapeutic perspectives for managing oncological patients exposed to VCR.

Keywords: vincristine, cancer pain, selenium, neuropathy, neurodevelopment.

LISTA DE FIGURAS

Revisão Bibliográfica

Figura 1. Estrutura química do 7-cloro-4-(fenilселanil) quinolina (4-PSQ) 22

Figura 2. Estrutura molecular da vincristina 23

Figura 3. Esquema de mecanismos de ação da VCR. (Adaptado de Triarico et al.(2021b)) 24

Figura 4. Esquema ilustrativo da ativação dos canais TRP (TRPA1, TRPV1, TRPV3, TRPV4 e TRPM8) por diferentes estímulos nociceptivos: térmicos, mecânicos, químicos, pH alterado e frio. A ativação desses canais em neurônios sensoriais do gânglio da raiz dorsal (DRG) provoca influxo de Ca^{2+} , despolarização neuronal e geração de potenciais de ação, que são transmitidos à medula espinhal e ao cérebro, resultando na evitação ou percepção da dor. O esquema também indica que quimioterápicos podem modular a excitabilidade nociceptiva por meio da ativação ou sensibilização desses canais (Figura desenvolvida pelo autor) 34

Figura 5 – Representação esquemática das principais evidências científicas reunidas nesta tese. A figura está organizada em cinco eixos temáticos: (1) Neuropatia periférica induzida pela vincristina (VCR) em animais idosos, caracterizada por hipernocicepção e degeneração walleriana; (2) Comorbidades associadas à exposição à VCR, incluindo prejuízos comportamentais e alterações moleculares, bem como os efeitos terapêuticos do composto 7-cloro-4-fenilселanil quinolina (4-PSQ); (3) Dimorfismo sexual na neuropatia induzida pela VCR, com destaque para maior susceptibilidade das fêmeas, e os efeitos antinociceptivos do 4-PSQ; (4) Neurotoxicidade induzida pela VCR em janela crítica de neurodesenvolvimento neonatal, envolvendo

prejuízo cognitivo, neurodegeneração e disfunção mitocondrial; e (5) Efeitos terapêuticos do 4-PSQ frente à dor oncológica induzida por VCR e sarcoma, incluindo potencialização da atividade antitumoral da VCR, modulação da neuroinflamação e do estresse oxidativo, além da regulação de ATPases como mecanismos-alvo de sua ação 419

LISTA DE TABELAS

Tabela 1. Características e fontes de plasmídeos de DNA	395

LISTA DE ABREVIATURAS

4-PSQ : 7-cloro-4-(fenilselanil) quinolina

AChE: acetilcolinesterase

AKT: proteína quinase B (do inglês - *Protein Kinase B*)

ATP: Adenosina trifosfato

BAX: proteína X associada a Bcl-2 (do inglês - *Bcl-2-associated X protein*)

CDS/CV: corno dorsal superficial da coluna vertebral

CHO: células de ovário de hamster chinês

COX-2: ciclo-oxigenase-2

CXCR: receptor de quimiocina (do inglês - *CXC chemokine receptor*)

DNA: Ácido Desoxirribonucleico

ERNS: Espécies reativas de nitrogênio

ERO: Espécies reativas de oxigênio

GPx: glutational peroxidase

GSH: glutational reduzida

HEK-293: Células renais embrionárias humanas -293

HL-60: Células da linhagem leucêmica promielocítica humana

HO-1: heme oxigenase

IASP: Associação Internacional do Estudo da Dor (do inglês -*International Association for the Study of Pain*)

IC₅₀: Concentração Inibitória 50%

IL-1 β : interleucina-1 β

IL-6: interleucina-6

I κ B: Inibidor de kappa B

Keap1: Proteína associada ao domínio ECH tipo Kelch 1 (do inglês - *Kelch-like*)

ECH-associated protein 1)

MCL-1: Leucemia de Células Mieloides 1 (do inglês - *Myeloid Cell Leukemia 1*)

MDA: malondialdeído

TBARS: Espécies Reativas ao ácido tiobarbitúrico (do inglês - *Thiobarbituric acid reactive species*)

SOD: Superóxido dismutase

CAT: catalase

mRNA: RNA mensageiro

NCAM: molécula de adesão de células neurais (do inglês - *Neural Cell Adhesion Molecule*)

NFκB: Fator Nuclear kappa B (do inglês - *Nuclear Factor kappa B*)

NMDA: receptor N-metil D-aspartato

nNOS: Sintase de Óxido Nítrico Neuronal

NOS: sintase de óxido nítrico

NOx: óxido nítrico

NPIO: neuropatia periférica induzida por oxaliplatina

NPIP: neuropatia periférica induzida por paclitaxel

NPIV: Neuropatia periférica induzida por vincristina

NPSH: tióis não-proteicos

Nrf2: Fator nuclear relacionado ao fator eritroide 2 (do inglês - *Nuclear factor erythroid 2-related factor 2*)

PARKIN: Proteína ligase E3 de ubiquitina Parkin (do inglês - *Parkin E3 ubiquitin ligase*)

PI3K: fosfatidilinositol-3-quinase (do inglês - *Phosphatidylinositol 3-kinase*)

PINK-1: Quinase 1 induzida por PTEN (do inglês - *PTEN-induced kinase 1*)

PND: Dia pós-natal (do inglês - *Postnatal Day*)

PRGC: peptídeo relacionado ao gene da calcitonina

RNA: Ácido Ribonucleico

S180: Sarcoma 180

SNC: Sistema nervoso central

STAT3: Sinal e Ativador de Transcrição 3 (do inglês – *Signal Transducer and Activator of Transcription 3*)

TLR-4: Receptor do tipo toll (do inglês – *Toll-like receptor 4*)

TNF- α : fator de necrose tumoral-alfa (do inglês – *Tumor necrosis factor-alpha*)

TRPA1: Receptor de Potencial Transitório Anquirina 1 (do inglês – *Transient Receptor Potential Ankyrin*)

TRPs: Receptores de Potencial Transitório (do inglês - *Transient Receptor Potential*)

TRPM8: Receptor de Potencial Transitório Melastatina 8 (do inglês – *Transient Receptor Melastatin*)

TRPV: Receptor de Potencial Transitório Vaniloide (do inglês – *Transient Receptor Potential Vanilloid*)

VCR: Vincristina

WHO: Organização Mundial da Saúde (do inglês - *World Health Organization*)

<i>Resultados obtidos durante o período de doutorado sanduíche em parceria com a Universidad Miguel Hernández De Elche</i>	<i>394</i>
4. DISCUSSÃO.....	405
5. CONCLUSÕES.....	418
6. PERSPECTIVAS	420
7. REFERÊNCIAS BIBLIOGRÁFICAS	420
8. ANEXOS.....	450
<i>Anexo I – Carta de aprovação dos protocolos experimentais pela Comissão de Ética em Experimentação Animal da Universidade Federal de Pelotas</i>	<i>450</i>
<i>Anexo II – Carta de aprovação dos protocolos experimentais pela Comissão de Ética em Experimentação Animal da Universidade Federal de Pelotas.....</i>	<i>453</i>
<i>Anexo III - Comprovante de submissão do manuscrito 1 na revista científica ACS Omega</i>	<i>455</i>

1. INTRODUÇÃO

O câncer é uma doença global com impactos a saúde, economia e qualidade de vida de uma população. De acordo com a *International Association for the Study of Pain* (IASP), estima-se que, anualmente, cerca de 10 milhões de pessoas recebam diagnóstico de neoplasia; entretanto, somente em 2022, mais de 20 milhões de novos casos de câncer foram registrados (World Health Organization (WHO), 2024), evidenciando o caráter epidêmico da doença em escala global. Aproximadamente um terço dos pacientes em tratamento oncológico ativo e até dois terços daqueles com neoplasia avançada apresentam dor significativa (IASP, 2025). Embora frequentemente subdiagnosticada, a dor oncológica é um sintoma relevante tanto para o diagnóstico quanto como consequência dos regimes terapêuticos instituídos (Brozović, 2022; Zhang, 2022).

Destaca-se, nesse contexto, a dor crônica induzida por quimioterapia como um dos principais fatores de piora na qualidade de vida desses pacientes (Starobova; Vetter, 2017a; Zajączkowska *et al.*, 2019; Zhang, 2021). Mesmo indivíduos previamente assintomáticos podem desenvolver dor neuropática com o início do tratamento, cuja prevalência pode chegar a 68% no primeiro mês, diminuindo para 60% em três meses e cerca de 30% após seis meses de quimioterapia (Colvin, 2019).

A vincristina (VCR) é um agente quimioterápico pertencente à classe dos alcaloides da vinca, caracterizado por elevado potencial antitumoral e amplo espectro de aplicação clínica, abrangendo neoplasias como leucemias agudas, neuroblastoma, linfomas, câncer de mama e melanoma (Alwhaibi *et al.*, 2023; Brown; Ross; Belsky, 2025; Li *et al.*, 2020a; Madsen *et al.*, 2019). Apesar de sua reconhecida eficácia, a utilização da VCR está fortemente associada ao

desenvolvimento de neuropatia periférica (Alwhaibi *et al.*, 2023; Li *et al.*, 2024; Triarico *et al.*, 2021a). A prevalência da neuropatia periférica induzida pela VCR (NPIV) apresenta considerável variabilidade, oscilando entre 10% e 90% em pacientes pediátricos, podendo atingir até 78% em adultos (Li *et al.*, 2024; Soriano *et al.*, 2024).

A fisiopatologia da NPIV envolve múltiplos mecanismos interconectados, destacando-se o estresse oxidativo exacerbado, que promove a geração de espécies reativas de oxigênio (ERO) e nitrogênio (ERN), resultando em danos oxidativos a lipídios, proteínas e DNA neuronal (Alenezi, 2023a; Chen; Wang; Song, 2020; da Motta *et al.*, 2024). Associado a isso, a neuroinflamação contribui para o recrutamento de células imunes e liberação de citocinas pró-inflamatórias, perpetuando o ambiente neurotóxico (Li, G. zhou *et al.*, 2021a; Singh *et al.*, 2019a). A VCR também induz degeneração axonal e neuronal por comprometer o transporte axonal e a integridade do citoesqueleto (da Motta *et al.*, 2024; Nagai; Goshima; Ohshima, 2012a). Além disso, há ativação de vias apoptóticas, disfunção da homeostase do cálcio intracelular, com sobrecarga de cálcio no citosol e mitocôndrias, e comprometimento da função mitocondrial, culminando em disfunção bioenergética e perda de viabilidade neuronal (Chen; Wang; Song, 2020; Filippi-Chiela *et al.*, 2022; Li, G. zhou *et al.*, 2021a). Esses eventos, de forma sinérgica, sustentam o quadro doloroso crônico característico da NPIV. Visto a alta incidência de NPIV em crianças, com papel de destaque, é válido mencionar que a VCR é o principal quimioterápico utilizado para o tratamento da leucemia linfóide aguda, principal malignidade infantil (Brown; Ross; Belsky, 2025; Uittenboogaard *et al.*, 2022). O uso da VCR em crianças é pouco reportado em termos da gravidade em que a neurotoxicidade pode afetar a fase de

desenvolvimento infantil a nível cognitivo, emocional e físico.

Além disso, o câncer afeta predominantemente indivíduos com mais de 60 anos de idade, os quais apresentam maior suscetibilidade à dor e podem sofrer agravamento dos quadros álgicos, uma vez que essa faixa etária é frequentemente acometida por condições dolorosas crônicas (Dagnino; Campos, 2022; Fane; Weeraratna, 2020; Tinnirello; Mazzoleni; Santi, 2021). Entre as neoplasias associadas ao envelhecimento mais frequentemente tratadas com VCR destacam-se os linfomas, que, em 2022, corresponderam a 12,4% de todos os novos casos de câncer no mundo (“Global Cancer Burden Growing, amidst Mounting Need for Services.,” 2024). Ademais, mulheres constituem o grupo de maior risco para o agravamento da neuropatia periférica, embora os mecanismos fisiopatológicos que justifiquem essa maior suscetibilidade ainda não estejam plenamente esclarecidos (Kuppusamy *et al.*, 2024; White *et al.*, 2023).

Dessa forma, observa-se que a NPIV pode acometer grupos com maior vulnerabilidade à dor crônica e neurotoxicidade, como: *i*) pacientes oncológicos pediátricos; *ii*) pacientes idosos; e *iii*) mulheres em tratamento quimioterápico. Além disso, a neurotoxicidade induzida pela VCR não se limita à neuropatia periférica, podendo também desencadear alterações neurocognitivas e emocionais, como ansiedade e depressão, com impacto significativo na qualidade de vida. Assim, esses grupos de risco representam uma população prioritária para investigação, considerando a possibilidade de coexistência entre disfunções neurológicas, cognitivas e emocionais ainda pouco exploradas (Moschetti *et al.*, 2019a; SU *et al.*, 2025).

Nesse contexto, destaca-se o 7-cloro-4-(fenilselanil) quinolina (4-PSQ) (Figura 1), composto extensivamente investigado pelo nosso grupo de pesquisa.

O 4-PSQ já demonstrou propriedades neuroprotetoras e efeitos analgésicos em modelos de neuropatia periférica induzida por oxaliplatina e paclitaxel (Paltian *et al.*, 2022a; Reis *et al.*, 2020c, 2020a, 2022). Sua estrutura contém um átomo de selênio, conferindo-lhe relevante atividade antioxidante, com capacidade de reduzir a produção de EROs e modular enzimas do sistema de defesa antioxidante (Motta *et al.*, 2021a; Reis *et al.*, 2022; Vogt *et al.*, 2018a; Wilhelm *et al.*, 2017). Além disso, estudos pré-clínicos evidenciaram seu potencial anti-inflamatório em modelos de dor inflamatória, com redução de citocinas pró-inflamatórias, favorecendo a neuroproteção em condições de caráter emocional e cognitivo, como a doença de Alzheimer, bem como promovendo neuroplasticidade durante o envelhecimento (Barth *et al.*, 2019a; de Oliveira *et al.*, 2022a; Paltian *et al.*, 2020a, 2025; Pinz *et al.*, 2016a, 2018a; Voss *et al.*, 2017a).

As propriedades neuroterapêuticas do 4-PSQ apresentam convergência com os mecanismos de neurotoxicidade induzidos pela VCR, indicando seu potencial como estratégia adjuvante para o manejo da NPIV e de suas comorbidades. Nesse sentido, postula-se que o 4-PSQ possa atenuar os impactos da NPIV em grupos de risco específicos. Ademais, hipotetiza-se que o 4-PSQ, isoladamente ou em associação à VCR, possa exercer efeito antitumoral adicional, contribuindo não apenas para a mitigação da dor oncológica, mas também para a redução dos efeitos adversos relacionados à quimioterapia com VCR, configurando-se como um potencial agente terapêutico adjuvante no tratamento oncológico.

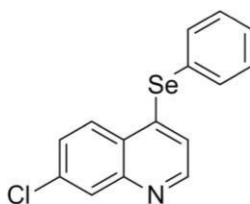


Figura 1. Estrutura química do 7-cloro-4-(fenilselanil) quinolina (4-PSQ).

2. OBJETIVOS

2.1. Objetivo geral

Investigar os mecanismos fisiopatológicos, os fatores de suscetibilidade biológica (envelhecimento, neurodesenvolvimento e dimorfismo sexual) e o potencial terapêutico do composto 4-PSQ como estratégia neuroprotetora e antitumoral frente à NPIV, alterações cognitivo-emocionais e dor oncológica induzidas pela VCR em modelos pré-clínicos.

2.2. Objetivos específicos

- Avaliar a influência do envelhecimento na susceptibilidade à NPIV, identificando alterações histopatológicas, bioquímicas e moleculares;
- Investigar o impacto da VCR em parâmetros comportamentais relacionados a alterações neurocognitivas e emocionais, e elucidar os mecanismos moleculares associados;
- Analisar o potencial antitumoral do composto sintético 4-PSQ em linhagens de células tumorais, bem como seu efeito antinociceptivo em modelos de NPIV;
- Examinar os efeitos da VCR no neurodesenvolvimento e crescimento físico de ratos neonatos, com ênfase em marcadores histológicos e moleculares relacionados à degeneração neural, mitofagia, apoptose e estresse oxidativo;
- Verificar a eficácia do 4-PSQ no manejo da dor oncológica associada à NPIV e tumor sólido (S180), avaliando parâmetros inflamatórios,

imunológicos (macrófagos peritoneais) e bioquímicos (atividade de ATPases e status oxidativo);

- Comparar possíveis diferenças relacionadas ao dimorfismo sexual na suscetibilidade à neurotoxicidade induzida pela VCR, assim como na resposta ao tratamento com o 4-PSQ;
- Avaliar o potencial do composto 4-PSQ modular *in vitro* os canais de receptor de Potencial Transitório (TRPs) por meio do ensaio de Registro de cálcio (*calcium imaging*).

3. REFERENCIAL TEÓRICO

3.1. Dor oncológica

A dor é caracterizada segundo a IASP (2020) como uma experiência sensorial e emocional desagradável associada a, ou semelhante à, dano tecidual real ou potencial. A dor oncológica, nesta mesma linha, é considerada uma síndrome de dor mista que engloba a nocicepção, bem como a neuropatia derivada dos tratamentos quimioterápicos (Brozović, 2022).

A prevalência da dor oncológica é muito variável visto que ela depende do local do tumor, estágio da doença, exposição às terapias anticâncer, predisposição a dor ou outros agravantes (Brozović, 2022; Mestdagh; Steyaert; Lavand'homme, 2023). Porém estima-se que a dor moderada a grave do câncer afeta 40–60% dos pacientes adultos com câncer (Breivik *et al.*, 2009; van den Beuken-van Everdingen *et al.*, 2007), 64% dos pacientes com doença avançada relatam dor (van den Beuken-van Everdingen *et al.*, 2007) e 40% dos pacientes com câncer são afetados pela dor neuropática do câncer (Bennett *et al.*, 2012).

A dor oncológica associada ao crescimento tumoral, por exemplo, se trata de um dos sintomas primários que auxiliam no diagnóstico – ela se caracteriza em tumores sólidos pela compressão que o crescimento tumoral exerce sobre os tecidos adjacentes como nervos, músculos, tendões, cartilagens e ossos (Bennett *et al.*, 2012; Brozović, 2022; Gómez *et al.*, 2020; Mestdagh; Steyaert; Lavand'homme, 2023). O crescimento tumoral também é paralelo ao desencadeamento de respostas imunológicas claras que acionam uma cascata de eventos pró-inflamatórios que elevarão a projeção de uma dor inicialmente

aguda que posteriormente tende a tornar-se crônica (Gouveia *et al.*, 2018; Mestdagh; Steyaert; Lavand'homme, 2023; Yoon; Oh, 2018).

Neste contexto, a dor neuropática associada à quimioterapia destaca-se como uma das formas de dor crônica de maior impacto para pacientes oncológicos (Brozović, 2022). Apesar da elevada eficácia dos regimes farmacológicos no controle da progressão tumoral, sabe-se que, em grande parte dos casos, os efeitos adversos dessas terapias resultam em danos significativos ao sistema nervoso central e periférico (Kang *et al.*, 2020; Timmins *et al.*, 2022; van de Velde *et al.*, 2017a). Sendo que essas dores podem levar a queda do pé, perda de reflexos tendinosos profundos, equilíbrio prejudicado e/ou formigamento (Evenepoel *et al.*, 2022; Li *et al.*, 2020a; Simão *et al.*, 2015; Starobova; Vetter, 2017a).

O manejo da dor oncológica é ainda um desafio clínico não possuindo terapias específicas, podendo causar dependência como no caso do uso de opióides e perda de eficiência (Wang *et al.*, 2022; Zhang, 2022). Órgãos internacionais como Joint Commission, National Comprehensive Cancer Network e American Society of Clinical Oncology recomendam que a terapia da dor precisa ser combinada, ou seja, ela é multifatorial, e carece da intervenção de diferentes frentes processuais e psicossociais (Baker, 2017; Paice *et al.*, 2016; Swarm *et al.*, 2013). Ou seja, é necessária desde a intervenção medicamentosa, de radiação ou até mesmo a terapia psicológica; visto que a dor possui um fator emocional eminente (Deng, 2019).

3.2. Toxicidade induzida por VCR

A VCR é um fármaco de estrutura molecular considerada complexa, constituída por um núcleo indol e outro diidroindol (Figura 2). Assim que administrada por via intravenosa, a VCR penetra as células por meio de sistemas de transporte ativo dependentes de energia e difusão passiva (Li *et al.*, 2020b). Já no meio intracelular, a VCR liga-se à tubulina, formando ligações perpétuas, tornando as fibras celulares desordenadas, incapazes de separar as cromátides na mitose.

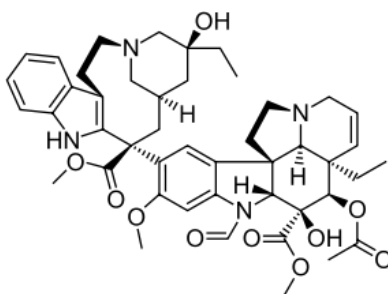


Figura 2. Estrutura molecular da vincristina

Em contrapartida, o mecanismo de ação antitumoral da VCR não é seletivo para células tumorais. Por este motivo, a interrupção da mitose celular acaba ocorrendo e levando a uma série de efeitos adversos incluindo a NPIV.

Outros sintomas mais característicos da NPIV são dormência, parestesia, equilíbrio prejudicado, reflexos tendinosos enfraquecidos e marcha alterada (Cheng *et al.*, 2022). A VCR causa ainda disfunções autonômicas como constipação, íleo paralítico, retenção urinária e hipotensão ortostática. Além disso, várias paralisias de nervos cranianos e algumas toxicidades do sistema nervoso central (SNC) foram relatadas (Gomber; Dewan; Chhonker, 2010a; Tay *et al.*, 2021a) muito embora a VCR seja relatada por penetrar “mal” a barreira sangue-cérebro. Apesar de a neurotoxicidade ser amplamente reconhecida como um efeito colateral comum do tratamento com VCR, pouco se sabe sobre a verdadeira incidência, manifestações de curto e longo prazo e gravidade.

É importante mencionar que apesar da VCR passar por metabolização no organismo, ela não apresenta metabólitos ativos. Ou seja, a ação antitumoral e neurotóxica da VCR se caracteriza essencialmente pela ação da molécula.

3.2.1. Fisiopatologia da NPIV

Num primeiro momento, é necessário classificar a injúria gerada pela VCR em três grupos de estruturas comprometidas: mitocôndrias, endotélio e microtúbulos (Triarico *et al.*, 2021b). O dano somatossensorial nessas estruturas vai estar relacionado à ativação de processos distintos (Figura 3).

Na mitocôndria, análises microscópicas têm demonstrado vacuolização e inchaço com cristas rompidas perante o tratamento com VCR (Canta; Pozzi; Carozzi, 2015a). Esses danos precedem a apoptose neuronal que pode envolver diferentes vias, como a ativação da cascata das caspases, a desregulação do

Ca^{2+} intracelular, o dano ao DNA mitocondrial, a alteração na cadeia transportadora de elétrons e no potencial de membrana e a perda de enzimas envolvidas em atividades antioxidantes (Areti *et al.*, 2014; Flatters, Dougherty, Colvin, 2017).

O processo mais prejudicado a nível mitocondrial é o movimento de Ca^{2+} através da membrana mitocondrial, levando a um déficit da quantidade e da taxa de captação de Ca^{2+} . A alteração destes processos resulta no aumento da exocitose de neurotransmissores, excitabilidade neuronal e função glial prejudicadas (Canta; Pozzi; Carozzi, 2015a).

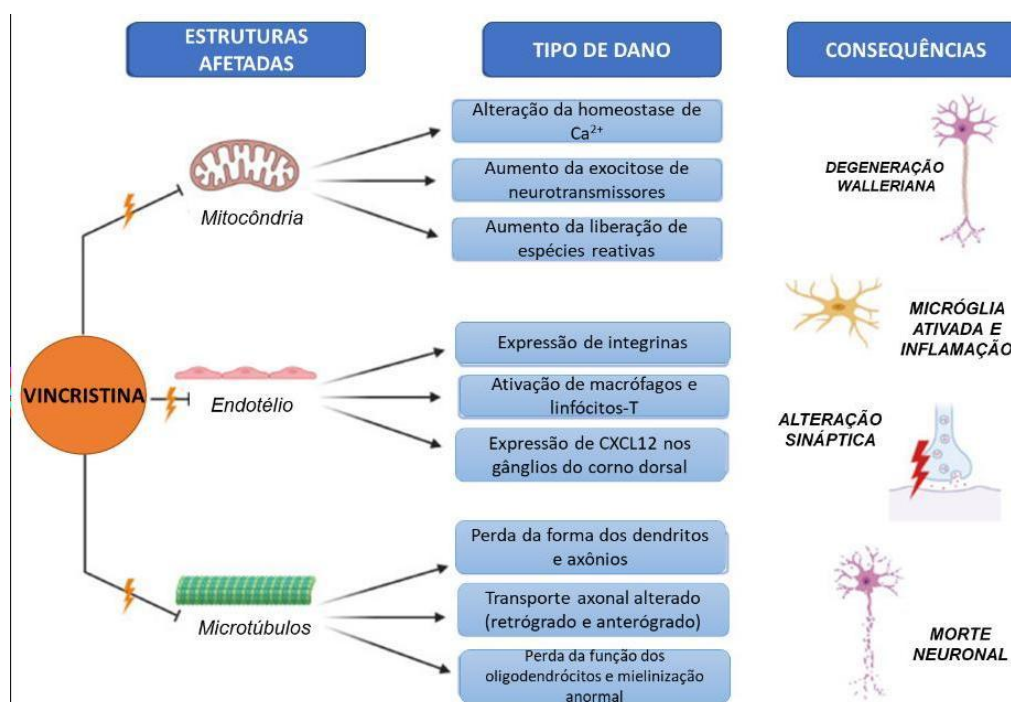


Figura 3. Esquema de mecanismos de ação da VCR. (Adaptado de Triarico et al.(2021b))

O segundo processo deletério gerado pela VCR acomete o endotélio. O endotélio é um revestimento epitelial de vasos sanguíneos, linfáticos e das câmaras do coração. O endotélio apresenta propriedades importantes que caracterizam a manutenção da circulação sanguínea, regulação do tônus muscular, permeabilidade vascular, sinalização, angiogênese e resposta inflamatória. Sabe-se que a VCR é um quimioterápico amplamente utilizado para o tratamento de malignidades hematológicas; entretanto, também se evidencia o dano hematológico como um efeito adverso grave da VCR (Sy *et al.*, 2019a).

A nível endotelial, a VCR induz o aumento da expressão de integrinas

(marcadores imunológicos), levando ao aumento da expressão do receptor de quimiocina (CXCR) na superfície das células endoteliais, permitindo a migração da VCR para o sistema nervoso (Montague *et al.*, 2018). Esse processo hematológico, desencadeia o aumento da produção de espécies reativas que atuam como mediadores químicos para a comunicação imune-neuronal e ativação do potencial receptor Transitório anquirina 1 (TRPA1) ocasionando a evocação da dor (Old *et al.*, 2014a).

Ainda, nos gânglios do corno dorsal, a VCR facilita a ligação do Transdutor de Sinal e Ativador de Transcrição 3 (STAT3) ao promotor do gene CXCL12 que atuará como um ligante da integrina CXCR4 (Xu *et al.*, 2017a). O CXCR4 acarretará o aumento de cálcio intracelular, resultando na liberação de linfócitos T e monócitos, gerando ativação do processo inflamatório desde o sistema nervoso periférico (Xu *et al.*, 2017a).

O terceiro mecanismo é o dano aos microtúbulos. A VCR provoca alterações na forma e estabilidade do neurônio devido à ação sobre os microtúbulos. As alterações celulares impedem o transporte axonal retrógrado e anterógrado com consequente degeneração Walleriana (Starobova *et al.*, 2019). A degeneração Walleriana é desenvolvida durante um episódio traumático ou isquêmico levando a uma injúria axonal, como na NPIV. As consequências desta degeneração são alterações na transmissão e condução de impulsos nervosos e posterior morte neuronal (Triarico *et al.*, 2021b).

De forma mais contundente, é necessário mencionar que o dano somatossensorial desenvolvido pela VCR é tão danoso a nível nervoso que resulta em eventos específicos da degeneração Walleriana como: alterações no citoesqueleto; alterações nas células de Schwann e na bainha de mielina; alterações nas barreiras hemato-nervosas; e respostas dos macrófagos. Especificamente, os microtúbulos desempenham um papel fundamental na mielinização das fibras nervosas, pois são constituintes essenciais dos oligodendrócitos (Lee; Hur, 2020). Logo, a NPIV é caracterizada de forma singular a alteração dos oligodendrócitos, gerando mielinização anormal ocasionando a perda de fibras sensoriais periféricas (Lee; Hur, 2020).

3.2.2. Estresse oxidativo e neuroinflamação induzidos por VCR

O dano oxidativo induzido pela VCR é associado ao mecanismo de ação

deletério às mitocôndrias e às alterações na homeostase de cálcio. O estresse oxidativo induzido pela VCR ainda pode ser relacionado ao processo neuroinflamatório e à liberação de quimiocinas e citocinas.

Khalilzadeh e colaboradores (2020a) demonstraram o aumento de citocinas pró-inflamatórias, incluindo o fator de necrose tumoral-alfa (TNF- α), interleucina-1 β (IL-1 β), e também a ativação da via de sinalização do fator nuclear kappa B (NF- κ B) na medula espinhal como fator contribuinte no desenvolvimento de NPIV. Hipotetiza-se que a ativação do NF- κ B se deva, pelo menos em parte, à produção excessiva de espécies reativas. O *início* do dano oxidativo parece ocorrer pelo aumento de ERO que são observados apenas após o dano mitocondrial (Starobova; Vetter, 2017b). Ainda, o dano oxidativo gerado pela VCR pode ativar vias de apoptose como a caspase-3 e proteína X associada a Bcl-2 (BAX) (Shayesteh *et al.*, 2022a).

Além disso, a VCR também resulta na degeneração dos axônios por produzir radicais livres altamente reativos e alterar a liberação de citocinas inflamatórias (Areti *et al.*, 2014). A VCR aumenta significativamente o estresse oxidativo celular, eleva as concentrações de malondialdeído (MDA), devido à peroxidação lipídica acelerada da membrana e a uma redução na glutatona reduzida (GSH) no tecido do nervo ciático (Alenezi, 2023b). Poucas ou raras pesquisas demonstram estresse oxidativo ou danos a nível de sistema nervoso central pela VCR na NPIV.

A administração de VCR regula positivamente a descarga de mediadores inflamatórios como interleucina-6 (IL-6), TNF- α e IL-1 β , resultando no estabelecimento de neuroinflamação e dor intensa na NPIV (Shen *et al.*, 2015a; Starobova; Vetter, 2017b; Xiaohong *et al.*, 2022). Da mesma forma, vários estudos têm defendido o papel do NF- κ B para o desenvolvimento da dor em NPIV, visto que a alodinia é induzida pela VCR através da expressão elevada de NF- κ B na medula espinhal (Singh *et al.*, 2019b).

O NF- κ B permanece dormente no citosol sob a influência da proteína Inibidor de kappa B (I κ B) quinase. No entanto, durante a inflamação, o I κ B é degradado e o NF- κ B torna-se ativo, translocando-se para o núcleo para induzir a expressão de citocinas inflamatórias, como IL-1 β , TNF- α , ciclo-oxigenase-2 (COX-2) e IL-6, induzindo genes apropriadamente envolvidos (Singh *et al.*, 2019b). Essas citocinas inflamatórias interagem com o Receptor toll-like-4 (TLR-

4) para agravar ainda mais a condição inflamatória, recrutando células inflamatórias e induzindo o estresse oxidativo (Moschetti *et al.*, 2019b). O NF- κ B também interage com proteínas antioxidantes endógenas como a Proteína associada ao domínio ECH tipo Kelch 1 (Keap1)/ Fator nuclear relacionado ao fator eritroide 2 (Nrf2) reduzindo sua indução para produzir uma proteína antioxidante como heme oxigenase-1 (HO-1) (Shen *et al.*, 2015a; Singh *et al.*, 2019b).

Shen *et al.* (2015) avaliaram os níveis de HO-1 durante a avaliação da sensibilidade no teste do von Frey em camundongos expostos a VCR. Foi verificado o aumento da sensibilidade mecânica e, paralelamente, o aumento de HO-1. O aumento de HO-1 ocorreu também no teste do levantamento da cauda (Shen *et al.*, 2015a).

O aumento dos mediadores inflamatórios e do estresse oxidativo causado pela VCR facilita a transição de macrófagos M1 para M2 no nervo ciático e aumenta a sensibilidade nociceptiva (Kiguchi *et al.*, 2008). No dano oxidativo consolidado pela neuroinflamação, espécies reativas interagem com macromoléculas celulares, incluindo proteínas, fosfolipídios e DNA, que promovem o dano à integridade neuronal pela VCR e facilitam o desenvolvimento do dano neuronal, além de aumentar a sensibilidade à dor (Canta; Pozzi; Carozzi, 2015a; Shayesteh *et al.*, 2022a).

As ERNs também aumentam pelo dano causado pela VCR. Um estudo anterior verificou o aumento da expressão de Sintase de Óxido Nítrico Neuronal (nNOS) e NF κ B nos gânglios da raiz dorsal (Khalilzadeh *et al.*, 2020a). É visto que logo após a lesão somatossensorial, a produção de óxido nítrico (NO) aumenta e os níveis aumentados de NO inibem a sintase de óxido nítrico (NOS) por meio de um mecanismo de feedback negativo. O duplo efeito do NO na dor pode depender do tempo, efeito colateral, quantidade de NO ou tipo de estímulo de dor (mecânico ou térmico) (Bujalska; Gumulka, 2008).

3.2.3. Excitabilidade neuronal induzida por VCR

A administração de VCR eleva a excitabilidade neuronal. A VCR leva à descarga espontânea anormal e maior capacidade de resposta a estímulos elétricos, mecânicos e térmicos (Li *et al.*, 2017; Schappacher *et al.*, 2019a).

Danos nos nervos periféricos, como os resultantes de trauma mecânico, podem evocar alterações no processamento nociceptivo dentro do corno dorsal superficial da coluna vertebral (CDS/CV)(Kohn et al., 2003). Além disso, conforme observado no sistema nervoso periférico, os efeitos da lesão nervosa no circuito CDS/CV podem variar dependendo da idade em que ocorre o insulto (McKelvey et al., 2015; Vega-Avelaira; Moss; Fitzgerald, 2007).

VCR aumenta a prevalência e a taxa de disparo repetitivo em neurônios sensoriais de diâmetro grande e médio, reduzindo a descarga de pico em neurônios de diâmetro pequeno, em comparação com grupos experimentais controle(Schappacher et al., 2019a). Em roedores neonatos a VCR aumentou significativamente a excitabilidade intrínseca da membrana dos neurônios espino-parabraquiais da lâmina I, como evidenciado por uma diminuição na reobase e elevação da frequência de disparo repetitivo em comparação com os controles (Schappacher et al., 2019a). A via ascendente da dor é a principal acionada pela VCR sendo esta responsável pela evocação da dor. A excitabilidade causada pela VCR pode explicar a persistência da dor inicial e a neuropatia periférica; a longo prazo, a VCR leva a hipoalgesia pelo dano grave somatosensorial que se segue a nível crônico.

A NPV despolariza os potenciais de membrana em repouso e diminui o limiar de corrente para gerar potenciais de ação em neurônios do gânglio da raiz dorsal (Jiang; Shi; Shi, 2019a). O aumento da excitabilidade neuronal desencadeia a produção e secreção de neurotransmissores, incluindo peptídeo relacionado ao gene da calcitonina (PRGC), substância P e glutamato dos axônios dos neurônios primários, levando à sensibilização central da medula espinhal e hiperalgesia (Zhao, J. Y. et al., 2017).

Foi demonstrado que em ratos submetidos a VCR a superativação de vias de evocação da dor resultou na desmielização do nervo ciático (Jiang; Shi; Shi, 2019a). Os autores supõem que o dano à bainha de mielina foi determinado pela medição do índice funcional ciático e da velocidade de condução do nervo ciático afetados pela ação da VCR (Jiang; Shi; Shi, 2019a).

3.2.4. Alterações na homeostase cálcio pela VCR

Acredita-se que alguns fatores bioquímicos podem estar relacionados à maior despolarização axonal, evocação da dor e prejuízo ao sistema nervoso sensorial. De fato, a via mais proposta e pontual na despolarização nervosa e

alterada pela VCR se dá por meio das alterações iônicas de cálcio (Li, G. Zhou *et al.*, 2021a).

A VCR é capaz de afetar o movimento do cálcio através da membrana mitocondrial neuronal dos gânglios da raiz dorsal, alterando sua homeostase e levando a uma excitabilidade neuronal anormal (Canta; Pozzi; Carozzi, 2015a). De fato, foi demonstrado que a VCR é capaz de afetar o movimento de Ca^{2+} através da membrana mitocondrial, reduzindo a quantidade e a taxa de captação de Ca^{2+} e diminuindo o efluxo de Ca^{2+} (Canta; Pozzi; Carozzi, 2015a). Alterações na captação mitocondrial de Ca^{2+} afetariam as mudanças espaço-temporais da concentração de Ca^{2+} (Chantal *et al.*, 1986).

As alterações iônicas de cálcio podem levar a excitabilidade neuronal e função glial prejudicada. Essas alterações também são corroboradas pela observação morfológica que relatou uma grande incidência de mitocôndrias inchadas e vacuolizadas com cristas rompidas localizadas na periferia da organela perante a ação da VCR (Flatters; Dougherty; Colvin, 2017).

Particularmente, proteína quinase II estimulada por cálcio/calmodulina modula a atividade ou a plasticidade dos neurônios por sinalização de Ca^{2+} no desenvolvimento de alodinia neuropática (Kim; Sharma, 2004; Song *et al.*, 2010). A subunidade 3.2 do canal de cálcio dependente de voltagem (CaV 3.2), um canal de cálcio de baixo limiar, é o substrato molecular da alodinia neuropática na medula espinhal (François *et al.*, 2015) e um regulador chave na excitabilidade neuronal nos gânglios da raiz dorsal (McCallum *et al.*, 2003).

Logo essas alterações de cálcio sinalizam um mecanismo importante pelo qual a excitabilidade neuronal causada pela VCR ocorre e como ela se perpetua (Li, G. Zhou *et al.*, 2021b). Somando a estes estudos, Li e colaboradores (Li, G. Zhou *et al.*, 2021b) descobriram que a NPIV foi acompanhada por ativação de astrócitos; regulação positiva da expressão de proteína quinase II estimulada por cálcio/calmodulina; modulação de canais de cálcio dependentes de voltagem; e a produção e liberação de citocinas e quimiocinas inflamatórias na medula espinhal.

3.2.5. Degeneração induzida por VCR

A VCR diferente de outros quimioterápicos que induzem neuropatia periférica leva a degeneração axonal e neural. De fato, a neuropatia induzida por

VCR possui diferenças quando comparada a outras neuropatias induzidas por quimioterápicos. A VCR causa inicialmente, neuropatia periférica e depois pode se agravar causando neuropatia autonômica e neuropatia motora (Gilchrist; Marais; Tanner, 2014; Shabani *et al.*, 2012a).

A degeneração das células nervosas causada pela VCR compromete o sistema somatosensorial onde a neuropatia periférica ocorre, por este fato, a hipernocicepção inicial causada pela VCR passa à hipoalgesia. A degeneração neural ou axonal promove a perda da sensibilidade e, com o tempo, pode levar a prejuízos motores e locomotores (Golchin *et al.*, 2015; Shabani *et al.*, 2012a). De maneira geral, os alcaloides da vinca por meio da superativação das vias nociceptivas por tempo prolongado interrompem o transporte axonal, levando à axonopatia distal e à degeneração das fibras sensoriais, o que explica a mudança da hiperalgesia precoce para a perda funcional e hipoalgesia posteriores (Laforgia *et al.*, 2021; Zajączkowska *et al.*, 2019).

A degeneração walleriana é o modelo mais simples e mais bem estudado de degeneração axonal. Um estudo anterior demonstrou que a degradação do citoesqueleto axonal em fibras nervosas axotomizadas é um processo dependente de Ca^{2+} (George; Glass; Griffin, 1995). A entrada de Ca^{2+} provavelmente ativa calpaínas axonais. As calpaínas são proteases de cisteína dependentes de cálcio onipresentes envolvidas em funções celulares fisiológicas e patológicas (Wang *et al.*, 2000a).

A degeneração walleriana causada pela VCR já foi descrita por diferentes autores (Geisler, 2021a; Starobova; Vetter, 2017b; Sy *et al.*, 2019a). A VCR desestabiliza microtúbulos evitando o crescimento de novas células neoplásicas. Nos neurônios do gânglio da raiz dorsal, a VCR leva à perda de proteína mediadora da resposta à colapsina 4, inibindo o crescimento axonal (por uma glicoproteína associada à mielina), causando colapso do cone de crescimento e levando à sensibilidade e à degeneração axonal (Nagai; Goshima; Ohshima, 2012b).

Ainda, a ligação da VCR nos fios mitóticos durante o processo de divisão celular, principalmente na tubulina, leva a injúria axonal tanto de células saudáveis quanto de células tumorais (Triarico *et al.*, 2021b). Em células saudáveis, a VCR ao ligar-se à tubulina causa um impedimento no transporte axonal anterógrado e retrógrado com consequente degeneração walleriana. De

fato, a degeneração walleriana pode ser associada ao dano na bainha de mielina e consequente morte celular (Triarico *et al.*, 2021b).

3.2.6. Canais iônicos de potencial Transitório

Os canais da família dos Receptores de Potencial Transitório (TRPs) são canais iônicos catiônicos não seletivos envolvidos na detecção e transdução de estímulos nocivos. Entre suas subfamílias, TRPA1, Receptor do Potencial Transitório Melastatina 8 (TRPM8) e Receptor do Potencial Transitório Vaniloide 1 (TRPV1) se destacam por seu papel na modulação da excitabilidade neuronal e no desenvolvimento da dor neuropática. Esses canais são ativados por estímulos térmicos, mecânicos ou químicos, promovendo despolarização neuronal, influxo de Ca^{2+} e sensibilização periférica e central, manifestando-se clinicamente como hiperalgesia e alodínia.

Diversos quimioterápicos, como vinca-alcaloides, taxanos, platinas e imunomoduladores, aumentam a excitabilidade nociceptiva por meio de desbalanço iônico, estresse oxidativo, neuroinflamação e alterações na expressão e função dos canais TRP em neurônios sensoriais dos gânglios da raiz dorsal (DRG) e de suas terminações periféricas. O aumento do influxo de Ca^{2+} ocorre não apenas pela ativação de TRPs, mas também de canais de cálcio dependentes de voltagem (VGCCs), contribuindo para a sensibilização neuronal. Após a percepção de estímulos periféricos, os nociceptores iniciam potenciais de ação nas fibras aferentes A δ e C, liberando mediadores da dor, como CGRP, substância P e glutamato, conectando o sistema nervoso periférico ao SNC.

Estudos demonstram que canais TRP distintos são funcionalmente expressos em nociceptores primários e nas fibras A δ e C, embora os mecanismos moleculares da dor periférica ainda não estejam totalmente esclarecidos. Dados de Salat *et al.* (2015) mostraram que antagonistas de TRPA1, TRPM8 e TRPV1 possuem efeitos antinociceptivos em modelos murinos de dor neurogênica e neuropática. Assim, essas evidências indicam que os canais TRP desempenham papel central nas vias da dor, incluindo a liberação de neuropeptídeos essenciais para a sinalização nociceptiva periférica. Canais da família dos TRPs constituem canais catiônicos não seletivos, envolvidos na detecção e transdução de estímulos nocivos. Dentre suas subfamílias, os canais TRPA1, TRPM8 e TRPV1 destacam-se pela relevância na modulação da

excitabilidade neuronal e no desenvolvimento da dor neuropática. A ativação dos canais TRPs por diferentes estímulos nociceptivos é ilustrada na Figura 4.

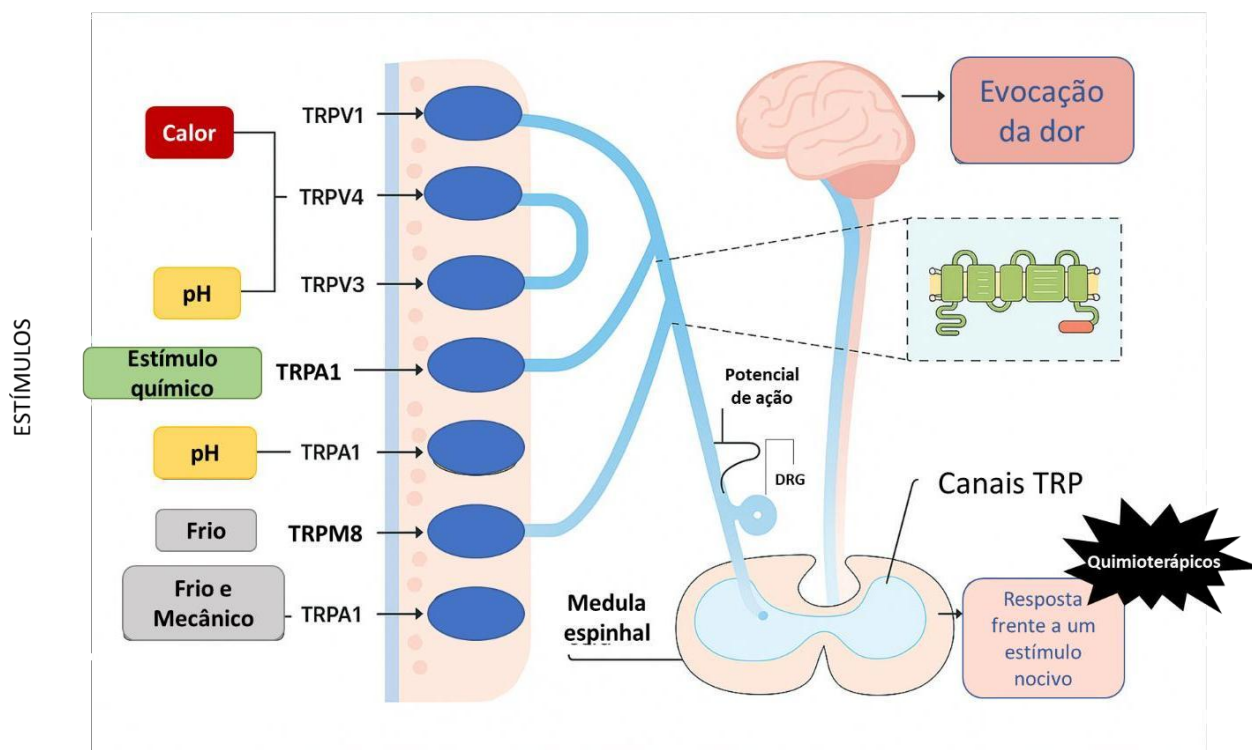


Figura 4. Esquema ilustrativo da ativação dos canais TRP (TRPA1, TRPV1, TRPV3, TRPV4 e TRPM8) por diferentes estímulos nociceptivos: térmicos, mecânicos, químicos, pH alterado e frio. A ativação desses canais em neurônios sensoriais do gânglio da raiz dorsal (DRG) provoca influxo de Ca^{2+} , despolarização neuronal e geração de potenciais de ação, que são transmitidos à medula espinhal e ao cérebro, resultando na evitação ou percepção da dor. O esquema também indica que quimioterápicos podem modular a excitabilidade nociceptiva por meio da ativação ou sensibilização desses canais (Figura desenvolvida pelo autor).

3.3. Idade e sexo como fatores que aumentam susceptibilidade a dor

3.3.1. Associação do envelhecimento com a dor

O envelhecimento é um processo natural e biológico inevitável caracterizado por uma série de mudanças estruturais e funcionais cumulativas, universais, progressivas e deletérias a nível morfológico (Hou *et al.*, 2019). O declínio de algumas funções biológicas básicas é intrínseco ao processo do envelhecimento que leva ao desgaste muscular, perda de plasticidade neuronal, metabolismo desacelerado, entre outros (Barth *et al.*, 2019a; Chen *et al.*, 2019;

Habif *et al.*, 2021; Şimşek, Oymak Soysal, Kaş Özdemir, 2023a). Todos estes fatores contribuem para o desenvolvimento de patologias de caráter doloroso e neurodegenerativo.

A senescência é o processo metabólico ativo decorrente do envelhecimento celular que contribui para a dor (Chen *et al.*, 2019; Şimşek; Oymak Soysal; Kaş Özdemir, 2023a). O manejo da dor em idosos é um desafio clínico visto que a permanência da sensação dolorosa é um sintoma clínico preocupante na velhice. A prevalência de dor aumenta mais do que o dobro após os 60 anos de idade, e a frequência da dor continua a aumentar a cada 10 anos (Kim *et al.*, 2017a). Estudos mostraram que 25% a 50% dos idosos sofrem de dor (Chancay; Guendsechadze; Blanco, 2019; Fitzmaurice *et al.*, 2017).

Além disso, a dor em idosos está diretamente associada ao sofrimento e está relacionada à deterioração de muitas condições, incluindo mobilidade prejudicada, diminuição da função física, distúrbios do sono e depressão, bem como aumento dos custos de utilização da saúde e diminuição da socialização (Şimşek; Oymak Soysal; Kaş Özdemir, 2023b).

A dor oncológica em idosos, particularmente, é de ordem crônica experimentada por 2/3 dos pacientes na fase terminal e por 1/3 dos pacientes na fase inicial do câncer (Dziechciaż; Balicka-Adamik; Filip, 2013). Boa parte da dor oncológica que acomete os idosos com câncer se deve ao tratamento quimioterápico (El Hachem *et al.*, 2019; Mortazavi, 2019). A pré-disposição à dor vivenciada, a dor oncológica derivada do próprio tratamento, é um agravante para o sofrimento dos idosos.

Além disso, a elevada exposição de idosos ao uso de analgésicos e medicamentos em geral pode dificultar o manejo de fármacos que exerçam efeito significativo no combate à dor (Grant *et al.*, 2025; Kakatkar; Narayan; Balkrishnan, 2022). Logo, a dor oncológica em idosos se caracteriza por ser um paradigma de difícil tratamento, agravada pela senescência e ainda pouco investigada no que diz respeito ao tratamento quimioterápico.

3.3.2. Dor pediátrica

O manejo da dor infantil ainda constitui um desafio clínico significativo, dada a dificuldade em sua identificação, mensuração e tratamento (Hodapp; Ali; Drendel, 2020). Inicialmente, os neurocientistas subestimavam que crianças seriam capazes de processar a sensação dolorosa como adultos devido à

imaturidade do sistema nervoso (Anand; Hickey, 1987). Com o passar dos anos, foi demonstrado por meio de evidências neurofisiológicas que o sistema nociceptivo é funcional desde a vida intrauterina (Lee *et al.*, 2005). Sabe-se, no entanto, que mecanismos inibitórios na via adjacentes da dor não estão totalmente completos nas fases neonatais e que podem levar a uma exacerbação na sensação dolorosa (Tucker; Tiwari; Carter, 2023).

É válido ressaltar, no entanto, que a dor não-tratada ou mau-tratada nesta fase da vida pode levar a alterações e complicações capazes de causar mudanças neuropsicológicas importantes (Cook *et al.*, 2023). Dentre estas alterações que podem alterar o cérebro da criança com dor está a hipersensibilidade à dor e alterações emocionais (Williams; Lascelles, 2020a). Entretanto, as modulações intrínsecas às condições dolorosas crônicas em pacientes oncológicos são uma área com muitas lacunas; ou seja, muitos processos fisiopatológicos que podem ser ativados ou inativados devido a condições de dor severas não são elucidadas plenamente (Cook *et al.*, 2023; Hoogen *et al.*, 2018; Williams; Lascelles, 2020b).

3.3.3. Dimorfismos sexuais na dor

As diferenças entre os comportamentos de homens e mulheres frente a estímulos dolorosos ainda permanecem pouco compreendidas. Evidências experimentais vêm mostrando que as mulheres apresentam limiares de dor mais baixos, classificações de dor mais altas e menor tolerância à dor do que os homens (Hashmi; Davis, 2009a).

Ensaios experimentais têm verificado que a dor nas mulheres se adapta e se habitua de forma proeminente, enquanto a dor nos homens é evocada consistentemente ao longo do tempo (Bilberg *et al.*, 2018; Hashmi; Davis, 2009b). Estudos sugerem também alterações na forma de evocação da dor entre homens e mulheres (Bartley; Fillingim, 2013; Quiton; Greenspan, 2007). Estudos sustentam a hipótese de mulheres apresentarem maior evocação da dor por meio das fibras A- δ , enquanto homens apresentam maior evocação por meio das fibras C. Quiton e colaboradores (2007b), ao averiguar a maior sensibilidade de mulheres à dor, constataram que mulheres detectam dor em intensidades de estímulo mais baixas do que os homens.

A dor neuropática, particularmente apresenta maior incidência em mulheres (Legakis; Bigbee; Negus, 2018; Miculescu *et al.*, 2022). Um fator que

pode contribuir para essa diferença na dor crônica em mulheres é a maior densidade de fibras nervosas nas mulheres em comparação com os homens (Mowlavi *et al.*, 2005). Ainda, outros fatores hormonais vêm sendo discutidos quanto à associação da dor no sexo feminino. O estrogênio parece regular funções sinápticas e de crescimento celular que quando afetados podem levar a prejuízos em células nervosas e aumentar a evocação da dor (Anbalagan *et al.*, 2012; Beyer & Karolczak, 2000).

3.4. Comorbidades associadas a dor neuropática causada por quimioterápicos

A ação neurotóxica causada por quimioterápicos pode desencadear danos severos a estruturas não-alvo. Além disso, a evocação da dor e o processamento da dor podem envolver vias paralelas à depressão, à ansiedade e ao déficit cognitivo, causando prejuízos severos (Kremer *et al.*, 2021; Markovic *et al.*, 2021). Ou seja, as pessoas podem desenvolver um problema de saúde mental, como depressão ou ansiedade, como consequência de viver com dor crônica (Edwards *et al.*, 2017; Kremer *et al.*, 2021).

Pacientes com dor e depressão comórbida também relatam maior gravidade da dor, pior funcionamento e mais incapacidade em comparação com pacientes com dor não deprimidos (Goesling; Lin; Clauw, 2018). Estudos relatam os transtornos psiquiátricos com a dor como uma via de mão dupla (Chancay; Guendsechadze; Blanco, 2019; Mok; Lok; Cheung, 2012). Em outras palavras, tanto a dor pode causar depressão e ansiedade como a depressão e ansiedade ocasionarem a dor.

Um mecanismo comum é descrito entre a depressão e a dor: a via serotoninérgica (Quines *et al.*, 2015; Sagalajev *et al.*, 2015). A depressão é uma patologia intimamente ligada a alterações serotoninérgicas. Já foi demonstrado que a depressão aumenta a atividade de monoaminas oxidases que depletam as monoaminas impedindo a ação da 5-hidroxitriptamina, por exemplo, nos receptores (Bhatt *et al.*, 2020; Yohn; Gergues; Samuels, 2017). Por este e outros motivos, atualmente os fármacos comercializados pro tratamento da depressão atuam em grande parte como inibidores da recaptação de serotonina (Edinoff *et al.*, 2021). Por outro lado, a dor evoca a via serotoninérgica por meio de diferentes receptores (da Motta *et al.*, 2023; Katsuyama *et al.*, 2014). A provavel

descompensação entre evocação e aumento da atividade das monoaminas oxidases pode ser um fator chave no desenvolvimento dessa comorbidade.

No aspecto de danos cognitivos a via colinérgica pode ser mencionada visto que é uma via comum entre a memória e a dor (Chen *et al.*, 2016; Hone; McIntosh, 2018-; Motta *et al.*, 2022; Wang *et al.*, 2019). A dor neuropática particularmente evoca a ativação de receptores nicotínicos $\alpha 6\beta 4$ e $\alpha 7$; em contrapartida, o dano cognitivo aumenta a atividade da acetilcolinesterase na fenda sináptica (Cox *et al.*, 2008; Eldufani; Blaise, 2019; Umana *et al.*, 2017-; Wieskopf *et al.*, 2015) . Mais uma vez uma provável descompensação na via colinérgica pode ser um ponto comum entre o prejuízo cognitivo e a dor.

Ainda, a ansiedade é o transtorno psiquiátrico mais alterado em pacientes com dor neuropática. Já foram reportados muitos modelos com indução de quimioterapia que levam ao desenvolvimento de ansiedade (Liu *et al.*, 2022; Reis *et al.*, 2020d). O aumento do estresse causado pela dor crônica pode levar a ativação do eixo hipotálamo-hipófise-adrenal levando a liberação de hormônios associados ao estresse que podem levar a ansiedade (de Oliveira *et al.*, 2022b). Apesar de existirem diversas especulações sobre como a relação entre a dor e comorbidades podem ocorrer; poucos estudos trazem pesquisas para explicar o mecanismo que evoca essas condições.

3.5. Plasticidade e Vulnerabilidade do Sistema Nervoso Neonatal

O sistema nervoso de recém-nascidos apresenta elevada plasticidade devido à sua imaturidade e ao intenso processo de desenvolvimento pelo qual está passando (Williams; Lascelles, 2020a). Por essa razão, os neonatos são particularmente suscetíveis a alterações no neurodesenvolvimento quando expostos a estímulos dolorosos (Hoogen *et al.*, 2018; Williams; Lascelles, 2020a). A ativação nociceptiva em fases precoces do desenvolvimento neurológico tem sido associada a efeitos deletérios, incluindo maior risco de comprometimentos físicos e psicológicos tanto em curto quanto em longo prazo (Tucker; Tiwari; Carter, 2023; Williams; Lascelles, 2020b).

Não obstante, evidências indicam ainda que essa exposição precoce a agentes tóxicos ou que podem penetrar a barreira sangue-cérebro pode provocar alterações adversas no desenvolvimento cerebral, na organização funcional do sistema somatossensorial e na percepção da dor (Baig; Panchal, 2019; Schappacher *et al.*, 2019b). Esses impactos podem perdurar ao longo da

infância e até mesmo se estender à vida adulta, sendo um tema amplamente reconhecido e documentado na literatura científica atual (Williams; Lascelles, 2020a).

3.6. Potencial terapêutico e farmacológico do 4-PSQ

O 4-PSQ é um composto sintético com estrutura quinolínica contendo uma porção de selênio estudado pelo nosso grupo de pesquisa e outros grupos há mais de 10 anos (Barth *et al.*, 2019b; de Oliveira *et al.*, 2022b; Duarte *et al.*, 2017a; Lemos *et al.*, 2021a; Motta *et al.*, 2021b; Paltian *et al.*, 2020b; Pinz *et al.*, 2018b; Reis *et al.*, 2020d, 2020b; Rodrigues *et al.*, 2021a; Savegnago *et al.*, 2013a; Silva *et al.*, 2017a; Vogt *et al.*, 2018b; Voss *et al.*, 2017b). A configuração estrutural do 4-PSQ o confere capacidade de interação biológica multialvo. Na perspectiva estrutural, a porção fenilselanil do composto é essencial na promoção de efeito antioxidante do 4-PSQ (Vogt *et al.*, 2018b). Não obstante, em uma análise de estrutura-atividade do nosso grupo de pesquisa, foi observado que a união do anel quinolina 7-cloro com o grupo fenilselênio na posição 4 confere ao 4-PSQ uma combinação única de lipofilicidade moderada e reatividade seletiva, favorecendo sua penetração tecidual e atividade biológica (da Rocha *et al.*, 2025).

A capacidade antioxidante do 4-PSQ está atrelada à redução de espécies reativas, promoção da homeostase das defesas antioxidantes e proteção do dano às macromoléculas em tecidos nervosos, tecido hepático e renal (Lemos *et al.*, 2021a; Motta *et al.*, 2021b; Pinz *et al.*, 2016b; Rodrigues *et al.*, 2021a). Pelo potencial antioxidante do 4-PSQ, muitas patologias que levam ao estresse oxidativo podem ser tratadas.

Além da alta ação antioxidante que pode auxiliar no tratamento da dor, outras vias a nível central são moduladas pelo 4-PSQ e promovem efeito analgésico. O 4-PSQ apresenta efeito antinociceptivo através da via glutamatérgica na modulação do receptor N-metil-D-aspartato (NMDA); em receptores serotoninérgicos (5-HT_{1A/1B} e 5-HT_{2A/2C}) e na via nitrérgica (Silva *et al.*, 2017a). Outras modulações do 4-PSQ foram reportadas a nível GABAérgico, por meio da ação sobre as monoaminas oxidases, e na via colinérgica por meio da ação sobre a acetilcolinesterase (AChE) (de Oliveira *et al.*, 2022b; Paltian *et al.*,

2022b; Rodrigues *et al.*, 2021a).

Além disso, o 4-PSQ apresenta atividades antiinflamatórias. O 4-PSQ já demonstrou reduzir a migração de macrófagos e neutrófilos em um modelo inflamatório de edema de orelha (Pinz *et al.*, 2016b). O 4-PSQ atenua os níveis de interleucina-1 β , interleucina-18, interleucina-33 e NF κ B alterados em um modelo de doença de Alzheimer (de Oliveira *et al.*, 2022b; Pinz *et al.*, 2018b). Ainda, em um estudo envolvendo o estresse de restrição, o 4-PSQ normalizou a via fosfatidilinositol-3-quinase (PI3K)/proteína quinase B (AKT) que é ativada por processos neuroinflamatórios que levam a desregulação neuronal prejudicando a sobrevivência neuronal e a neuroplasticidade (de Oliveira *et al.*, 2022b).

Corroborando o potencial de proteção neuronal e de neuroplasticidade do 4-PSQ, verificou-se a modulação do 4-PSQ sobre a diminuição da expressão da molécula de adesão de células neurais (NCAM) (Barth *et al.*, 2019b). Efeitos terapêuticos contra desordens psiquiátricas e associadas a memória - por meio do tratamento com 4-PSQ - demonstram que o composto é capaz de proteger contra danos neurológicos significativos e assim promover neuroproteção (Barth *et al.*, 2019a; de Freitas Couto *et al.*, 2019a; Pinz *et al.*, 2018a; Reis *et al.*, 2020c).

Por fim, porém, uma análise inovadora do nosso grupo de pesquisa, de Paltian *et al.* (2025) demonstrou que é possível potencializar os efeitos do 4-PSQ perante a incorporação do composto em nanocápsulas poliméricas. O 4-PSQ nanoencapsulado apresentou atividades farmacológicas importantes como aumento da estabilidade físico-química do fármaco, facilitação da liberação controlada garantindo maior biodisponibilidade e proteção contra degradação (Paltian *et al.*, 2025).

3.6.1. Efeitos analgésicos do 4-PSQ em neuropatia induzida por quimioterapia

O 4-PSQ já foi observado em modelos de neuropatia periférica induzidos por oxaliplatina e paclitaxel (Paltian *et al.*, 2022a; Reis *et al.*, 2020c, 2020a, 2022, 2025).

Na neuropatia periférica induzida por oxaliplatina (NPIO) nosso grupo de pesquisa já demonstrou que o potencial antioxidante do 4-PSQ pode ser extremamente importante na redução da hiperalgesia (Reis *et al.*, 2020a). Podemos destacar que o potencial do 4-PSQ neste modelo pode ser atribuído à modulação da atividade e expressão de glutathione peroxidase (GPx), superóxido

dismutase (SOD) e catalase (CAT). Além do efeito antioxidante do 4-PSQ, foi sugerido que parte do efeito antinociceptivo na NPIO pode ser atribuída a modulação da AchE (Reis *et al.*, 2020a).

Nesta linha, o 4-PSQ na NPIO aguda foi capaz de reverter a hiperalgesia exacerbada induzida em camundongos velhos (Reis *et al.*, 2022). Sendo que a modulação na atividade da Na^+ , K^+ - ATPase foi verificada como uma das ações-chave do 4-PSQ na reversão da NPIO aguda (Reis *et al.*, 2022). Em outro estudo foi abordada uma correlação entre a inibição da Na^+ , K^+ - ATPase e a neurotoxicidade induzida por oxaliplatina capaz de gerar ansiedade e prejuízo à memória - ambos prejuízos (emocionais e cognitivos) foram revertidos pela administração de 4-PSQ (Reis *et al.*, 2020c).

Em relação à neuropatia periférica induzida por paclitaxel (NPIP), o 4-PSQ, além de reduzir a hiperalgesia mecânica e térmica, também reverteu o comportamento tipo-ansioso e declínio cognitivo em camundongos (Paltian *et al.*, 2022a). O potencial terapêutico do 4-PSQ nesse modelo foi associado principalmente a redução de marcadores inflamatórios como NF- κ B, IL-1 β , TNF- α e iNOS os quais foram superexpressos após a administração do paclitaxel (Paltian *et al.*, 2022a). Outras atividades exercidas pelo 4-PSQ na NPIP foram a modulação da atividade de Ca^{2+} -ATPase suprimida pelo paclitaxel e restauração da atividade de enzimas antioxidantes (Paltian *et al.*, 2022a).

4. CAPÍTULOS

Os resultados que fazem parte desta tese estão divididos em capítulos e apresentados sob a forma de artigo e manuscritos. As seções materiais e métodos, resultados, discussão e referências encontram-se no artigo e nos manuscritos, representando a íntegra deste estudo. Os estudos já finalizados estão estruturados de acordo com as regras das revistas científicas.

4.1. Capítulo 1 – Artigo Científico 1

Insights sobre a Neuropatia periférica induzida por vincristina em ratos idosos: degeneração walleriana, dano oxidativo e alterações nas enzimas ATPase

Como parte inicial, afim de explorar, grupos mais susceptíveis à NPIV, investigamos como ratos velhos responderiam a nocicepção a partir da indução com VCR. Esta etapa contou com a comparação entre as respostas nociceptivas de ratos jovens em relação a ratos velhos. Além da avaliação da resposta nociceptiva, verificamos outros comportamentos associados ao déficit cognitivo e comportamento tipo-ansioso. Paralelamente, verificamos mecanismos intrínsecos a susceptibilidade à NPIV em ratos velhos por meio de histopatologia, resposta de enzimas ATPases associadas a excitabilidade neuronal e estresse oxidativo.

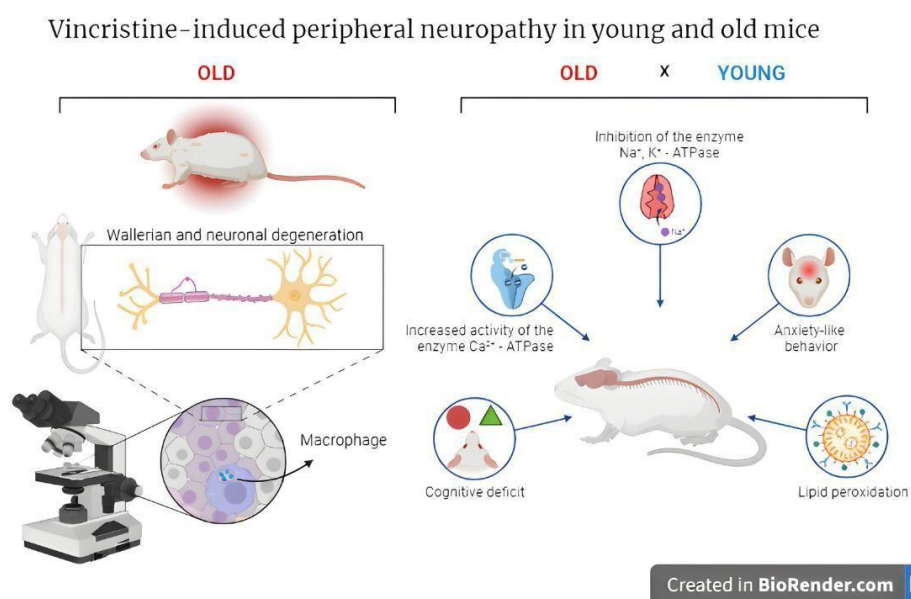
O conjunto de dados expostos neste artigo auxiliam na compreensão de como a VCR pode desencadear uma hipernocicepção em ratos velhos quando comparados a ratos jovens. Ademais, a VCR ocasionou o desenvolvimento de disfunções para além da neurotoxicidade apenas reportada em relação a dor – verificamos prejuízos neurocognitivos na memória de curto e/ou longo prazo além de comportamento do tipo-depressivo em ratos jovens e velhos. Pela primeira vez, exploramos a degeneração walleriana como um mecanismo-alvo da neurotoxicidade causada pela VCR em ratos velhos.

A VCR levou ao desencadeamento de danos oxidativos, demonstrados pelo aumento de peroxidação lipídica e aumento dos níveis de nitritos e nitratos. Em relação a atividade de ATPases totais, a VCR promoveu, de maneira geral a excitabilidade neuronal por meio da ativação da Ca^{2+} -ATPase, bem como por meio de disfunções na atividade da Mg^{2+} -ATPase. Em contrapartida, a atividade da Na^+ , K^+ -ATPase foi inibida perante a ação da VCR – fator contribuinte também para a excitabilidade neuronal.

Em suma, o artigo a seguir trouxe uma contribuição científica relevante uma vez que observa pela primeira vez a hipersensibilidade neuropática de ratos velhos perante a administração de VCR e mecanismos fisiopatológicos associados.

ARTIGO 1

Os resultados do Capítulo 1 da tese estão apresentados sob a forma de artigo científico, o qual se encontra assim organizado. Os itens Materiais e Métodos, Resultados, Discussão dos Resultados e Referências Bibliográficas encontram-se no próprio artigo. O artigo científico encontra-se publicado na revista *ACS Chemical Neuroscience*.



Insights into Vincristine-Induced Peripheral Neuropathy in Aged Rats: Wallerian Degeneration, Oxidative Damage, and Alterations in ATPase Enzymes

Ketlyn P. da Motta, Carolina C. Martins, Vanessa M. E. da Rocha, Mauro P. Soares, Marcia F. Mesko, Cristiane Luchese,* and Ethel A. Wilhelm*

Cite This: *ACS Chem. Neurosci.* 2024, 15, 3954–3969

Read Online

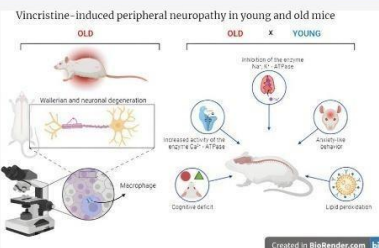
ACCESS |

Metrics & More

Article Recommendations

ABSTRACT: This study aimed to elucidate vincristine (VCR)-induced peripheral neuropathy in aged rats, a poorly understood neurotoxicity. Both young and old Wistar rats were administered VCR (0.1 mg/kg, intraperitoneally (i.p.)) and compared to age-matched controls (0.9% saline; 10 mg/mL, i.p.). Mechanical (MN) and thermal nociceptive (TN) responses were assessed on days 0, 6, 11, and 17. Locomotor response, cognitive ability, and anxious-like behavior were evaluated on days 14, 15, and 16. Results showed MN and TN responses in both young and old VCR-exposed rats. In old rats, VCR exacerbated MN (on days 6, 11, and 17) and TN (on days 6 and 17) responses. VCR also induced cognitive impairments and anxiety-like behavior. Histological analysis revealed Wallerian degeneration in the spinal cords of VCR-exposed rats accompanied by macrophage migration. Furthermore, VCR increased Ca^{2+} -ATPase activity while inhibiting Na^+ , K^+ -ATPase activity in young and old rats. VCR altered the homeostasis of Mg^{2+} -ATPase activity. Lipid peroxidation and nitrite and nitrate levels increased in young and old rats exposed to VCR. This study provides valuable insights into VCR's mechanistic pathways in aged rats, emphasizing the need for further research in this area.

KEYWORDS: Wallerian degeneration, vincristine, neuropathy in the old, Ca^{2+} -ATPase, lipoperoxidation



1. INTRODUCTION

Old age is the stage of life where diseases, pain, and neurodegenerative disorders tend to settle and develop in the body.^{1,2} Undoubtedly, pain is the most common limiting symptom in older people.¹ Still, cancer is a frequent disease and tends to devastate the vast majority of people over 60 years of age.³ In this sense, three factors need to be pointed out regarding the painful state that older people with cancer face: (I) common pain already faced by the wear and tear of the aging process, (II) oncological pain caused by cancer, and (III) pain developed by chemotherapy treatment—peripheral neuropathy.^{2,4,5} Therefore, painful suffering stands out as a severe clinical condition that older people with cancer experience.

Accordingly, the chemotherapy drug vincristine (VCR) has stood out as an antineoplastic agent commonly used in clinical oncology.⁶ Despite the clinical action of VCR being focused on child cancer care, it is known that the antitumor potential of VCR is therapeutically focused on the treatment of cancers that are common in the elderly. These cancers include neuroblastomas, lymphomas (Hodgkin and non-Hodgkin),

stomach adenocarcinomas, leukemias in general, and others.⁷ Unfortunately, the antitumor action of VCR is associated with the development of peripheral neuropathy.^{7,8} Peripheral neuropathy induced by VCR is one of the factors mentioned that lead to exacerbated suffering in older people with cancer. Of even more concern, VCR often develops neuropathic pain so debilitating as to promote nerve degeneration causing Wallerian degeneration.^{9,10} Wallerian degeneration developed during somatosensory injury (peripheral neuropathy) leads to impairment of anterograde and retrograde axonal transport.^{4,5} In addition, this degeneration compromises the myelin sheath of nerve cells, altering the transmission and conduction of impulses and causing cell death.⁴

Received: June 4, 2024
Revised: August 19, 2024
Accepted: August 20, 2024
Published: August 29, 2024



Despite the scientific appeal that peripheral neuropathy caused by VCR brings about the calamity of the subject, few or rare studies have focused on exploring neurotoxicity in the elderly. Therefore, this study proposes to assist in investigating oxidative pathways, the activity of ATPase enzymes involved in the electrochemical gradient of the nervous system, and Wallerian degeneration within peripheral neuropathy induced by VCR in rats. Here, we compare the mechanisms altered by VCR in aged and young rats, aiming to elucidate the neurospecificity of actions in the elderly.

2. RESULTS AND DISCUSSION

This study provides groundbreaking insight into the peripheral neuropathy process in aged rats exposed to VCR. It reveals Wallerian degeneration, neuronal damage, and macrophage migration as direct consequences of VCR exposure in the spinal cord, a novel finding. Our research also demonstrates VCR-induced mechanical and thermal nociception in young and old rats, with old rats experiencing exacerbated nociception. Notably, we observe for the first time that VCR exposure leads to cognitive and emotional impairments in both age groups. We also confirm alterations in ATPase homeostasis. We also find increased lipid peroxidation, elevated nitrite and nitrate (NO_x) levels in brain tissues, and reduced nonprotein thiol (NPSH) levels in young rats exposed to VCR.

2.1. VCR Induces Mechanical and Thermal Nociception in Old and Young Rats. VCR is widely described as triggering severe peripheral neuropathy. Young and old rats showed differences in the VCR induction profile. We found that general nociception occurred more quickly in young rats and persistently in old rats. In our study, the onset of immediate mechanical (Figure 1A) and thermal (Figure 1B) nociception was observed after the end of the last session with VCR, which persisted until day 17 of the protocol. Young and old rats exposed to VCR developed mechanical (30 and 17%, respectively) and thermal (23 and 77%) nociception on day 6 of the experimental protocol. According to the relative change in data, on day 6, VCR increased mechanical and thermal sensitivities in young rats by 0.7 and 0.8 times, respectively. Meanwhile, mechanical sensitivity increased by 0.8 times in old rats, while thermal sensitivity increased by 0.2 times. On day 11, the permanence of mechanical sensitivity (43 and 20%, respectively) was also verified in young and old rats. VCR increased mechanical and thermal sensitivities in young rats by 0.6 and 0.9 times, respectively. Similarly, both mechanical and thermal sensitivities of old rats increased by 0.8 times. The repetition of the hot plate test on day 11 was avoided to minimize the suffering of the old and young animals that were already debilitated due to exposure to VCR. On day 17 of the experimental protocol, mechanical sensitivity was verified in young (31%) and old (34%) rats that received VCR. Regarding thermal sensitivity, young (39%) and old (63%) rats retained the nociceptive response to heat. According to the relative change in data, on day 17, VCR increased the mechanical and thermal sensitivities of young rats by 0.7 and 0.6 times, respectively. In old rats, there was a 0.6 times increase in mechanical sensitivity and a 0.4 times increase in thermal sensitivity. Regarding mechanical sensitivity, old rats that received VCR also showed greater mechanical sensitivity compared to young rats that received VCR on days 6 (0.7 times), 11 (0.8 times), and 17 (0.6 times) of the experimental protocol. Still, given the data presented here, old rats exposed to VCR showed more significant thermal hypersensitivity than

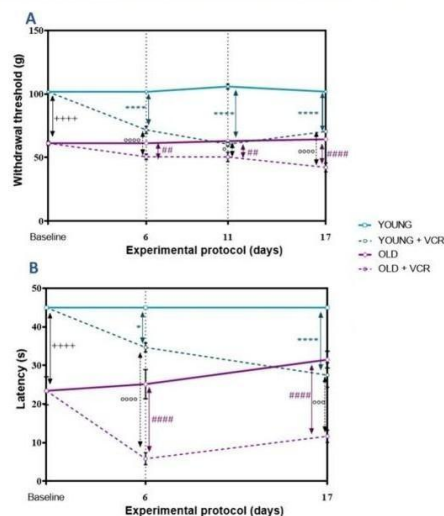


Figure 1. Effects of VCR sulfate (0.1 mg kg^{-1} , i.p.) exposure on the paw withdrawal threshold to mechanical stimulus in the digital aesthesiometer (A) and on thermal stimulation in the hot plate test (B) in young and old rats. Each column represents the mean $\pm$ standard error of the mean (S.E.M.) of 7 animals per group. (****) $P < 0.0001$ denotes levels of significance when comparing the young control group to the old control group; (*) $P < 0.05$ and (****) $P < 0.0001$ denote significance levels when comparing the young VCR group to the young control group; (##) $P < 0.01$ and (####) $P < 0.0001$ denote significance levels when comparing the old VCR group to the old control group; and (°) $P < 0.05$, (°°) $P < 0.001$, and (°°°°) $P < 0.0001$ denote significance levels when comparing the old VCR group to the young VCR group. Two-way ANOVA followed by Tukey's test was used.

young rats receiving VCR on 6 (0.16 times) and 17 days (0.42 times) of behavioral evaluation.

Our study followed the development of the nociceptive condition in old rats from the last day of exposure to VCR until day 17. Mechanical presensitization was observed in old rats compared to young ones (nociception processed from the $A\delta$ and $A\beta$ fibers). In this regard, the linear graph of the mechanical sensitivity test shows a tendency on day 17 of the old rats to worsen the mechanical sensitization concerning the curve of the young rats, which is rising. Several authors have observed the worsening of nociceptive sensitization and consequent total loss of sensitivity due to the action of VCR, which is linked to damage to the myelin sheath and A fibers.^{6,11,12}

On the other hand, young rats exposed to VCR have a greater percentage of mechanical sensitivity (day 11) than old rats. These data can be explained by the nociceptive response not compromised by degeneration in young rats exposed to VCR. That is, nondegenerated $A\delta$ and $A\beta$ fibers are highly activated, causing increased mechanical hyperalgesia and evoking pain. In contrast, young rats' nerve repair capacity partially restores this exacerbation to mechanical hyperalgesia on day 17.

Table 1. Spontaneous Locomotor and Exploratory Activities of Young and Old Rats Exposed to VCR^a

open field test				
	crossings ^b	rearrings ^c	crossings ^b	rearrings ^c
<i>young groups</i>			<i>old groups</i>	
control	23.2 ± 3.4	14.3 ± 1.5	control	28.3 ± 3.6
VCR	30.8 ± 4.2	14.6 ± 2.2	VCR	21.3 ± 4.0
				12 ± 1.0
				9 ± 1.5

^aData are reported as means ± S.E.M. for 7 animals per group. Statistical analyses were performed by two-way ANOVA, followed by the Tukey multiple comparison test when appropriate. ^bData are expressed as the number of crossings. ^cData are expressed as the number of rearrings.

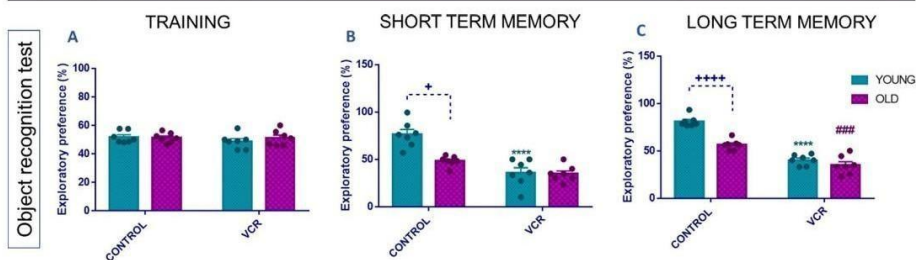


Figure 2. Effects of exposure to VCR sulfate (0.1 mg kg⁻¹, i.p.) on the training phase (A), short-term (B), and long-term (C) memories in the object recognition test in young and old rats. Each column represents the mean ± standard error of the mean (S.E.M.) of 7 animals per group. (+) $P < 0.05$ and (++++) $P < 0.0001$ denote levels of significance when comparing the young control group to the old control group; (***) $P < 0.0001$ denotes significance levels when comparing the young VCR group to the young control group; and (##) $P < 0.001$ denotes significance levels when comparing the old VCR group to the old control group. Two-way ANOVA followed by Tukey's test was used.

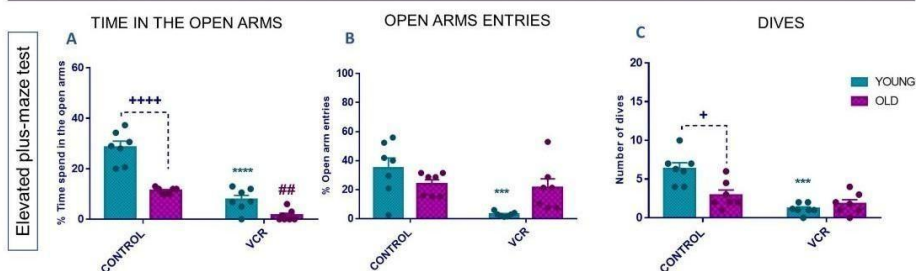


Figure 3. Effects of exposure to VCR sulfate (0.1 mg kg⁻¹, i.p.) on the percentage of time spent in the open arms (A), percentage of open arm entries (B), and number of dips (C) in the elevated plus-maze test in young and old rats. Each column represents the mean ± standard error of the mean (S.E.M.) of 7 animals per group. (+) $P < 0.05$ and (++++) $P < 0.0001$ denote levels of significance when comparing the young control group to the old control group; (***) $P < 0.001$ and (####) $P < 0.0001$ denote significance levels when comparing the young VCR group to the young control group; and (##) $P < 0.01$ denotes significance levels when comparing the old VCR group to the old control group. Two-way ANOVA followed by Tukey's test was used.

Along these lines, a study reported that myelinated and nonmyelinated fibers in the dorsal root ganglia, spinal cord, and supraspinal cord are responsible for pain signaling and are the most altered by aging.² In this study, we verified the neuronal and axonal degeneration caused by VCR, indicating that abnormal excitability can lead to uncontrolled pain evocation and degeneration in the spinal cord. Based on VCR-induced excitability, we hypothesize that VCR exacerbates the nociceptive response to heat and causes degeneration in the old rats.^{13,14} It is also worth noting that senescence impairs nerve recovery, which can perpetuate the somatosensory damage caused by VCR.

Old rats exposed to VCR show a more significant decrease in latency to thermal stimuli than young rats with VCR. It is worth mentioning that the old rats presented a thermal presensitization about the young ones. The C fibers are unmyelinated and do not suffer the same action as the A fibers. However, the processing of C fibers involves calcium ions as a second messenger, which VCR parallelly alters.¹⁵ Our study unveils an elevation in Ca²⁺-ATPase activity in older rats, underscoring this as a crucial mechanism potentially contributing to the heightened thermal sensitivity observed. Consequently, the combined data from mechanical and thermal sensitivities suggest mechanisms underlying VCR effects on afferent fibers. These findings underscore that

VCR-induced peripheral neuropathy can be modulated by varying mechanisms dependent on age.

2.2. Locomotor and Exploratory Abilities. Table 1 presents the results of the locomotor and exploratory activities of young and old rats in the open field test. Exposure to VCR and aging did not change the animals' locomotion and exploration.

2.3. VCR-Induced Neurological Damage Can Cause Cognitive and Emotional Impairments. **2.3.1. Investigation of Memory and Cognition Impairments.** Damage to the nervous system, such as peripheral neuropathy, can damage the most diverse cognitive systems, including memory. Our study demonstrated, through the object recognition test (Figure 2), alterations in the short-term memory (STM) and long-term memory (LTM) of animals exposed to VCR. In the training phase, behavioral alterations between the experimental groups were not identified (Figure 2A). In the STM test (Figure 2B), cognitive impairment was observed only in young rats exposed to VCR compared to young control rats, with a 53% increase, indicating a 0.5 times increase in impairment. In the LTM test (Figure 2C), both young (57% increase, 0.5 times) and old (41% increase, 0.6 times) rats exposed to VCR showed impaired functionality in the transfer, evocation, and consolidation of this type of memory. It is also necessary to mention that old control rats showed cognitive impairment compared to young control rats in both STM and LTM.

Aging triggers the loss of nerve cells and the loss of neuroplasticity.^{16,17} We found that old rats previously had STM impairment, whereas VCR-induced STM impairment was found only in young ones. In LTM, both young and old rats exposed to VCR showed cognitive impairment. We found, therefore, that in LTM, VCR can affect both young and old rats in terms of memorization capacity. This finding is in line with previous studies that demonstrated the potential of VCR to destroy dentate granule cells and damage other neurons, including hippocampal pyramidal cells.¹⁸ Another similar study reported the neurotoxic effect of VCR on memory retention in young rats.¹⁹ The VCR-induced cognitive impairment in young and old rats in this study is unprecedented.

2.3.2. Investigation of the Emotional Behavior. The elevated plus maze is validated and widely tested for assessing rodent anxious-like behavior. As shown in Figure 3A, aging per se reduced the time spent in the open arms compared to the young group; it also reduced the number of dips compared to the young group (Figure 3C). Exposure to VCR led to anxiety-like behavior in young rats, evidenced by a reduction in time spent in the open arms (Figure 3A; 82%), representing a 0.3 times decrease, a reduction in the number of entries into the open arms (Figure 3B; 90%), a 0.09 times decrease, and a reduction in the number of dives (Figure 3C; 90%), a 0.2 times decrease compared to the young control group. In old rats, VCR exposure reduced the time spent in the open arms (Figure 3A; 98%), representing a 0.1 times decrease, indicating anxiety-like behavior.

For the emotional aspect, we verified the anxiety-like behavior of young and old rats exposed to VCR. The neurotoxicity triggered by VCR leads to dangerous neuro-inflammatory processes associated with increased macrophage infiltration into dorsal root ganglia and the release of cytokines and chemokines.^{4,20,21} These neuroinflammatory actions in supraspinal regions can compromise cognitive and emotional behaviors, as demonstrated in a VCR-induced neuroinflammation model with young mice.²² Our preclinical study is a

pioneer in verifying anxiety-like behavior in old VCR-induced rats.

2.4. VCR Induces Neurodegeneration in the Spinal Cord of Old Rats. The control animals are represented histologically in the following images (Figure 4; blades 1 and

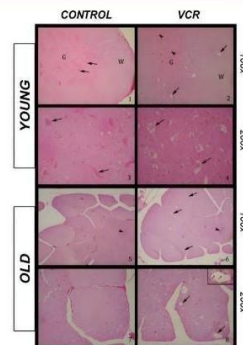


Figure 4. Effects of exposure to VCR sulfate (0.1 mg kg^{-1} , i.p.) on histological analysis of the spinal cord of young and old rats stained with hematoxylin-eosin (HE). Blade 1: the histological profile of the lumbar spinal cord of young control rats; G denotes the gray matter, and W denotes the white matter (HE; 100X). Blade 2: the histological profile of the lumbar cord of young rats exposed to VCR; the arrow denotes large vacuoles in the white matter; the arrowhead denotes small vacuoles in the gray matter; G denotes the gray matter; and W denotes the white matter (HE; 100X). Blade 3: the histological profile of the lumbar spinal cord of young control rats; the arrow denotes motor neurons (HE; 200X). Blade 4: the histological profile of the lumbar spinal cord of young rats exposed to VCR; the arrow denotes vacuolated motor neurons (HE; 200X). Blade 5: the histological profile of the sacral spinal cord of old control rats; the arrowhead denotes the central medullary canal (HE; 100X). Blade 6: the histological profile of the sacral cord of old rats exposed to VCR; the arrow denotes white matter vacuoles; and the arrowhead denotes the central medullary canal (HE; 100X). Blade 7: the histological profile of the sacral medulla of old control rats; the image denotes lateral funiculi (HE; 200X). Blade 8: the histological profile of the sacral cord of old rats exposed to VCR; the arrow denotes white matter vacuoles; and the arrowhead image magnification (400X) denotes macrophages inside a vacuole (HE; 200X).

3) young control group and (Figure 4; blades 5 and 7) old control group. No histological changes were observed between the control groups. The histological images of the animals submitted to VCR exposure are as follows: (Figure 4; blades 2 and 4) young VCR group and (Figure 4; blades 6 and 8) old VCR group.

The spinal cord of groups of animals subjected to VCR treatment (young and old) showed uniform development of bilateral and symmetric focally extensive vacuolation of the periaxonal space and occasional axonal spheroids. In old rats exposed to VCR, damage to the myelin sheaths was observed by the development of fragments with vacuoles of different sizes, which sometimes formed digestion chambers containing macrophages, mainly in the ventral and lateral funiculi (Figure 4; blades 6 and 8). The damage to myelin sheaths and macrophage digestion pattern was evident in aged animals exposed to VCR. In young rats exposed to VCR, the cell

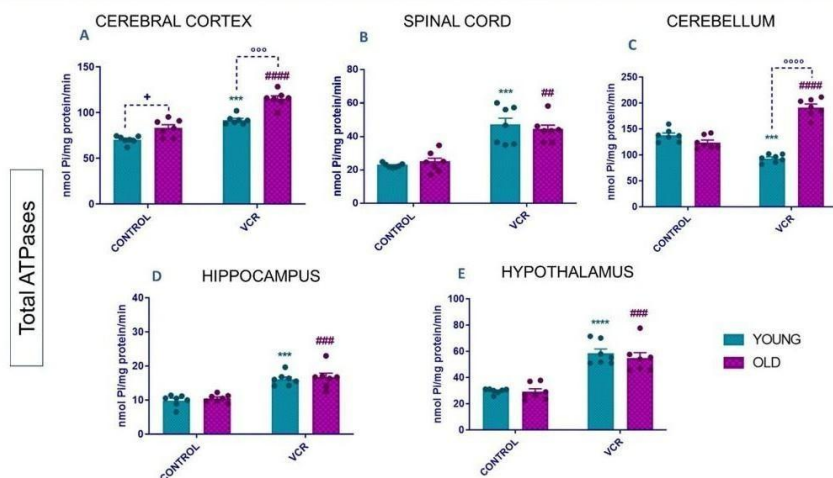


Figure 5. Effects of VCR sulfate (0.1 mg kg^{-1} , i.p.) exposure on total ATPase activity in the cerebral cortex (A), spinal cord (B), cerebellum (C), hippocampus (D), and hypothalamus (E) of young and old rats. Each column represents the mean $\pm$ standard error of the mean (S.E.M.) of 7 animals per group. (+) $P < 0.05$ denotes levels of significance when comparing the young control group to the old control group; (***) $P < 0.001$ and (****) $P < 0.0001$ denote significance levels when comparing the young VCR group to the young control group; (#) $P < 0.01$, (##) $P < 0.001$, and (###) $P < 0.0001$ denote significance levels when comparing the old VCR group to the old control group; and (****) $P < 0.0001$ and (*****) $P < 0.00001$ denote significance levels when comparing the old VCR group to the young VCR group. Two-way ANOVA followed by Tukey's test was used.

bodies of motor neurons were vacuolated, and spongiosis foci were present in this region's medullary H (Figure 4; blades 2 and 4). This change was more intense in young rats exposed to VCR. Both groups submitted to VCR presented vacuolization in the white matter of the spinal cord in the lumbar and sacral segments with moderate intensity.

Indeed, the relationship between neuropathic pain and Wallerian degeneration at the peripheral level has been well reported.^{23–25} Despite this, peripheral Wallerian degeneration in old rats exposed to VCR has not yet been elucidated. Our research focuses on the deleterious effects of VCR at the central level, representing a novel aspect of our study. Previously, only the peripheral actions of VCR, contributing to neuropathy and nerve cell degeneration, had been known.^{5,7,26,27} Our study specifically targeted the spinal cord to evaluate Wallerian degeneration in a context more directly related to pain. The spinal cord was chosen for analysis because it is a critical part of the central nervous system that mediates nociceptive responses between the brain and the peripheral nervous system.^{27,28} The spinal cord is essential for processing pain and is particularly affected in chronic pain conditions.

The spinal cord plays essential roles in chronic pain, including ascending and descending pain signal transmission, pain processing through interneurons, pain perception, and descending modulation.^{29,30} Therefore, evaluation of degenerative damage in the spinal cord provides significant insights into how VCR-induced peripheral neuropathy can impact peripheral tissues and the central nervous system.

Here, histological analysis of spinal cord tissues revealed significant bilateral and symmetrical vacuolation in the

periaxonal space and occasional axonal spheroids in both young and old rats exposed to VCR. Periaxonal vacuolation indicates the presence of fluid-filled spaces surrounding axons, potentially reflecting disruptions in the typical cellular environment.³¹ Axonal spheroids, on the other hand, represent rounded accumulations of the axonal material, often associated with axonal swelling, degeneration, or changes in transport processes.³² In summary, these histological findings induced by VCR suggest disruptions in the axonal integrity and potential disturbances in the surrounding nerve cell environment.

Notably, the damage appears more severe in old rats exposed to VCR. These rats exhibited fragments containing vacuoles of varying sizes, occasionally forming digestion chambers with macrophages, primarily in the ventral and lateral funiculi. Tissue vacuoles with macrophages suggest Wallerian degeneration, indicating ongoing phagocytic processes.³³ The histological evidence in old rats exposed to VCR implies a neuronal body lesion, given the extensive vacuolation within neuron bodies extending to axons, ultimately leading to Wallerian degeneration. Based on the data, two scenarios can be identified: initial neuronal degeneration followed by nonclassical Wallerian degeneration resulting from neuronal injury.

Our study reveals previously unreported VCR-induced axonal damage and neuronal degeneration in the spinal cords of old rats. These data underscore how cellular apoptosis triggered by VCR can intensify in old rats, resulting in more severe neurological damage compared to their young rats. While earlier studies have documented nerve cell degeneration due to VCR in young rodents,^{5,9,10} our research illuminates the simultaneous disruption of synaptic signaling, particularly

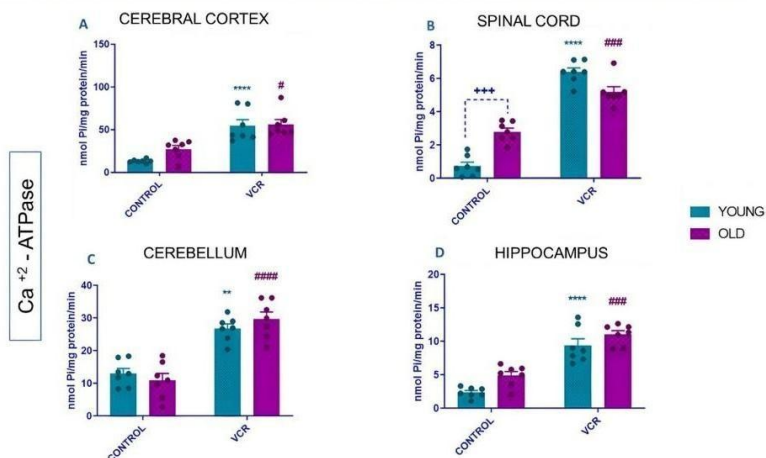


Figure 6. Effects of VCR sulfate (0.1 mg kg⁻¹, i.p.) exposure on Ca²⁺-ATPase activity in the cerebral cortex (A), spinal cord (B), cerebellum (C), and hippocampus (D) of young and old rats. Each column represents the mean $\pm$ standard error of the mean (S.E.M.) of 7 animals per group. (++) $P < 0.001$ denotes levels of significance when comparing the young control group to the old control group; (**) $P < 0.01$ and (****) $P < 0.0001$ denote significance levels when comparing the young VCR group to the young control group; and (#) $P < 0.05$, (###) $P < 0.001$, and (####) $P < 0.0001$ denote significance levels when comparing the old VCR group to the old control group. Two-way ANOVA followed by Tukey's test was used.

affecting pain transmission. Additionally, macrophage migration suggests that VCR may induce peripheral immune cells to release macrophages, aligning with existing research.³⁴ Inflammatory macrophages, in turn, significantly influence neuroinflammation and serve as common regulators of neuropathic pain, anxiety, and depression.^{35–37}

2.5. Imbalance Caused by VCR in the Activity of ATPases Can Compromise Neurological Activity, Causing Neuropathy and Comorbidities. **2.5.1. Total ATPases and Ca²⁺-ATPase Activities.** ATPase enzymes are directly related to the functioning of the intracellular electrochemical gradient. Consequently, ATPases are directly related to the pathophysiology of neurodegenerative processes such as peripheral neuropathy.^{38,39}

As shown in Figure 5, we can observe the overall activity of the ATPases. The old rats per se showed an increase in total ATPase activity compared to the young group in the cerebral cortex. Exposure to VCR resulted in increased total ATPase activity in several regions of young rats compared to the young control group: cerebral cortex (Figure 5A), with a 17% increase or 1.3-fold; spinal cord (Figure 5B), with a 58% increase or 2-fold; hippocampus (Figure 5D), with a 47% increase or 1.6-fold; and hypothalamus (Figure 5E), with a 77% increase or 2-fold. However, in cerebellar tissue, total ATPase activity was inhibited in young rats exposed to VCR.

In older rats, VCR similarly led to increased total ATPase activity across various brain regions compared to the old control group: cerebral cortex (Figure 5A), with a 61% increase or 1.4-fold; spinal cord (Figure 5B), with a 124% increase or 1.8-fold; cerebellum (Figure 5A), with an 81% increase or 1.5-fold; hippocampus (Figure 5A), with an 86% increase or 1.6-fold; and hypothalamus (Figure 5A), with a 100% increase or 1.9-fold. The induction with VCR notably

exacerbated the increase in total ATPase activity in older rats compared to younger rats exposed to VCR. Specifically, in the cerebral cortex, there was a 32% greater increase in ATPase activity in older rats, equating to a 1.25-fold rise. In the cerebellum, this increase was even more pronounced, with older rats showing a 107% higher activity, which is twice the level observed in younger rats.

To prove the idea that the excitability induced by VCR can trigger nerve degeneration, we verified the increase of enzymes that control the exchange of ions.⁴⁰ Indeed, peripheral neuropathy caused by VCR is associated with increased excitability; pain, in particular, raises the levels of glutamate, the main excitatory neurotransmitter. Thus, the permanence of axonal depolarization generates the permanence of activation of nociceptors and the consequent painful sensation.^{21,41}

Furthermore, the exacerbation of the activity of total ATPases in brain tissues of old rats was verified. Based on this factor, we hypothesized the possibility of worsening brain damage in these brain regions since this mechanism caused by VCR is linked to cell damage, such as impaired glial function and cell death.⁴ The cerebral cortex and cerebellum may be linked to cognitive ability. Thus, severe alterations in these regions can lead to the appearance of motor neuropathy and cognitive damage caused by VCR, as verified by our research group.¹²

Changes around the rate of Ca²⁺ uptake between mitochondria and the cytosolic environment are critical points in the harmful action of VCR.⁴ It was possible to verify only in the spinal cord the per se increase in Ca²⁺-ATPase activity in old rats about the group of young rats (Figure 6A). Exposure of young rats to VCR resulted in significant increases in Ca²⁺-ATPase enzyme activity compared to the young control group: in the cerebral cortex (Figure 6A), activity increased by 175%

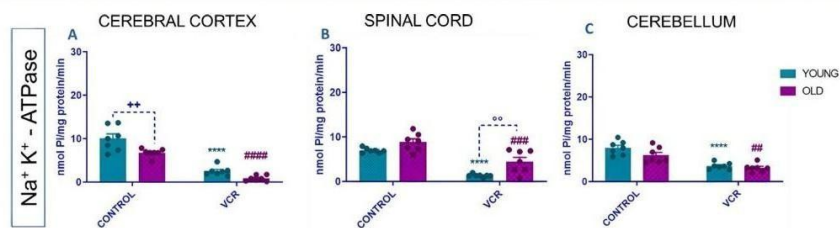


Figure 7. Effects of VCR sulfate (0.1 mg kg^{-1} , i.p.) exposure on Na^+ , K^+ -ATPase activity in the cerebral cortex (A), spinal cord (B), and cerebellum (C) of young and old rats. Each column represents the mean $\pm$ standard error of the mean (S.E.M.) of 7 animals per group. (++) $P < 0.01$ denotes levels of significance when comparing the young control group to the old control group; (****) $P < 0.0001$ denotes significance levels when comparing the young VCR group to the young control group; (##) $P < 0.01$, (###) $P < 0.001$, and (####) $P < 0.0001$ denote significance levels when comparing the old VCR group to the old control group; and (°°) $P < 0.01$ denotes significance levels when comparing the old VCR group to the young VCR group. Two-way ANOVA followed by Tukey's test was used.

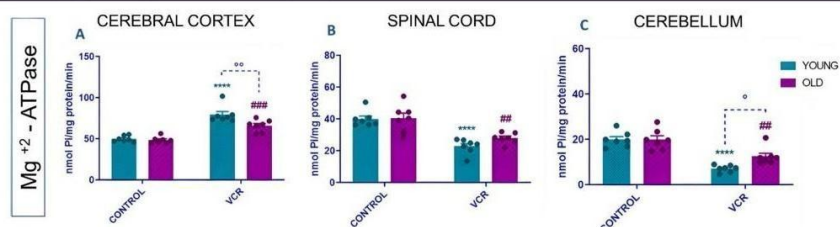


Figure 8. Effects of VCR sulfate (0.1 mg kg^{-1} , i.p.) exposure on Mg^{2+} -ATPase activity in the cerebral cortex (A), spinal cord (B), and cerebellum (C) of young and old rats. Each column represents the mean $\pm$ standard error of the mean (S.E.M.) of 7 animals per group. (****) $P < 0.0001$ denotes significance levels when comparing the young VCR group to the young control group; (##) $P < 0.01$ and (###) $P < 0.001$ denote significance levels when comparing the old VCR group to the old control group; and (°°) $P < 0.05$ and (°°°) $P < 0.01$ denote significance levels when comparing the old VCR group to the young VCR group. Two-way ANOVA followed by Tukey's test was used.

or 4.1-fold; in the spinal cord (Figure 6B), by 3000% or 8.6-fold; in the cerebellum (Figure 6C), by 145% or 2-fold; and in the hippocampus (Figure 6D), by 155% or 4-fold. In contrast, in older rats exposed to VCR, Ca^{2+} -ATPase activity increased as follows: in the cerebral cortex (Figure 6A), by 141% or 2-fold; in the spinal cord (Figure 6B), by 166% or 1.8-fold; in the cerebellum (Figure 6C), by 118% or 2.7-fold; and in the hippocampus (Figure 6D), by 484% or 2.2-fold, compared to the old control group.

Our study identified the enzyme Ca^{2+} -ATPase as the primary ATPase responsible for the observed outcomes in the total ATPase test. Disruptions in calcium homeostasis are recognized as a fundamental mechanism behind VCR-induced damage. When VCR operates through this mechanism, it increases calcium ions, triggering microglial activation and promoting neuroinflammatory damage, including the migration of macrophages observed in our study.^{4,17,13} Notably, VCR affects macrophage integrins, and activated integrins enhance the expression of the chemokine receptor 1 (CX3CR) motif, facilitating cell adhesion and VCR migration across the blood–brain barrier.²⁰ The increased calcium levels and Ca^{2+} -ATPase activity are pivotal to establishing this mechanism. Increased activity of the enzyme Ca^{2+} -ATPase is presented for the first time as a common pathophysiological mechanism in young and old rats induced with VCR.

Unlike Ca^{2+} -ATPase, induction with VCR inhibited the enzymatic activity of Na^+ , K^+ -ATPase from young and old rats.

Such inhibition can lead to impaired sodium and potassium transport across the membrane, promoting cell swelling.⁴² Furthermore, Na^+ , K^+ -ATPase inhibitors alter neuronal firing^{43,44} and impair cognition.^{45,46} At the same time, deficiency in the Na^+ , K^+ -ATPase genes has been reported to cause memory deficits and anxiety-related behavior in mice.⁴⁷

2.5.2. Na^+ , K^+ -ATPase and Mg^{2+} -ATPase Activities. The Na^+ , K^+ -ATPase is an enzyme with crucial transmembrane activity involved in membrane depolarization and synapse functionality around the axon. Our data demonstrated that aging per se led to inhibition of the enzymatic activity of Na^+ , K^+ -ATPase only in the cerebral cortex of the young rats' group (Figure 7A). Induction with VCR led to significant inhibition of Na^+ , K^+ -ATPase enzyme activity in young rats: in the cerebral cortex (Figure 7A), activity decreased by 90% or 0.25-fold; in the spinal cord (Figure 7B), by 86% or 0.19-fold; and in the cerebellum (Figure 7C), by 41% or 0.46-fold, compared to the young control group. In older rats exposed to VCR, Na^+ , K^+ -ATPase activity was similarly inhibited: in the cerebral cortex (Figure 7A), by 93% or 0.13-fold; in the spinal cord (Figure 7B), by 55% or 0.51-fold; and in the cerebellum (Figure 7C), by 72% or 0.52-fold, compared to the old control group. In the spinal cord (Figure 7B), there was an exacerbation in the inhibition of the Na^+ , K^+ -ATPase enzyme activity in young rats that received VCR compared to the old group that received VCR (217%).

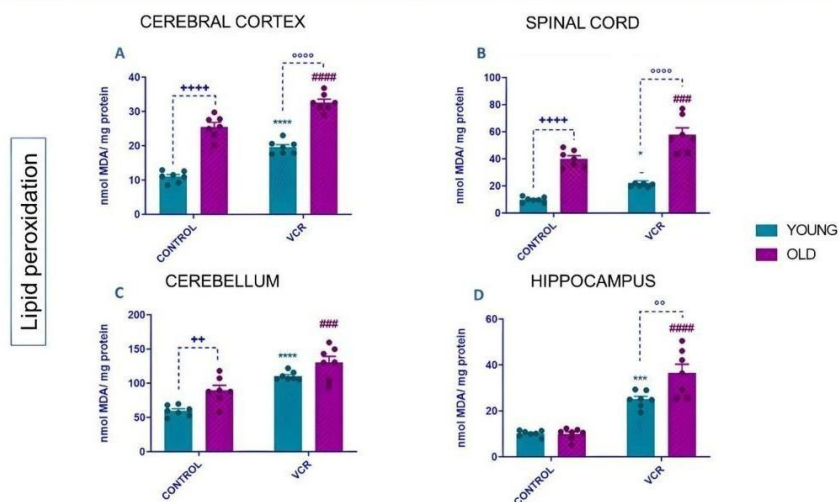


Figure 9. Effects of VCR sulfate (0.1 mg kg^{-1} , i.p.) exposure on levels of thiobarbituric acid reactive species (TBARS) in the cerebral cortex (A), spinal cord (B), cerebellum (C), and hippocampus (D) of young and old rats. Each column represents the mean $\pm$ standard error of the mean (S.E.M.) of 7 animals per group. (++) $P < 0.01$ and (++++) $P < 0.0001$ denote levels of significance when comparing the young control group to the old control group; (*) $P < 0.05$, (**) $P < 0.01$, and (***) $P < 0.001$ denote significance levels when comparing the young VCR group to the young control group; (###) $P < 0.001$ and (####) $P < 0.0001$ denote significance levels when comparing the old VCR group to the old control group; and (**) $P < 0.01$ and (****) $P < 0.0001$ denote significance levels when comparing the old VCR group to the young VCR group. Two-way ANOVA followed by Tukey's test was used.

The damage caused by VCR on Na^+ , K^+ -ATPase has not been previously reported. In neuropathic pain caused by chemotherapy drugs, Na^+ , K^+ -ATPase inhibition is supposed to be a target for pain consolidation.^{44,48} It seems that this inhibition caused by VCR in both young and old rats clarifies yet another target of action that VCR is causing. Furthermore, previous studies have suggested that dysfunctional Na^+ , K^+ -ATPase activity throughout the aging process makes neurons more susceptible to degeneration.^{48,49} In fact, the inhibition of Na^+ , K^+ -ATPase in young rats exposed to other chemotherapeutic agents has already been verified.^{38,44} However, it is hypothesized that changes in Na^+ , K^+ -ATPase activity in old rats may corroborate a greater susceptibility to neuronal damage compared to young ones.

Figure 8 illustrates the activity of the Mg^{2+} -ATPase enzyme. Exposure of young rats to VCR resulted in increased Mg^{2+} -ATPase activity in the cerebral cortex (Figure 8A), with a 69% increase or 1.4-fold, and a decrease in activity in the spinal cord (Figure 8B) and cerebellum (Figure 8C), showing a 63% or 0.6-fold inhibition and a 71% or 0.4-fold inhibition, respectively, compared to the young control rats. In older rats exposed to VCR, an increase in Mg^{2+} -ATPase activity was observed in the cerebral cortex (Figure 8A), with a 36% increase or 1.3-fold. At the same time, there was inhibition of enzymatic activity in the spinal cord (Figure 8B) and cerebellum (Figure 8C), showing a 59% or 0.7-fold inhibition and a 56% or 0.6-fold inhibition, respectively, compared to the older control group.

In the cerebral cortex, the activity of the Mg^{2+} -ATPase was more suppressed in old rats exposed to VCR than in young rats

exposed to VCR (Figure 8A, 12%); in terms of fold change, this suppression was 0.8 times. At the same time, in the cerebellum, the enzyme activity was more suppressed in young rats exposed to VCR compared to old rats exposed to VCR (Figure 8C, 24%); in terms of fold change, this increase was 1.7 times.

Finally, changes in homeostasis in Mg^{2+} -ATPase activity were observed. Mg^{2+} -ATPase is the main enzyme in maintaining high intracellular brain Mg^{2+} concentrations, which is involved in the control of protein synthesis and cell growth.⁴² Based on the observation of the decrease in Mg^{2+} -ATPase activity in the spinal cord and cerebellum, it is assumed that in these target tissues, VCR may be leading to impairments in the development and maintenance of new cells, which may be leading to cognitive impairments, for example. Furthermore, aging itself already leads to the loss of nerve cells, so the inhibition of Mg^{2+} -ATPase activity may be a contributing factor to neurological damage.

The changes observed in Ca^{2+} -ATPase, Na^+ , K^+ -ATPase, and Mg^{2+} -ATPase indicate important pathophysiological mechanisms by which VCR promotes neuropathy and emotional and cognitive alterations. Briefly, changes in the homeostasis of these ATPases indicate increased cerebral excitability by Ca^{2+} flow, changes in neuronal firing and synaptic signaling, and damage in the development and maintenance of new cells.

2.6. Oxidative and Inflammatory Changes May Contribute to Neurodegeneration and Peripheral Neuropathy Induced by VCR. 2.6.1. TBARS Levels. Considering that chemotherapy drugs can contribute to the

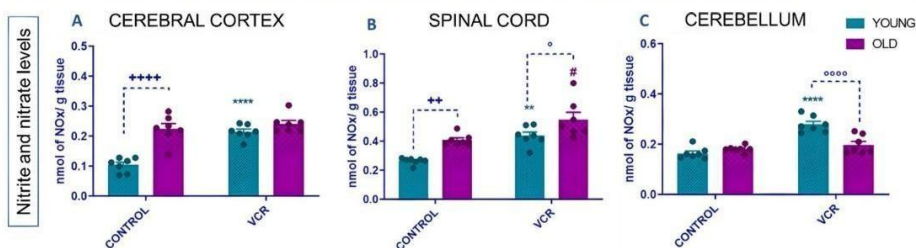


Figure 10. Effects of VCR sulfate (0.1 mg kg⁻¹, i.p.) exposure on nitrite and nitrate levels (NO_x) in the cerebral cortex (A), spinal cord (B), and cerebellum (C) of young and old rats. Each column represents the mean $\pm$ standard error of the mean (S.E.M.) of 7 animals per group. (++) $P < 0.01$ and (++++) $P < 0.0001$ denote levels of significance when comparing the young control group to the old control group; (**) $P < 0.01$ and (****) $P < 0.0001$ denote significance levels when comparing the young VCR group to the young control group; (#) $P < 0.05$ denotes significance levels when comparing the old VCR group to the old control group; and (*) $P < 0.05$ and (****) $P < 0.0001$ denote significance levels when comparing the old VCR group to the young VCR group. Two-way ANOVA followed by Tukey's test was used.

occurrence of oxidative damage⁴⁰ and that the generation of lipid peroxides serves as a key marker for macromolecular oxidative injury, this study evaluated lipid peroxidation levels in brain tissues, as depicted in Figure 9.

Here, aging per se caused increased levels of lipid peroxidation in the cerebral cortex, spinal cord, and cerebellum of rats. Exposure of young rats to VCR resulted in increased lipid peroxidation in several brain regions compared to the control group of young rats: cerebral cortex (Figure 9A), with a 77% increase or 1.7-fold; spinal cord (Figure 9B), with a 105% increase or 2.2-fold; cerebellum (Figure 9C), with a 102% increase or 1.8-fold; and hippocampus (Figure 9D), with a 183% increase or 2.4-fold. In older rats, VCR also increased lipid peroxidation, although to varying extents: cerebral cortex (Figure 9A), with a 24% increase or 1.3-fold; spinal cord (Figure 9B), with a 123% increase or 1.4-fold; cerebellum (Figure 9C), with a 63% increase or 1.4-fold; and hippocampus (Figure 9D), with a 120% increase or 3.6-fold, compared to the control group of older rats. It is important to highlight that the combination of VCR and aging exacerbated the elevation of lipid peroxidation levels in the cerebral cortex (25%), spinal cord (141%), and hippocampus (33%) of these animals, in comparison to the group of young rats that were administered VCR. In terms of fold change evaluation, the data showed that an elevation of lipid peroxidation levels in the cerebral cortex was 1.6 times, that in the spinal cord was 2.6 times, and that in the hippocampus was 1.4 times in the old rats exposed to VCR when compared to young rats exposed to VCR.

The TBARS test evaluates one of the fragments of lipid peroxidation, malondialdehyde (MDA). The formation of MDA protein and MDA-acetaldehyde-protein ducts is indispensably associated with a proinflammatory reaction throughout the organism. MDA leads to the activation of Th17 lymphocytes, and MDA-acetaldehyde-protein leads to the activation of nuclear factor- κ B (NF κ B), influencing the activation of intercellular adhesion molecule 1 (ICAM-1) and vascular adhesion molecules (VCAM), leading directly to an increase in tumor necrosis factor- α (TNF α) expression.^{51,52}

Our findings highlight increased lipid peroxidation, specifically the exacerbation of MDA fragments, as a potential trigger for the VCR-initiated inflammatory response. It is important to emphasize that this lipid damage may be directly related to the impairment of the ATPase enzymes' activity in the

phospholipid cell membrane.⁴⁰ Our hypothesis is that such lipid damage could affect cell membrane fluidity, indirectly influencing ion exchange by altering the activity of the ATPase enzymes. Among the various tests performed, increased lipid peroxidation in old rats exposed to VCR emerges as a significant mechanism contributing to the induction of peripheral neuropathy. Lipoperoxidation can mean increased pain severity and serves as a critical contributor to neuroinflammation, as evidenced by elevated NO_x levels.

2.6.2. NO_x Levels. The NO_x levels can be related to the formation of reactive nitrogen species and the involvement of inflammatory damage caused by nitric oxide. NO_x levels in brain tissues are shown in Figure 10.

Aging per se increases NO_x levels in the cerebral cortex and spinal cord of old rats compared to those of young rats. VCR treatment increased NO_x levels in the cerebral cortex (Figure 10A), rising by 143% or 2-fold compared with the control group of young rats. In the spinal cord (Figure 10B), NO_x levels increased by 52% or 1.6-fold, and in the cerebellum (Figure 10C), they rose by 60% or 1.7-fold, relative to the control group of young rats. In contrast, in older rats, VCR elevated only NO_x levels in the spinal cord (Figure 10B), with a 5% increase or 1.3-fold, compared to the control group of older rats. Furthermore, NO_x levels were exacerbated in the spinal cord (6%); in relationship to fold change, this increase was 1.2 times of old rats exposed to VCR compared to the young group exposed to VCR. However, in the cerebellum, there was an exacerbation of NO_x levels in young rats exposed to VCR compared to the group of old ones exposed to VCR (49%), and this increase was 0.7 times.

In this study, we verified the increase of NO_x in the spinal cord being a target of the VCR action, exacerbating the NO_x levels in old rats. According to Kamei et al.,⁵³ one of the mechanisms by which VCR triggers peripheral neuropathy is through the formation of NO_x. It is noteworthy that strong evidence suggests the pro-nociceptive action of NO_x. It has been reported that a NO_x donor, L-arginine, inhibits voltage-gated Ca²⁺ channels in the dorsal root ganglia of cultured neurons.⁵⁴ These results suggested that decreased NO_x-cGMP pathway activity may be involved in the genesis of hyperalgesia since Ca²⁺ and Na⁺ currents are closely associated with nociception.^{55,56}

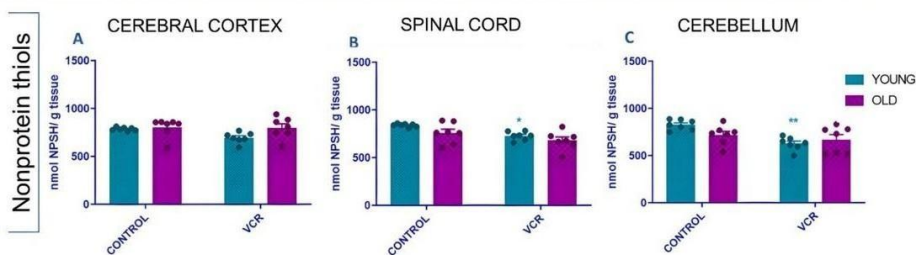


Figure 11. Effects of VCR sulfate (0.1 mg kg^{-1} , i.p.) exposure on levels of nonprotein thiols (NPSH) in the cerebral cortex (A), spinal cord (B), and cerebellum (C) of young and old rats. Each column represents the mean $\pm$ standard error of the mean (S.E.M.) of 7 animals per group. (+) $P < 0.05$ denotes levels of significance when comparing the young control group to the old control group; (*) $P < 0.05$ and (**) $P < 0.01$ denote significance levels when comparing the young VCR group to the young control group. Two-way ANOVA followed by Tukey's test was used.

Vincristine-induced peripheral neuropathy in young and old mice

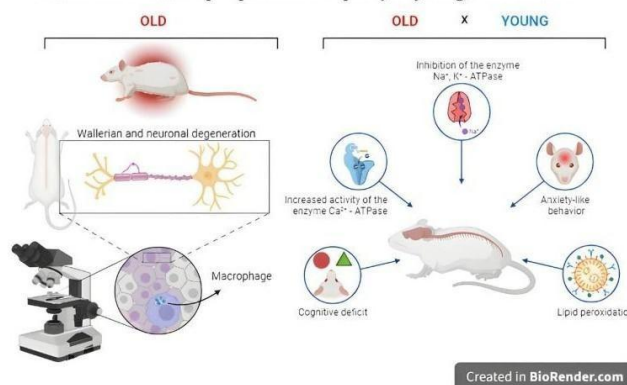


Figure 12. Graphical summary of neurotoxic effects induced by VCR in young and old rats. The left side of the illustration highlights the principal discovery of the study, demonstrating that neuronal and Wallerian degeneration exacerbates VCR neurotoxicity in aged rats alongside macrophage migration. On the right side, the primary mechanisms investigated in the pathophysiology of VCR-induced peripheral neuropathy in young and aged rats are delineated.

2.6.3. NPSH Levels. The NPSH are markers of non-enzymatic oxidative damage and were concomitantly used for the indirect investigation of GSH, the main thiol measured in the analysis.⁵⁷ The results of the assessment of NPSH levels can be seen in Figure 11. Exposure of young rats to VCR resulted in a significant reduction in NPSH levels in the spinal cord (Figure 11B), with a decrease of 13% or 0.86-fold, compared to the control group. Similarly, in the cerebellum (Figure 11C), NPSH levels decreased by 16% or 0.76-fold, compared to the control group of young rats. No changes in NPSH levels were observed in the cerebral cortex (Figure 11A).

We also assessed NPSH levels, specifically focusing on GSH. Young rats exposed to VCR exhibited a reduction in GSH, indicating potential damage to GSH activity, which may contribute to the persistence of VCR's neurotoxic effects. GSH plays a crucial role in detoxifying xenobiotics in conjunction with glutathione S-transferase (GST). Hence, we propose the depletion of NPSH in the spinal cord and cerebellum of young

rats exposed to VCR as a mechanism of specific oxidative damage, unrelated to senescence.

3. CONCLUSIONS

Based on the data presented in this study, the primary mechanisms arising from the neurotoxic effects of VCR in young and old rats were examined (Figure 12). The hypothesis of mechanical and thermal hypernociception in old rats exposed to VCR was substantiated for the first time. The main mechanisms potentially contributing to the somatosensory impairment caused by VCR in old rats as reported here encompass: (I) elevated lipid peroxidation in the central nervous system, (II) increased levels of NO_x in the spinal cord of old rats, and (III) Wallerian degeneration and macrophage migration impacting the spinal cord in the context of VCR-associated senescence. Alterations in ATPases suggest heightened excitability, changes in neuronal firing and signaling, and disruptions in cellular maintenance. These findings imply a potential mechanism underpinning the

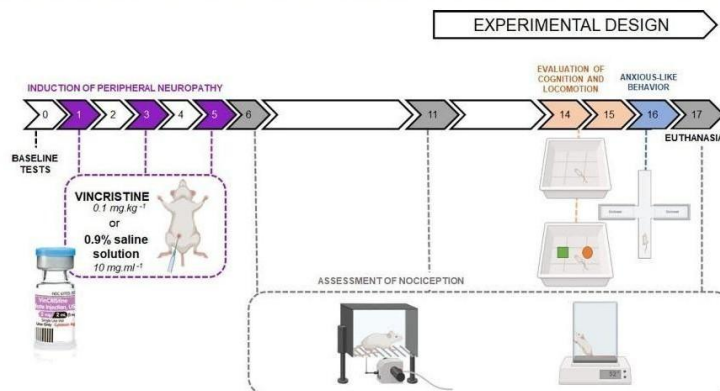


Figure 13. Experimental design. Young and old rats were divided into four experimental groups. On days 1, 3, and 5 of the experimental protocol, 2 groups received VCR sulfate (0.1 mg kg^{-1} , intraperitoneally), while the other 2 groups received 0.9% saline solution (10 mL kg^{-1} , intraperitoneally). On days 0, 6, 11, and 17, the response to mechanical hyperalgesia was verified using the digital aesthesiometer. The hot plate test verified thermal sensitivity on days 0, 6, and 17. On days 14 and 15, the locomotor and exploratory capacities of the animals were observed, followed by cognitive evaluation of the object recognition test. On day 16, the animals' anxiety-like behavior was evaluated. Finally, on day 17 of the experimental protocol, all animals were euthanized, and nervous system structures were dissected for histological and biochemical analysis.

emergence of cognitive impairment, anxiety-like behavior, and peripheral neuropathy in both young and old rats. Undoubtedly, this study advances the comprehension of VCR's neurospecific pathways that trigger peripheral neuropathy and associated conditions. Nevertheless, further investigations are imperative to delve into VCR-induced damage, particularly concerning the aging aspect.

4. MATERIALS AND METHODS

4.1. Animals. The experiments used young (2 months old) and old (16 months old) male Wistar rats. The animals were housed with free access to standard food and water; humidity (20–80%) and temperature ($22 \pm 2^\circ\text{C}$) were controlled with respect to the light/dark cycle (12/12 h) of rodents. All experimental procedures were conducted following the described worldwide experimentation standards, which were recommended and previously approved by the Ethics Commission for the Use of Experimental Animals (CEUA 035767/2021-41) of the Federal University of Pelotas. Animal experiments followed the standards recommended by the Declaration of Helsinki (1964). The size, as well as the experimental number, was determined by our group using previous studies as a parameter.^{44,58–60} For euthanasia, the animals were first subjected to inhalation exposure with isoflurane, and after proof of death, decapitation was performed.

4.2. Drugs. VCR was acquired from INTAS Pharmaceuticals (Batch: M2103904) and allocated at 4°C . All other chemicals used in this study were of analytical grade or obtained from Sigma-Aldrich (St. Louis, MO, USA). Rats were induced with VCR intraperitoneally (i.p.) at a constant volume of 10 mL kg^{-1} of body weight. VCR was diluted in 0.9% saline solution, which was used as a vehicle for the control groups, not submitted to chemotherapy.

4.3. Experimental Design. Young adult (2 months) and old (16 months) male Wistar rats were divided into four experimental groups: (I) young control, (II) young + VCR, (III) old control, and (IV) old + VCR (7 animals per group). On days 1, 3, and 5 of the experimental protocol, the animals in groups II and IV received induction with the chemotherapeutic agent VCR (0.1 mg kg^{-1} , intraperitoneally), while groups I and III received a 0.9% saline solution vehicle (10 mL kg^{-1} , intraperitoneally).

To investigate the induction of peripheral neuropathy, nociceptive responses were assessed: mechanical response (on days 6, 11, and 17 of the experimental protocol) was verified using the digital aesthesiometer; thermal response (on days 6 and 17 of the experimental protocol) was verified using the hot plate test. Subsequently, comorbidities associated with VCR-induced neuropathy were observed, including locomotor and exploratory abilities (on day 14), cognitive impairment (on days 14 and 15), and anxiety-like behavior (on day 16).

On day 17, the animals were euthanized by inhalation with isoflurane, and nervous system tissues related to pain processing and peripheral neuropathy were dissected for further biochemical and histological analyses. The experimental design is graphically summarized in Figure 13.

4.4. Evaluation of VCR-Induced Peripheral Neuropathy.

4.4.1. Investigation of Mechanical Hyperalgesia. Mechanical sensitivity in rats was assessed following the method described by Alamri et al.,⁶¹ on days 6, 11, and 17 of the experimental protocol (with some modifications). For this procedure, rats were individually allocated inside an acrylic box with wire grid floors, which was conducted in a quiet room. The test involved eliciting a hind paw flexion reflex using a hand-held force transducer (digital aesthesiometer, Insight, São Paulo, Brazil) equipped with a polypropylene tip. The withdrawal threshold of the paw was measured by applying progressive pressure perpendicular to the middle of the plantar surface of the hind paw until withdrawal occurred, with the pressure value automatically recorded. A line graph was plotted from the data generated and statistically computed to evaluate the mechanical sensitivity during the experiment. Data were expressed as the withdrawal threshold (g).

4.4.2. Investigation of Thermal Hyperalgesia. Thermal sensitivity was assessed in rats following the protocol described by Woolfe and MacDonald,⁶² with some modifications. The hot plate test, a behavioral model for nociception, was utilized to investigate responses such as jumping and hind paw-licking in response to a noxious thermal stimulus. Thermal sensitivity was evaluated on days 6 and 17 of the experiment. The rats were placed in an acrylic box on a heated metal plate maintained at $52 \pm 1^\circ\text{C}$. The latency of nociceptive responses was measured. Significant decreases in paw withdrawal latency were interpreted as indicative of heat hyperalgesia. The time

spent on the plate was limited to 45 s to prevent harm to the animals' paws. A line graph was drawn from the data generated and statistically computed to evaluate the thermal sensitivity during the experiment. Data were expressed as latency (s).

4.5. Locomotor and Exploratory Abilities. The open field test was performed as described by Woolfe and Macdonald⁶² on day 14 of the experimental protocol. The apparatus for the open field test was made of plywood and surrounded by walls that were 30 cm high. The open field floor, 45 cm long and 45 cm wide, was divided by masking tape markers into 9 squares (3 rows of 3). In this test, each animal was placed in the center of the open field and observed for 4 min to record the locomotion (number of segments crossed with the four paws) and exploration (number of rearings with the hind limbs) of the animals. Locomotion and exploration data were expressed as the number of crossings and the number of rearings, respectively.

4.6. Assessment of Cognitive and Emotional Comorbidities Associated with VCR-Induced Peripheral Neuropathy. **4.6.1. Investigation of Memory and Cognition Impairments.** The object recognition task was conducted on days 14 and 15 of the experimental protocol following the previously described method by Stangherlin et al.⁶³ This behavioral test is widely employed to assess STM and LTM. On the task day (day 14 of the experimental protocol), each rat underwent a 5 min habituation session without objects to evaluate locomotor and exploratory behaviors.

Following habituation, rats underwent a training session, individually placed in the arena with two identical objects (objects A1 and A2) for 5 min. Exploration was recorded when the rat directed its nose within approximately 2 cm of the object while sniffing, touching, or looking at it. To assess STM, 1.5 h after training, rats were presented with a familiar object (A1) and a novel object (B). The exploration time was set at 5 min, enabling the measurement of learning and recognition memory. Subsequently, LTM was evaluated 24 h after training. Rats were allowed to explore a familiar object (A1) and a novel object (C) for 5 min, and the time spent exploring each object was recorded.

The objects used were positioned symmetrically within the arena. Objects A1 and A2 were identical balls, object B was a cube, and object C was a square. These objects, made of plastic material, measured 10 × 10 cm (length × height) and had distinct color patterns (blue, red, and yellow). The arena and objects were cleaned with 30% ethanol between trials to remove residues and odors. The data were expressed as percentages of exploratory preference, calculated as follows: Training = $(A2/(A1 + A2)) \times 100$; STM = $(B/(A1 + B)) \times 100$; LTM = $(C/(A1 + C)) \times 100$.

4.6.2. Investigation of the Emotional Behavior. The elevated plus-maze test (EPM), a validated method for measuring anxiety-like behavior in rodents, was conducted on day 16 of the experimental protocol following the procedure described by Pellow et al.⁶⁴ The EPM apparatus consisted of two open arms (16 × 5 cm) and two closed arms (16 × 5 × 10 cm) arranged at a 90° angle, all connected to a central platform (5 × 5 cm) elevated 50 cm from the floor. Each animal was placed individually in the center of the maze, facing one of the open arms.

During a 5 min session, the frequency of entries into the open and closed arms, the time spent in the open arm, and the number of head dips (leaning toward the edge) were recorded. The data were expressed as a percentage of entries (using all four paws) and time spent in the open arms relative to the total number of entries and time in both the open and closed arms, respectively. The number of entries into the closed arms was also documented.

4.7. Ex Vivo Assays. **4.7.1. Preparation of Samples for Biochemical Analysis.** Behavioral tests were instrumental in comprehending the symptomatology resulting from VCR and aging. These factors, when combined, can also induce neurospecific alterations. Consequently, biochemical assays conducted on brain and spinal cord tissues can provide further evidence of mechanistic processes affected by VCR-induced neuropathy and their association with aging.

The primary objective of the biochemical tests was to investigate axonal damage, which encompassed the disruption of the electro-

chemical gradient and subsequent oxidative stress. These assays encompassed the analysis of ATPase enzymes (Na⁺, K⁺-ATPase, Ca²⁺-ATPase, Mg²⁺-ATPase, and total ATPase), thiobarbituric acid reactive species (TBARS), nonprotein thiols (NPSH), and levels of nitrites and nitrates (NO_x). The nervous system structures analyzed included the cerebral cortex, spinal cord, cerebellum, hippocampus, and hypothalamus. Moreover, the spinal cord was isolated for histological examination for medullary cell apoptosis analysis and Wallerian degeneration.

For biochemical analyses, samples were homogenized in 50 mM Tris-HCl buffer (pH 7.4) and subsequently centrifuged at 900 × g for 10 min to obtain a supernatant (S1). Specifically, for the assessment of NO_x levels, samples were homogenized in 200 mM ZnSO₄ and acetonitrile (96%), followed by centrifugation at 13,000 × g at 4 °C for 30 min, and the resulting S2 fraction was collected. It is worth noting that some biological tissues were not processed using all techniques due to the sample quantity not covering a sufficient volume.

4.7.2. Analysis of the Medullary Histological Profile. The spine was collected and fixed by immersion in a 10% buffered formalin solution for 24 h. The spinal cord was not removed; it remained in place. The bones were decalcified in a solution of 8% hydrochloric acid and formic acid in a 1:1 ratio for an approximate period of 5 days. The samples were then cross-sectioned and routinely processed, embedded in paraffin, cut into 3–4 μm sections, stained with hematoxylin-eosin (HE), and examined under an optical microscope.

4.7.3. Evaluation of the Activity of ATPase Enzymes.

4.7.3.1. Total ATPases and Ca²⁺-ATPase Activities. Total ATPase and Ca²⁺-ATPase activities were determined following the methodology described by Rohn et al.⁶⁵ and adapted by Trevisan et al.⁶⁶ Tissue samples (50 μL) were added to an incubation medium containing all the requisite substrates for the functioning of ionic pumps: 30 mM Tris-HCl (pH 7.4), 50 mM NaCl, 5 mM KCl, 6 mM MgCl₂, 4 mM CaCl₂, and 3 mM ATP. To correct for nonenzymatic substrate hydrolysis, control samples were prepared by adding trichloroacetic acid (TCA) after reaction termination.⁶⁶

The activity of the Ca²⁺-ATPase enzyme was determined by subtracting the measured activity in the presence of Ca²⁺ from that determined in the absence of Ca²⁺. Meanwhile, the activity of total ATPases was assessed by analyzing the medium containing all the substrates. The color reaction was spectrophotometrically analyzed at 650 nm, and the enzymatic activities were expressed as nmol of Pi/min/mg of protein.

4.7.3.2. Na⁺, K⁺-ATPase and Mg²⁺-ATPase Activities. The reaction mixture consisted of S1, 3 mM MgCl₂, 125 mM NaCl, 20 mM KCl, and 50 mM Tris/HCl (pH 7.4), with a final volume of 500 μL. The reaction was initiated by adding ATP to a final concentration of 3.0 mM. Control samples were prepared under the same conditions with the addition of 0.1 mM ouabain. Ouabain is an inhibitor of the Na⁺, K⁺ pump, and its inclusion allowed the observation of enzyme activity related to the Mg²⁺ pump. To determine the Mg²⁺-ATPase activity, 1 mM ouabain was added to the reaction medium. The reactions were initiated by adding ATP and stopped after 30 min of incubation with the addition of 10% TCA.

The samples were further incubated at 37 °C for 30 min, and the incubation was halted by adding 10% TCA with 10 mM HgCl₂. Enzyme activity was calculated by measuring the difference in inorganic phosphate (Pi) levels between incubations conducted in the absence and presence of ouabain. The quantification of released inorganic phosphate (Pi) was performed following the method described by Fiske and Subbarow.⁶⁷ The color reaction mixture was spectrophotometrically analyzed at 650 nm. Results were expressed as nmol of Pi/mg protein/min.

4.7.4. Involvement of Oxidative Stress. **4.7.4.1. TBARS Levels.** TBARS levels were used as an indirect measure to assess the amount of MDA, one of the products released by lipoperoxidation. TBARS levels were measured as described by Ohkawa et al.⁶⁸ An aliquot of S1 was added to the reaction mixture containing thiobarbituric acid (0.8%), sodium dodecyl sulfate (8.1%), and acetic acid (pH 3.4) and incubated at 95 °C for 2 h. Absorbance was measured at 532 nm with

a spectrophotometer. Results were reported as nanomoles of MDA/mg of protein.

4.7.4.2. NO_x Levels. The nitrite and nitrate (NO_x) content was measured to assess levels of reactive nitrogen species. The measurement of NO_x levels was performed following the method described by Miranda et al.⁶⁹ The content of NO_x was determined in a medium consisting of 2% VCl_3 (in 5% HCl), 0.1% *N*-(1-naphthyl)ethylenediamine dihydrochloride, and 2% sulfanilamide (in 5% HCl).

After incubating at 37 °C for 60 min with an aliquot of S2, the nitrite levels were determined spectrophotometrically at 540 nm, based on the VCl_3 -mediated reduction of nitrate to nitrite. The data were expressed as nmol of NO_x /g tissue.

4.7.4.3. NPSH Levels. NPSH levels were assessed to directly measure oxidative damage to thiols and indirectly assess reduced glutathione (GSH) levels. The determination of NPSH levels was carried out using Ellman's method.⁷⁰ The supernatant was mixed with 10% TCA in a 1:1 volume ratio. The tubes were then centrifuged at 900 × g for 10 min, and the protein pellet was discarded. The clear supernatant was used to determine the levels of the free-thiol (SH) groups.

An aliquot of the supernatant was added to a solution containing 1 M potassium phosphate buffer (pH 7.4) and 10 mM 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB). The color reaction was measured at 412 nm by using a spectrophotometer. NPSH levels were expressed as nanomoles of NPSH per gram of tissue.

4.7.5. Protein Quantification. The protein concentration was measured by the method of Bradford et al.,⁷¹ using bovine serum albumin as the standard.

4.8. Statistical Analysis. The normality of the data was assessed using the D'Agostino and Pearson omnibus normality test. Statistical analysis was conducted using GraphPad Prism 7.0 software (San Diego, CA, USA). Two-way ANOVA followed by Tukey's multiple comparisons test was employed for statistical analysis. Data were presented as mean ± standard error of the mean (S.E.M.). Main effects were reported only when the highest second-order interaction was not statistically significant. Statistical significance was defined as $P < 0.05$.

AUTHOR INFORMATION

Corresponding Authors

Cristiane Luchese — Postgraduate Program in Biochemistry and Bioprospecting, Research Laboratory in Biochemical Pharmacology (LaFarBio), Center for Chemical, Pharmaceutical and Food Sciences, Federal University of Pelotas, 96010-900 Pelotas, RS, Brazil; Phone: +55-53-32757233; Email: cristiane_luchese@yahoo.com.br

Ethel A. Wilhelm — Postgraduate Program in Biochemistry and Bioprospecting, Research Laboratory in Biochemical Pharmacology (LaFarBio), Center for Chemical, Pharmaceutical and Food Sciences, Federal University of Pelotas, 96010-900 Pelotas, RS, Brazil; orcid.org/0000-0002-2875-9962; Phone: +55-53-32757360; Email: ethelwilhelm@yahoo.com.br

Authors

Ketlyn P. da Motta — Postgraduate Program in Biochemistry and Bioprospecting, Research Laboratory in Biochemical Pharmacology (LaFarBio), Center for Chemical, Pharmaceutical and Food Sciences, Federal University of Pelotas, 96010-900 Pelotas, RS, Brazil

Carolina C. Martins — Postgraduate Program in Biochemistry and Bioprospecting, Research Laboratory in Biochemical Pharmacology (LaFarBio), Center for Chemical, Pharmaceutical and Food Sciences, Federal University of Pelotas, 96010-900 Pelotas, RS, Brazil

Vanessa M. E. da Rocha — Postgraduate Program in Biochemistry and Bioprospecting, Research Laboratory in Biochemical Pharmacology (LaFarBio), Center for Chemical, Pharmaceutical and Food Sciences, Federal University of Pelotas, 96010-900 Pelotas, RS, Brazil

Mauro P. Soares — Regional Diagnostic Laboratory Faculty of Veterinary Medicine, Federal University of Pelotas (UFPEL), 96010-900 Pelotas, RS, Brazil

Marcia F. Mesko — Contaminant Control Laboratory in Biomaterials (LCCBio), Federal University of Pelotas (UFPEL), 96010-900 Pelotas, RS, Brazil; orcid.org/0000-0002-7399-446X

Complete contact information is available at:

<https://pubs.acs.org/10.1021/acschemneuro.4c00342>

Author Contributions

K.P.M., C.C.M., and E.A.W. conceived and designed the study. K.P.M., C.C.M., and V.M. performed the biochemical and behavioral analyses. M.P.S. was responsible for the histological analysis. K.P.M. and E.A.W. wrote the manuscript. E.A.W., M.F.M., and C.L. supervised the study. All authors approved the final version of the manuscript.

Funding

The Article Processing Charge for the publication of this research was funded by the Coordination for the Improvement of Higher Education Personnel - CAPES (ROR identifier: 00x0ma614).

Notes

The authors declare no competing financial interest. During the preparation of this work, the authors used GPTchat (OpenAI, 2023) to improve readability and language. After using this tool, the authors have reviewed and edited the content as necessary and take full responsibility for the content of the publication.

ACKNOWLEDGMENTS

This study received financial support and scholarships from the following Brazilian agencies: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) (312747/2020-9, 406118/2021-3, 442284/2023-3) and Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS) (PqG 21/2551-0001943-3, RITES 22/2551-0000389-3). This study was also financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior—Brasil (CAPES)—Finance Code 001. M.F.M., C.L., and E.A.W. are recipients of CNPq fellowship. This study also received financial assistance from L'ORÉAL-UNESCO-ABC for Women in Science.

ABBREVIATIONS

VCR, vincristine; TBARS, thiobarbituric acid reactive species; NPSH, nonprotein thiols; NO_x , nitrites and nitrates; TCA, trichloroacetic acid; GSH, reduced glutathione; CX3CR, chemokine receptor 1 motif; $\text{TNF-}\alpha$, tumor necrosis factor- α ; ICAM-1, intercellular adhesion molecule 1; VCAM, vascular adhesion molecules; $\text{NF}\kappa\text{B}$, nuclear factor- κB ; GST, glutathione S-transferase; MDA, malondialdehyde

REFERENCES

- (1) Huang, Y. L.; Tsay, W. I.; Her, S. H.; Ho, C. H.; Tsai, K. T.; Hsu, C. C.; Wang, J. J.; Huang, C. C. Chronic Pain and Use of Analgesics

- in the Elderly: A Nationwide Population-Based Study. *Arch. Med. Sci.* **2020**, *16* (2), 627–634.
- (2) Tinnirello, A.; Mazzoleni, S.; Santi, C. Chronic Pain in the Elderly: Mechanisms and Perspectives. *Biomolecules* **2021**, *11* (March), 1256.
- (3) DeSantis, C. E.; Miller, K. D.; Dale, W.; Mohile, S. G.; Cohen, H. J.; Leach, C. R.; Goding Sauer, A.; Jemal, A.; Siegel, R. L. Cancer Statistics for Adults Aged 85 Years and Older, 2019. *CA. Cancer J. Clin.* **2019**, *69* (6), 452–467.
- (4) Triarico, S.; Romano, A.; Attinà, G.; Capozza, M. A.; Maurizi, P.; Mastrangelo, S.; Ruggiero, A. Vincristine-Induced Peripheral Neuropathy (Vipn) in Pediatric Tumors: Mechanisms, Risk Factors, Strategies of Prevention and Treatment. *Int. J. Mol. Sci.* **2021**, *22* (8), 4112.
- (5) Starobova, H.; Vetter, I. Pathophysiology of Chemotherapy-Induced Peripheral Neuropathy. *Front. Mol. Neurosci.* **2017**, *10* (May), 1–21.
- (6) Gomber, S.; Dewan, P.; Chhonker, D. Vincristine Induced Neurotoxicity in Cancer Patients. *Indian J. Pediatr.* **2010**, *77* (1), 97–100.
- (7) Li, G. Z.; Hu, Y. H.; Li, D. Y.; Zhang, Y.; Guo, H. L.; Li, Y. M.; Chen, F.; Xu, J. Vincristine-Induced Peripheral Neuropathy: A Mini-Review. *Neurotoxicology* **2020**, *81*, 161–171.
- (8) Sisignano, M.; Baron, R.; Scholich, K.; Geisslinger, G. Mechanism-Based Treatment for Chemotherapy-Induced Peripheral Neuropathic Pain. *Nat. Rev. Neurol.* **2014**, *10* (12), 694–707.
- (9) Geisler, S. Vincristine- and Bortezomib-Induced Neuropathies – from Bedside to Bench and Back. *Exp. Neurol.* **2021**, *336*, No. 113519.
- (10) Sy, A.; Cheng, J.; Cooper, R.; Mueller, L. Heterozygosity for CMT Type 4 Predicts a Severe Vincristine-Induced Polyneuropathy Phenotype: A Case Report and Review of Literature. *J. Pediatr. Hematol. Oncol.* **2019**, *41* (1), E41–E43.
- (11) Schappacher, K. A.; Styczynski, L.; Baccei, M. L. Early Life Vincristine Exposure Evokes Mechanical Pain Hypersensitivity in the Developing Rat. *Pain* **2017**, *158*, 1647.
- (12) Madsen, M. L.; Due, H.; Ejlskjær, N.; Jensen, P.; Madsen, J.; Dybkær, K. Aspects of Vincristine-Induced Neuropathy in Hematologic Malignancies: A Systematic Review. *Cancer Chemother. Pharmacol.* **2019**, *84* (3), 471–485.
- (13) Canta, A.; Pozzi, E.; Carozzi, V. A. Mitochondrial Dysfunction in Chemotherapy-Induced Peripheral Neuropathy (CIPN). *Toxics* **2015**, *3* (2), 198–223.
- (14) Jiang, K.; Shi, J.; Shi, J. Morin Alleviates Vincristine-Induced Neuropathic Pain via Nerve Protective Effect and Inhibition of NF- κ B Pathway in Rats. *Cell. Mol. Neurobiol.* **2019**, *39* (6), 799–808.
- (15) Raasing, L. R. M.; Vogels, O. J. M.; Veltkamp, M.; Van Swol, C. F. P.; Grutters, J. C. Current View of Diagnosing Small Fiber Neuropathy. *J. Neuromuscul. Dis.* **2021**, *8* (2), 185–207.
- (16) Barth, A.; Vogt, A. G.; dos Reis, A. S.; Pinz, M. P.; Krüger, R.; Domingues, W. B.; Alves, D.; Campos, V. F.; Pinton, S.; Paroul, N.; Wilhelm, E. A.; Luchese, C. 7-Chloro-4-(Phenylselenyl) Quinoline with Memory Enhancer Action in Aging Rats: Modulation of Neuroplasticity, Acetylcholinesterase Activity, and Cholesterol Levels. *Mol. Neurobiol.* **2019**, *56*, 6398.
- (17) Barnes, R. P.; Fouquerel, E.; Opreko, P. L. The Impact of Oxidative DNA Damage and Stress on Telomere Homeostasis. *Mech. Ageing Dev.* **2019**, *177* (2010), 37–45.
- (18) Shabani, M.; Larizadeh, M. H.; Parsania, S.; Shekari, M. A.; Shahrokhi, N. Profound Destructive Effects of Adolescent Exposure to Vincristine Accompanied with Some Sex Differences in Motor and Memory Performance. *Can. J. Physiol. Pharmacol.* **2012**, *90* (4), 379–386.
- (19) Golchin, L.; Shabani, M.; Harandi, S.; Razavinasab, M. Pistachio Supplementation Attenuates Motor and Cognition Impairments Induced by Cisplatin or Vincristine in Rats. *Adv. Biomed. Res.* **2015**, *4* (1), 92.
- (20) Montague, K.; Simeoli, R.; Valente, J.; Malcangio, M. A Novel Interaction between CX3 CR1 and CCR2 Signalling in Monocytes Constitutes an Underlying Mechanism for Persistent Vincristine-Induced Pain. *J. Neuroinflammation* **2018**, *15* (1), 1–15.
- (21) Starobova, H.; Mueller, A.; Allavena, R.; Lohman, R. J.; Sweet, M. J.; Vetter, I. Minocycline Prevents the Development of Mechanical Allodynia in Mouse Models of Vincristine-Induced Peripheral Neuropathy. *Front. Neurosci.* **2019**, *13* (JUN), 1–10.
- (22) Moschetti, G.; Amodeo, G.; Paladini, M. S.; Molteni, R.; Balboni, G.; Panerai, A.; Sacerdote, P.; Franchi, S. Prokineticin 2 Promotes and Sustains Neuroinflammation in Vincristine Treated Mice: Focus on Pain and Emotional like Behavior. *Brain. Behav. Immun.* **2019**, *82*, 422–431.
- (23) Marmiroli, P.; Riva, B.; Pozzi, E.; Ballarín, E.; Lim, D.; Chiorazzi, A.; Meregalli, C.; Distasi, C.; Renn, C. L.; Semperboni, S.; Morosi, L.; Ruffinatti, F. A.; Zucchetti, M.; Dorsey, S. G.; Cavaletti, G.; Genazzani, A.; Carozzi, V. A. Susceptibility of Different Mouse Strains to Oxaliplatin Peripheral Neurotoxicity: Phenotypic and Genotypic Insights. *PLoS One* **2017**, *12* (10), 1–25.
- (24) Wang, M. S.; Wu, Y.; Culver, D. G.; Glass, J. D. Pathogenesis of Axonal Degeneration: Parallels between Wallerian Degeneration and Vincristine Neuropathy. *J. Neuropathol. Exp. Neurol.* **2000**, *59* (7), 599–606.
- (25) Bluet, C. T.; Shoiab, A. M.; Peng, Q.; Manickam, B.; Huang, W.; Shin, E.; Zhang, W.; Song, Y.-H.; Liu, C.-N. Behavioral, Histopathologic, and Molecular Biological Responses of Nanoparticle- and Solution-Based Formulations of Vincristine in Mice. *Int. J. Toxicol.* **2021**, *40* (1), 40–51.
- (26) Nagai, J.; Goshima, Y.; Ohshima, T. CRMP4 Mediates MAG-Induced Inhibition of Axonal Outgrowth and Protection against Vincristine-Induced Axonal Degeneration. *Neurosci. Lett.* **2012**, *519* (1), 56–61.
- (27) Schomberg, D.; Olson, J. K. Immune Responses of Microglia in the Spinal Cord: Contribution to Pain States. *Exp. Neurol.* **2012**, *234* (2), 262–270.
- (28) Taves, S.; Berta, T.; Chen, G.; Ji, R.-R. Microglia and Spinal Cord Synaptic Plasticity in Persistent Pain. *Neural Plast.* **2013**, *2013*, 1–10.
- (29) Sun, L.; Peng, C.; Joosten, E.; Cheung, C. W.; Tan, F.; Jiang, W.; Shen, X. Spinal Cord Stimulation and Treatment of Peripheral or Central Neuropathic Pain: Mechanisms and Clinical Application. *Neural Plast.* **2021**, *2021*, 1–9.
- (30) Ramos, D.; Cruz, C. D. Involvement of Microglia in Chronic Neuropathic Pain Associated with Spinal Cord Injury – a Systematic Review. *Rev. Neurosci.* **2023**, *34* (8), 933–950.
- (31) Ohara, S.; Ohama, E.; Takahashi, H.; Ikuta, F.; Nishizawa, M.; Tanaka, K.; Miyatake, T. Alterations of Oligodendrocytes and Demyelination in the Spinal Cord of Patients with Mitochondrial Encephalomyopathy. *J. Neurol. Sci.* **1988**, *86* (1), 19–29.
- (32) Dietmann, A. S.; Kruse, N.; Stork, L.; Gloth, M.; Brück, W.; Metz, I. Neurofilament Light Chains in Serum as Biomarkers of Axonal Damage in Early MS Lesions: A Histological–Serological Correlative Study. *J. Neurol.* **2023**, *270* (3), 1416–1429.
- (33) Xu, J.; Wen, J.; Fu, L.; Liao, L.; Zou, Y.; Zhang, J.; Deng, J.; Zhang, H.; Liu, J.; Wang, X.; Zuo, D.; Guo, J. Macrophage-Specific RhoA Knockout Delays Wallerian Degeneration after Peripheral Nerve Injury in Mice. *J. Neuroinflammation* **2021**, *18* (1), 1–17.
- (34) Kiguchi, N.; Maeda, T.; Kobayashi, Y.; Kondo, T.; Ozaki, M.; Kishioka, S. The Critical Role of Invading Peripheral Macrophage-Derived Interleukin-6 in Vincristine-Induced Mechanical Allodynia in Mice. *Eur. J. Pharmacol.* **2008**, *592* (1–3), 87–92.
- (35) Kobayashi, Y.; Kiguchi, N.; Fukazawa, Y.; Saika, F.; Maeda, T.; Kishioka, S. Macrophage-T Cell Interactions Mediate Neuropathic Pain through the Glucocorticoid-Induced Tumor Necrosis Factor Ligand System. *J. Biol. Chem.* **2015**, *290* (20), 12603–12613.
- (36) Simon, M. S.; Schiweck, C.; Arteaga-Henriquez, G.; Poletti, S.; Haarman, B. C. M.; Dik, W. A.; Schwarz, M.; Vrieze, E.; Mikova, O.; Joergens, S.; Musil, R.; Claes, S.; Baune, B. T.; Leboyer, M.; Benedetti, F.; Furlan, R.; Berghmans, R.; de Wit, H.; Wijkhuijs, A.; Arolt, V.; Müller, N.; Drexhage, H. A. Monocyte Mitochondrial Dysfunction, Inflammaging, and Inflammatory Pyroptosis in Major Depression.

- Prog. Neuro-Psychopharmacology Biol. Psychiatry* **2021**, *111* (June), No. 110391.
- (37) Frösen, J.; Cebal, J.; Robertson, A. M.; Aoki, T. Flow Induced Inflammation Mediated Artery Wall Remodeling in the Formation and Progression of Intracranial Aneurysms. *Neurosurg Focus* **2019**, *47* (1), 139–148.
- (38) da Motta, K. P.; Santos, B. F.; Domingues, N. L. D. C.; Luchese, C.; Wilhelm, E. A. Target Enzymes in Oxaliplatin-Induced Peripheral Neuropathy in Swiss Mice: A New Acetylcholinesterase Inhibitor as Therapeutic Strategy. *Chem. Biol. Interact.* **2022**, *352*, No. 109772.
- (39) Paltian, J. J.; dos Reis, A. S.; Martins, A. W. S.; Blödmann, E. B.; Dellagostin, E. N.; Soares, L. K.; Schumacher, R. F.; Campos, V. F.; Alves, D.; Luchese, C.; Wilhelm, E. A. 7-Chloro-4-(Phenylselanyl) Quinoline Is a Novel Multitarget Therapy to Combat Peripheral Neuropathy and Comorbidities Induced by Paclitaxel in Mice. *Mol. Neurobiol.* **2022**, *59*, 6567.
- (40) Nishi, T.; Forgac, M. The Vacuolar (H⁺)-ATPases - Nature's Most Versatile Proton Pumps. *Nat. Rev. Mol. Cell Biol.* **2002**, *3* (2), 94–103.
- (41) Haass, M.; Kübler, W. Notice and Sympathetic Neurotransmission. *Cardiovasc. Drugs Ther.* **1997**, *10* (6), 657–665.
- (42) Schweinberger, B. M.; Schwieder, L.; Scherer, E.; Sitta, A.; Vargas, C. R.; Wyse, A. T. S. Development of an Animal Model for Gestational Hypomethioninemia in Rat and Its Effect on Brain Na⁺/K⁺-ATPase/Mg²⁺-ATPase Activity and Oxidative Status of the Offspring. *Metab. Brain Dis.* **2014**, *29* (1), 153–160.
- (43) Kang, L.; Tian, Y.; Xu, S.; Chen, H. Oxaliplatin-Induced Peripheral Neuropathy: Clinical Features, Mechanisms, Prevention and Treatment. *J. Neurol.* **2021**, *268*, 3269. No. 0123456789.
- (44) Reis, A. S.; Paltian, J. J.; Domingues, W. B.; Costa, G. P.; Alves, D.; Giongo, J. L.; Campos, V. F.; Luchese, C.; Wilhelm, E. A. Pharmacological Modulation of Na⁺, K⁺-ATPase as a Potential Target for OXA-Induced Neurotoxicity: Correlation between Anxiety and Cognitive Decline and Beneficial Effects of 7-Chloro-4-(Phenylselanyl) Quinoline. *Brain Res. Bull.* **2020**, *162* (June), 282–290.
- (45) Holliday, L. S. Vacuolar H⁺-ATPases (V-ATPases) as Therapeutic Targets: A Brief Review and Recent Developments. *Biotarget* **2017**, *1* (7), 18–18.
- (46) Rodrigues, K. C.; Bortolotto, C. F.; da Motta, K. P.; de Oliveira, R. L.; Paltian, J. J.; Krüger, R.; Roman, S. S.; Boeira, S. P.; Alves, D.; Wilhelm, E. A.; Luchese, C. The Neurotherapeutic Role of a Selenium-Functionalized Quinoline in Hypothalamic Obese Rats. *Psychopharmacology (Berl.)* **2021**, *238* (7), 1937–1951.
- (47) Moseley, A. E.; Williams, M. T.; Schaefer, T. L.; Bohanan, C. S.; Neumann, J. C.; Behbehani, M. M.; Vorhees, C. V.; Lingrel, J. B. Deficiency in Na,K-ATPase α Isoform Genes Alters Spatial Learning, Motor Activity, and Anxiety in Mice. *J. Neurosci.* **2007**, *27* (3), 616–626.
- (48) Reis, A. S.; Martins, C. C.; da Motta, K. P.; Paltian, J. J.; Costa, G. P.; Alves, D.; Luchese, C.; Wilhelm, E. A. Interface of Aging and Acute Peripheral Neuropathy Induced by Oxaliplatin in Mice: Target-Directed Approaches for Na⁺, K⁺-ATPase, Oxidative Stress, and 7-Chloro-4-(Phenylselanyl) Quinoline Therapy. *Mol. Neurobiol.* **2022**, *59* (3), 1766–1780.
- (49) Kinoshita, P. F.; Leite, J. A.; Orellana, A. M. M.; Vasconcelos, A. R.; Quintas, L. E. M.; Kawamoto, E. M.; Scavone, C. The Influence of Na⁺, K⁺-ATPase on Glutamate Signaling in Neurodegenerative Diseases and Senescence. *Front. Physiol.* **2016**, *7* (JUN), 1–19.
- (50) Waseem, M.; Parvez, S.; Tabassum, H. Mitochondria As the Target for the Modulatory Effect of Curcumin in Oxaliplatin-Induced Toxicity in Isolated Rat Liver Mitochondria. *Arch. Med. Res.* **2017**, *48* (1), 55–63.
- (51) Busch, C. J.; Binder, C. J. Malondialdehyde Epitopes as Mediators of Sterile Inflammation. *Biochim. Biophys. Acta - Mol. Cell Biol. Lipids* **2017**, *1862* (4), 398–406.
- (52) Gegotek, A.; Skrzydlewska, E. Biological Effect of Protein Modifications by Lipid Peroxidation Products. *Chem. Phys. Lipids* **2019**, *221*, 46–52.
- (53) Kamei, J.; Tamura, N.; Saitoh, A. Possible Involvement of the Spinal Nitric Oxide/CGMP Pathway in Vincristine-Induced Painful Neuropathy in Mice. *Pain* **2005**, *117* (1–2), 112–120.
- (54) Kim, H.; Sasaki, T.; Maeda, K.; Koya, D.; Kashiwagi, A.; Yasuda, H. Protein kinase C β selective inhibitor LY333531 attenuates diabetic hyperalgesia through ameliorating cGMP level of dorsal root ganglion neurons. *Diabetes* **2003**, *52*, 2102.
- (55) Benoit, E.; Brienza, S.; Dubois, J. M. Oxaliplatin, an Anticancer Agent That Affects Both Na⁺ and K⁺ Channels in Frog Peripheral Myelinated Axons. *Gen. Physiol. Biophys.* **2006**, *25* (3), 263–276.
- (56) Schappacher, K. A.; Xie, W.; Zhang, J. M.; Baccei, M. L. Neonatal Vincristine Administration Modulates Intrinsic Neuronal Excitability in the Rat Dorsal Root Ganglion and Spinal Dorsal Horn during Adolescence. *Pain* **2019**, *160* (3), 645–657.
- (57) Varnes, M. E.; Biaglow, J. E.; Roizin-Towle, L.; Hall, E. J. Depletion of Intracellular Gsh and Npsh by Buthionine Sulfoximine and Diethyl Maleate: Factors That Influence Enhancement of Aerobic Radiation Response. *Int. J. Radiat. Oncol.* **1984**, *10* (March), 1229–1233.
- (58) Martins, C. C.; Reis, A. S.; da Motta, K. P.; Luchese, C.; Wilhelm, E. A. Mechanistic Pathways of Fibromyalgia Induced by Intermittent Cold Stress in Mice Is Sex-Dependently. *Brain Res. Bull.* **2022**, *187*, 11–23.
- (59) Paltian, J. J.; dos Reis, A. S.; de Oliveira, R. L.; da Fonseca, C. A. R.; Domingues, W. B.; Dellagostin, E. N.; Campos, V. F.; Krüger, R.; Alves, D.; Luchese, C.; Wilhelm, E. A. The Anxiolytic Effect of a Promising Quinoline Containing Selenium with the Contribution of the Serotonergic and GABAergic Pathways: Modulation of Parameters Associated with Anxiety in Mice. *Behav. Brain Res.* **2020**, *393* (June), No. 112797.
- (60) da Motta, K. P.; Martins, C. C.; Macedo, V. M.; Santos, B. F.; Lu, N.; Luchese, C.; Wilhelm, E. A. The Antinociceptive Responses of MTDZ to Paclitaxel-Induced Peripheral Neuropathy and Acute Nociception in Mice: Behavioral, Pharmacological, and Biochemical Approaches. *Pharmaceuticals* **2023**, *16* (9), 1217.
- (61) Alamri, F. F.; Shoyab, A. A.; Biggers, A.; Jayaraman, S.; Guindon, J.; Karamyan, V. T. Applicability of the Grip Strength and Automated von Frey Tactile Sensitivity Tests in the Mouse Photothrombotic Model of Stroke. *Behav. Brain Res.* **2018**, *336*, 250–255.
- (62) Woolfe, G.; Macdonald, A. D. The Evaluation of the Analgesic Action of Pethidine Hydrochloride (Demerol). *J. Pharmacol. Exp. Ther.* **1944**, *80* (3), 300–307.
- (63) Stangherlin, E. C.; Rocha, J. B. T.; Nogueira, C. W. Diphenyl Ditoluride Impairs Short-Term Memory and Alters Neurochemical Parameters in Young Rats. *Pharmacol. Biochem. Behav.* **2009**, *91* (3), 430–435.
- (64) Pellow, S.; Chopin, P.; File, S. E.; Briley, M. Validation of Open: Closed Arm Entries in an Elevated plus-Maze as a Measure of Anxiety in the Rat. *J. Neurosci. Methods* **1985**, *14* (3), 149–167.
- (65) Rohn, T. T.; Hinds, T. R.; Vincenzi, F. F. Ion Transport ATPases as Targets for Free Radical Damage. *Biochem. Pharmacol.* **1993**, *46* (3), 525–534.
- (66) Trevisan, G.; Maldaner, G.; Velloso, A.; Sant, S.; Ilha, V.; De Campos Velho Gewehr, C.; Rubin, M. A.; Morel, A. F.; Ferreira, J. Antinociceptive Effects of 14-Membered Cyclopeptide Alkaloids. *J. Nat. Prod.* **2009**, *72*, 608–612.
- (67) Fiske, B. C. H.; Subbarow, Y. The Colorimetric Determination of Phosphorus. *J. Biol. Chem.* **1925**, *66*, 375–400.
- (68) Ohkawa, H.; Ohishi, N.; Yagi, K. Assay for Lipid Peroxides in Animal Tissues by Thiobarbituric Acid Reaction. *Anal. Biochem.* **1979**, *95* (2), 351–358.
- (69) Miranda, K. M.; Espey, M. G.; Yamada, K.; Krishna, M.; Ludwick, N.; Kim, S.; Jour, D.; Grisham, M. B.; Feelisch, M.; Fukuto, J. M.; Wink, D. A. Unique Oxidative Mechanisms for the Reactive Nitrogen Oxide Species. *Nitroxyl Anion* **2001**, *276* (3), 1720–1727.
- (70) Ellman, G. L. Tissue Sulfhydryl Groups. *Arch. Biochem. Biophys.* **1959**, *82* (1), 70–77.

(71) Bradford, M. M. A Rapid and Sensitive Method for the Quantitation of Microgram Quantities of Protein Utilizing the Principle of Protein-Dye Binding. *Anal. Biochem.* **1976**, *72* (1–2), 248–254.



CAS BIOFINDER DISCOVERY PLATFORM™

BRIDGE BIOLOGY AND CHEMISTRY FOR FASTER ANSWERS

Analyze target relationships,
compound effects, and disease
pathways

Explore the platform



3969

<https://doi.org/10.1021/acscchemneuro.4c00342>
ACS Chem. Neurosci. **2024**, *15*, 3954–3969

4.2. CAPÍTULO 2 – Manuscrito Científico 1

Correlação entre a sinalização NFκB e a inibição da Na⁺, K⁺-ATPase em comorbidades emocionais e cognitivas induzidas por vincristina em camundongos: potencial neuroprotetor do 4-PSQ

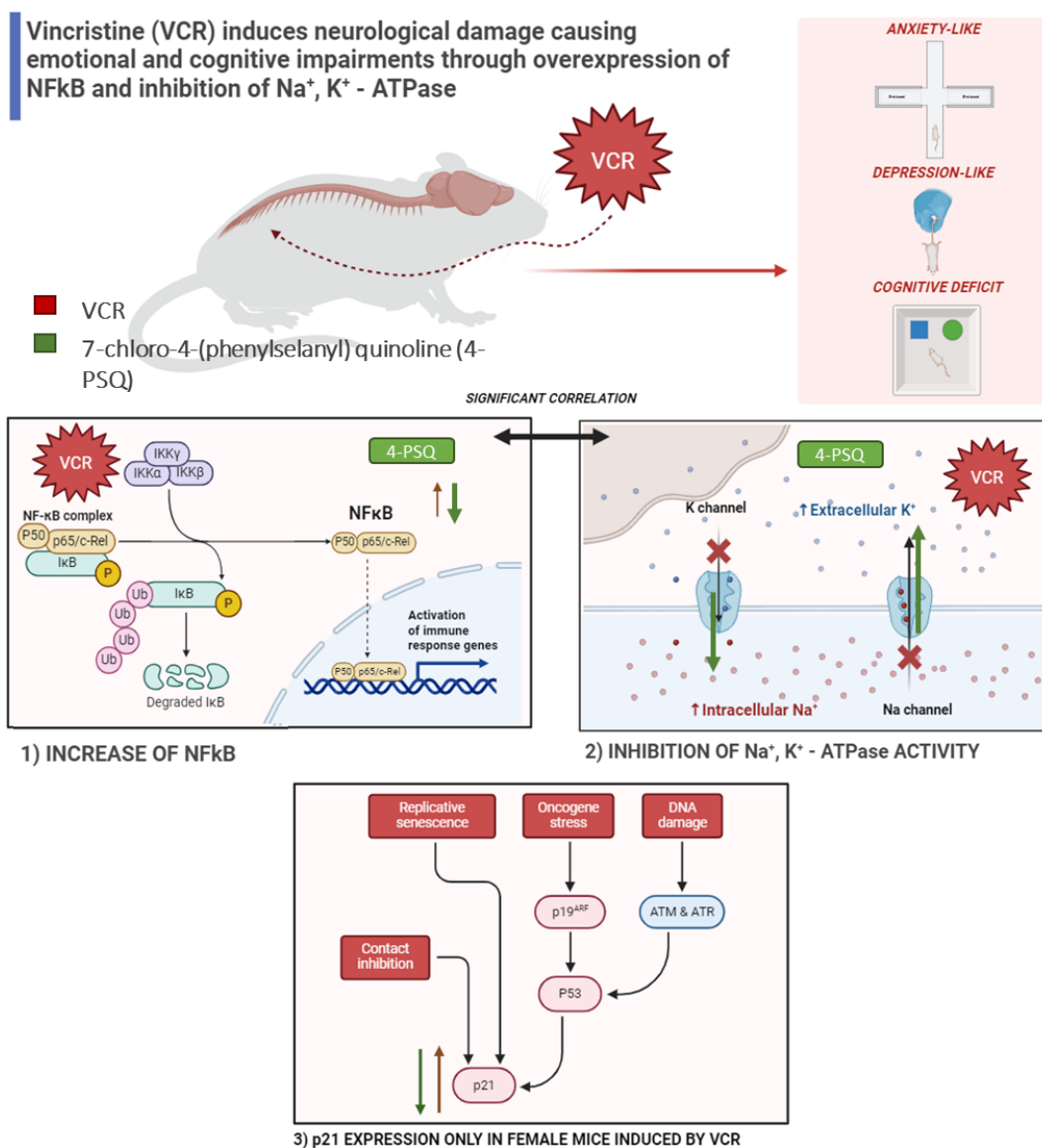
Diante dos resultados instigantes evidenciados pela ação neurotóxica da VCR em ratos idosos — que não se restringiu apenas à neuropatia periférica, mas também envolveu disfunções cognitivas e emocionais — realizamos o segundo estudo. O objetivo do estudo foi investigar se camundongos machos e fêmeas expostos à VCR desenvolveriam alterações neurocognitivas, avaliadas por meio de testes comportamentais de memória, assim como prejuízos emocionais manifestados em comportamentos tipo-ansioso e tipo-depressivo. Além das investigações a nível comportamental, observamos mecanismos que quando correlacionados poderiam auxiliar na compreensão de como o prejuízo neurológico estava sendo desenvolvido neste modelo (atividade da enzima Na⁺, K⁺ - ATPase, e expressão gênica da proteína 21 (p21) e NFκB). Os potenciais efeitos neuroterapêuticos do composto 4-PSQ foram também observados neste estudo.

Os dados presentes neste manuscrito correlacionam pela primeira vez como as disfunções neurológicas associadas ao prejuízo emocional e cognitivo podem estar atreladas a uma via que nomeamos como Na⁺, K⁺ - ATPase/ NFκB. Comprovamos que a VCR inibe a atividade da Na⁺, K⁺-ATPase, promovendo alterações na despolarização neuronal, o que resulta em déficits cognitivos e distúrbios emocionais. Enquanto que, o aumento da expressão de NFκB sugere a ativação de vias neuroinflamatórias e apoptóticas em animais expostos ao VCR.

Um ponto de destaque associado a disfunção sexual neste estudo o aumento exclusivo da expressão de p21 no córtex cerebral de camundongos fêmeas que receberam VCR podendo indicar maior comprometimento emocional e cognitivo, particularmente na memória de curto prazo. Não obstante, propomos ainda o 4-PSQ como uma molécula inovadora com resultados neuroprotetores relevantes, capaz de mitigar comportamentos depressivos, ansiosos e que prejudicam a memória em camundongos machos e fêmeas expostos a VCR.

MANUSCRITO 1

Os resultados do Capítulo 2 da tese estão apresentados sob a forma de manuscrito científico, o qual se encontra assim organizado. Os itens Materiais e Métodos, Resultados, Discussão dos Resultados e Referências Bibliográficas encontram-se no próprio artigo. O manuscrito científico encontra-se submetido na revista *ACS Omega*.



Correlation between NFκB Signaling and Na⁺, K⁺-ATPase Inhibition in Vincristine-Induced Emotional and Cognitive Comorbidities in Mice: Neuroprotective Potential of 4-PSQ

Ketlyn Pereira da Motta^a, Carolina Cristóvão Martins^a, Vanessa Macedo Esteves da Rocha^a, Ingrid Cardoso Oliveira^b, Diego Alves^b, Larissa Daniele Bobermin^c, André Quincozes-Santos^c, Ethel Antunes Wilhelm^{a*}

^a *Postgraduate Program in Biochemistry and Bioprospecting, Biochemical Pharmacology Research Laboratory – LaFarBio, CCQFA - Federal University of Pelotas (UFPel), P.O., Box 354 - 96010-900, Pelotas, RS, Brazil.*

^b *Postgraduate Program in Chemistry, Clean Organic Synthesis Laboratory, CCQFA, Federal University of Pelotas (UFPel), P.O., Box 354 - 96010-900, Pelotas, RS, Brazil.*

^c *Postgraduate Program in Biological Sciences: Biochemistry, Institute of Basic Health Sciences, Federal University of Rio Grande do Sul (UFRGS), 90035 -003, Porto Alegre, RS, Brazil.*

*Address for Correspondence:

Ethel Antunes Wilhelm; e-mail: ethelwilhelm@yahoo.com.br / Phone: +55-53-32757360

Postgraduate Program in Biochemistry and Bioprospecting (PPGBBio), Center for Chemical, Pharmaceutical and Food Sciences, Federal University of Pelotas (UFPel), Capão do Leão Campus, Pelotas, Zip Code 96010-900, RS, Brazil.

Abstract

Vincristine (VCR), a widely used chemotherapeutic agent, is associated with persistent neurotoxic effects, including psychiatric and cognitive impairments in cancer survivors. This study investigated the neurobehavioral and molecular impacts of VCR in male and female Swiss mice, emphasizing sex-specific outcomes and evaluating the neuroprotective efficacy of 7-chloro-4-(phenylselanyl)quinoline (4-PSQ). Mice received daily intraperitoneal injections of VCR (0.1 mg/kg) or vehicle for five days, followed by daily oral administration of 4-PSQ (1 mg/kg) or vehicle from day 7 to 16. Behavioral assessments for depressive- and anxiety-like responses and cognitive performance were conducted, followed by biochemical analyses of the cerebral cortex and spinal cord. VCR significantly increased nuclear factor kappa B (NFκB) expression and inhibited Na⁺,K⁺-ATPase activity in both sexes, while selectively upregulating protein-21 (p21) mRNA in the cerebral cortex of females. These molecular alterations correlated with behavioral impairments, as shown by a robust pattern of sex-specific associations: in males, behavioral changes were strongly correlated with Na⁺,K⁺-ATPase inhibition, while in females, increased NFκB expression was more strongly associated with emotional and cognitive deficits. Notably, p21 overexpression emerged as a unique marker of neurotoxicity in females. Treatment with 4-PSQ attenuated molecular and behavioral alterations in both sexes, supporting its neuroprotective efficacy. By establishing specific correlations between biochemical and behavioral parameters, this study provides mechanistic insights into VCR-induced neurotoxicity and proposes 4-PSQ as a promising therapeutic candidate to prevent or reverse chemotherapy-related cognitive and emotional dysfunctions.

Keywords: 4-PSQ, anxiety, chemotherapy, depression, memory, sexual dimorphism.

1. Introduction

Vincristine (VCR) is a widely utilized chemotherapy agent in oncology, effectively suppressing tumor proliferation across various age groups (Moschetti *et al.*, 2019b; Triarico *et al.*, 2021b; van de Velde *et al.*, 2017b). However, its usage is associated with neurotoxicity, inducing mechanisms recently described as "*chemo-brain*" (Eide; Feng, 2020; Turcu-Stiolica *et al.*, 2022). VCR-triggered events can compromise neurological functions, potentially leading to cognitive and emotional dysfunctions (Geisler, 2021; Gomber; Dewan; Chhonker, 2010a; Meléndez *et al.*, 2020; Moschetti *et al.*, 2019b; Shabani *et al.*, 2012b). The interconnected pathways disrupted by VCR suggest a neurochemical mechanism, activating concurrent cascades and disrupting normal neural functionality.

Nuclear factor kappa B (NFκB) regulates essential biochemical pathways in healthy conditions (Albensi, 2019a). Its activation is linked to inflammation, with changes in NFκB expression causing damage to mitochondria, DNA, and the cytoplasm (Albensi, 2019a; Kaltschmidt; Kaltschmidt, 2015). Evidence indicates that NFκB might act as a regulator in mitochondria, influencing the balance between cytoplasmic glycolysis and mitochondrial respiration in normal cells. In the cytoplasm, NFκB can trigger cell apoptosis by releasing cytochrome C, initiating caspase cascades (Albensi, 2019a). In the nucleus, NFκB can enhance the expression of pro-inflammatory proteins. Although VCR is known to hyperactivate NFκB, its association with psychiatric and cognitive disorders remains underexplored (Khalilzadeh *et al.*, 2020a; Shayesteh *et al.*, 2022a).

Conversely, the enzyme Na⁺, K⁺ - ATPase is highly involved in axonal depolarization processes and neuronal signaling (Dobretsov, 2005a; Sung *et al.*, 2015a). Inhibition of Na⁺, K⁺ - ATPase can be linked to depressive and anxious

behaviors by preventing the release of neurotransmitters associated with well-being (Moseley *et al.*, 2007; Reis *et al.*, 2020d; Rodrigues *et al.*, 2021a). The relationship between Na⁺, K⁺ - ATPase activity inhibition and VCR effects is also unexplored.

Therefore, identifying axonal impairment altered by VCR, its correlation with Na⁺, K⁺ - ATPase inhibition, and linking this inhibition with NFκB hyperactivation could represent a neurobiological mechanism fostering neuroinflammation, cell apoptosis, and consequent cognitive deficits and emotional disorders. Furthermore, considering cellular damage, the role of protein-21 (p21) as a crucial element in cellular health maintenance might indicate another pathway modulated by VCR. It is important to highlight that the role of p21 has already been described as it is hyperexpressed by VCR in situations of Janus Kinase 2 (JAK2) inactivation and medulloblastoma cells. However, the isolated modulation of p21 expression by VCR is unknown (Cheon *et al.*, 2017a; Shinwari *et al.*, 2008). Therefore, given the neurotoxic potential provided by VCR, therapeutic alternatives that can minimize neurological effects are necessary.

7-Chloro-4-(phenylselanyl) quinoline (4-PSQ) exhibits broad therapeutic potential, particularly in pathologies involving neurological impairments such as Alzheimer's, anxiety, Parkinson's disease, cognitive decline, and chemotherapy-associated comorbidities in animal models (Barth *et al.*, 2019b; de Freitas Couto *et al.*, 2019b; de Oliveira *et al.*, 2022b; Paltian *et al.*, 2020b, 2022b; Pinz *et al.*, 2018b; Reis *et al.*, 2017a, 2020d). Its pharmacological properties, including antioxidant and anti-inflammatory capacities, neuroplasticity promotion, and modulation of glutamatergic, GABAergic, nitroergic, and serotonergic pathways,

are noteworthy (Paltian et al., 2020b; Silva et al., 2017; Vogt et al., 2018b). Specifically, its serotonergic modulation through 5-HT_{1A/1B} and 5-HT_{2A/2C} receptors significantly alleviates anxiety-like and depression-like behaviors (Silva et al., 2017). Furthermore, 4-PSQ increases the expression of the cell adhesion molecule (NCAM), favoring neuroplasticity and learning and reversing cognitive problems (Barth et al., 2019b).

Considering the neurological impairment caused by VCR through pathways associated with neuroinflammation and oxidative damage, together with the neuroprotective potential of 4-PSQ reported by several studies, we hypothesize that VCR induces neurochemical changes correlated with emotional and cognitive damage. We propose that 4-PSQ, a multi-target molecule, has therapeutic potential to counteract the neurotoxic effects of VCR. Therefore, this study aimed to investigate VCR-induced neurotoxicity manifested through emotional and cognitive impairments, focusing on pathways involving NFκB, Na⁺, K⁺-ATPase, and p21 and evaluating the therapeutic efficacy of 4-PSQ.

2. Results

2.1. Behavior tests

2.1.1. Locomotor and exploratory abilities

As demonstrated in Fig. 1, no alterations were observed in the animals' locomotor and exploratory capacities. Administration of VCR, 4-PSQ, or the combination of VCR + 4-PSQ did not change the number of crossings of male (Fig. 1a) and female (Fig. 1c) mice, nor did it alter the number of rearings of male (Fig. 1b) and female (Fig. 1d) mice.

OPEN FIELD TEST

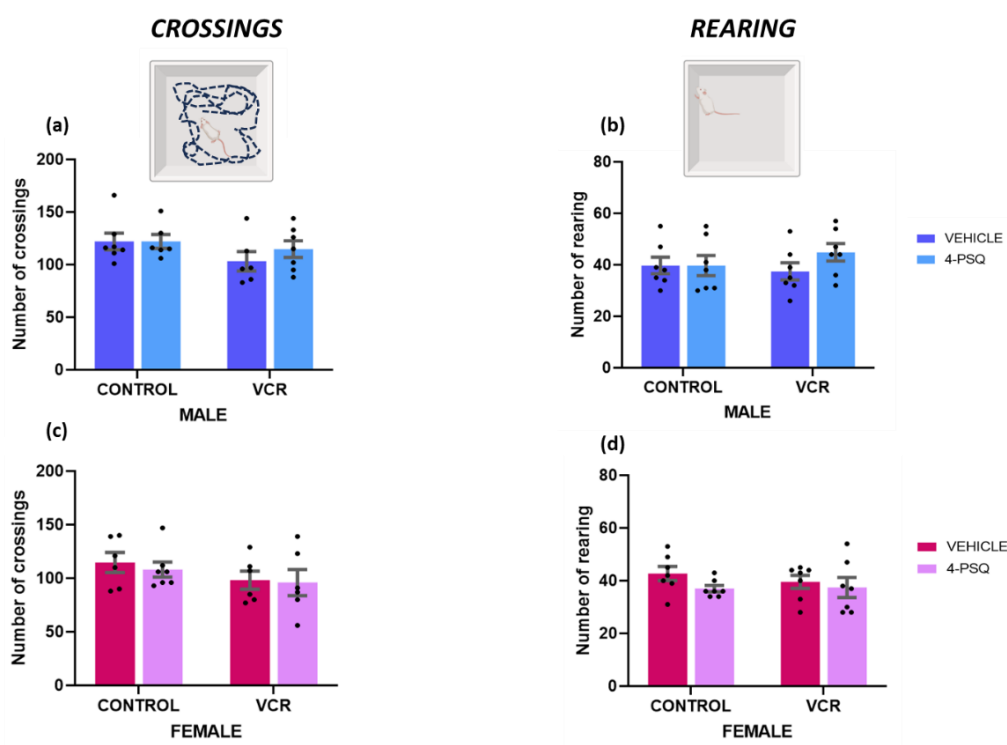


Fig. 1 - Effect of 7-chloro-4-(phenylselanyl) quinoline (4-PSQ) (1 mg.kg⁻¹, p.o.) and vincristine (VCR) (0.1 mg.kg⁻¹, i.p.) on the number of crossings of male (a) and female (c), and the number of rearings of male (b) and female (d) mice. Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 7 animals per group. Two-way ANOVA followed by Tukey's test was used.

2.1.2. Investigation of memory and cognition

Impairments in STM and LTM can characterize cognitive deficits. Damage to the central nervous system and exposure to neurotoxic drugs like VCR can hinder cognitive function. Training sessions were conducted with male (Fig. 2a) and female (Fig. 2d) mice to familiarize the animals with the testing apparatus. No significant differences were observed between the groups during training for the object recognition task. VCR induced decreased exploratory preference in the STM in male (Fig. 2b; 55%) and female (Fig. 2e; 48%) mice. Furthermore, LTM

was also compromised by the effects of VCR in male (Fig. 2c; 42%) and female (Fig. 2f; 48%) mice.

Therefore, treatment with the compound 4-PSQ restored the cognitive abilities impaired by VCR. The compound's therapeutic potential on the nervous system proved effective in reinstating STM and LTM in male and female mice subjected to VCR.

OBJECT RECOGNITION TEST

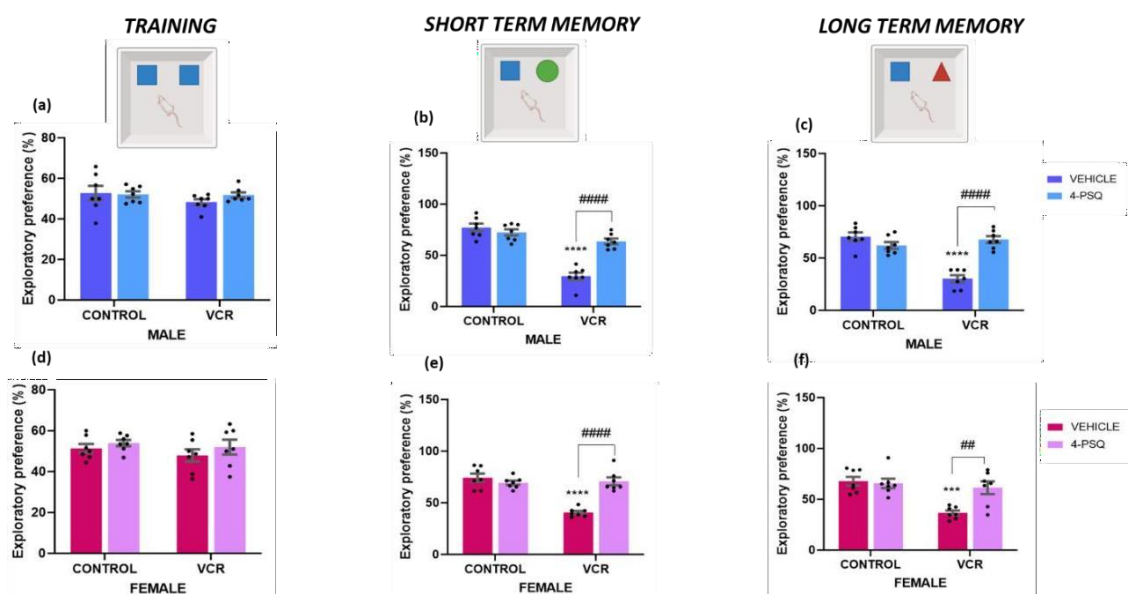


Fig. 2 - Effect of 7-chloro-4-(phenylselanyl) quinoline (4-PSQ) (1 mg.kg^{-1} , p.o.) and vincristine (VCR) (0.1 mg.kg^{-1} , i.p.) on training of male (a) and female (d) mice; in the short term memory of male (b) and female (e) mice and in the long-term memory of male (c) and female (f) mice in the object recognition task. Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 7 animals per group. (***) $P < 0.001$ and (****) $P < 0.0001$ denote significance levels when compared with the control group; (##) $P < 0.01$ and (####) $P < 0.0001$ denote significance levels compared with the VCR groups. Two-way ANOVA followed by Tukey's test was used.

2.1.3. Assessment of depressive-like behavior

Painful conditions are often linked to the onset of depression. In the tail suspension test, we examined the immobility response to a stressful situation (Fig. 3). VCR induced depressive-like behavior in male mice, indicated by a reduced latency time to immobility (Fig. 3a; 70%) and an increase in overall immobility (Fig. 3b; 97%). Similarly, female mice exposed to VCR exhibited depressive-like behavior, evident in reduced latency time to immobility (Fig. 3c; 53%) and heightened general immobility (Fig. 3d; 159%).

Typically, antidepressant medications demonstrate the ability to normalize changes in this test. 4-PSQ normalized depressive-like behavior in both male and female mice subjected to VCR. The antidepressant effect of 4-PSQ restored latency and general immobility in both genders following chemotherapy induction.

TAIL SUSPENSION TEST

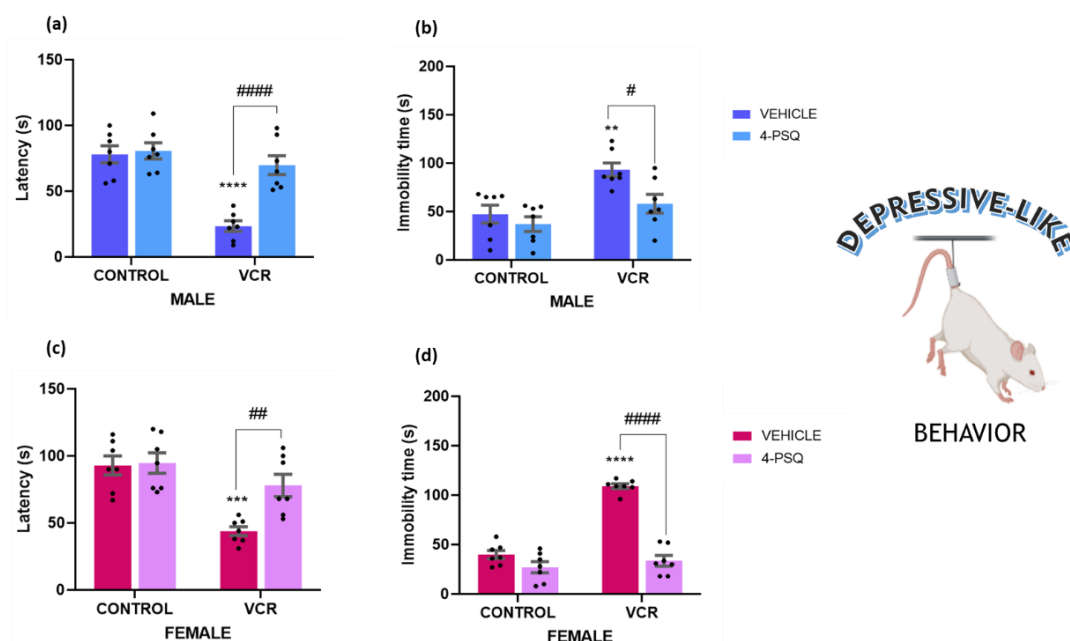


Fig. 3 - Effect of 7-chloro-4-(phenylselanyl) quinoline (4-PSQ) (1 mg.kg^{-1} , p.o.) and vincristine (VCR) (0.1 mg.kg^{-1} , i.p.) on male (a) and female (c) latency and immobility of male (b) and female (d) in the tail suspension test. Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 7 animals per group.

(**) $P < 0.01$; (***) $P < 0.001$ and (****) $P < 0.0001$ denote significance levels when compared with the control group; (#) $P < 0.05$; (##) $P < 0.01$ and (####) $P < 0.0001$ denote significance levels compared with the VCR groups. Two-way ANOVA followed by Tukey's test was used.

2.1.4. Assessment of anxious-like behavior

Anxiety-like behavior reflects emotional changes occurring at a psychological level. The elevated plus maze test is a well-established method for assessing rodent anxiety-like behavior. The VCR exposure resulted in emotional disturbances, as demonstrated in the elevated plus maze test conducted by male and female mice (Fig. 4). Among male mice, anxiety-like behavior induced by VCR was observed, indicated by the reduction in time spent in the open arms (Fig. 4a; 53%), fewer entries into the open arms (Fig. 4b; 30%), and a decrease in the number of dives (Fig. 4c; 68%). Similarly, female mice exposed to VCR exhibited reduced time spent in the open arms (Fig. 4d; 81%), fewer entries into the open arms (Fig. 4e; 67%), and a decreased number of dives (Fig. 4f; 54%).

The therapeutic effect of 4-PSQ restored the reduction in time spent in the open arms, the decrease in entries into the open arms, and the diminished number of dives caused by VCR. The potential anxiolytic effect of 4-PSQ was observed in male and female mice subjected to VCR induction.

ELEVATED PLUS MAZE TEST

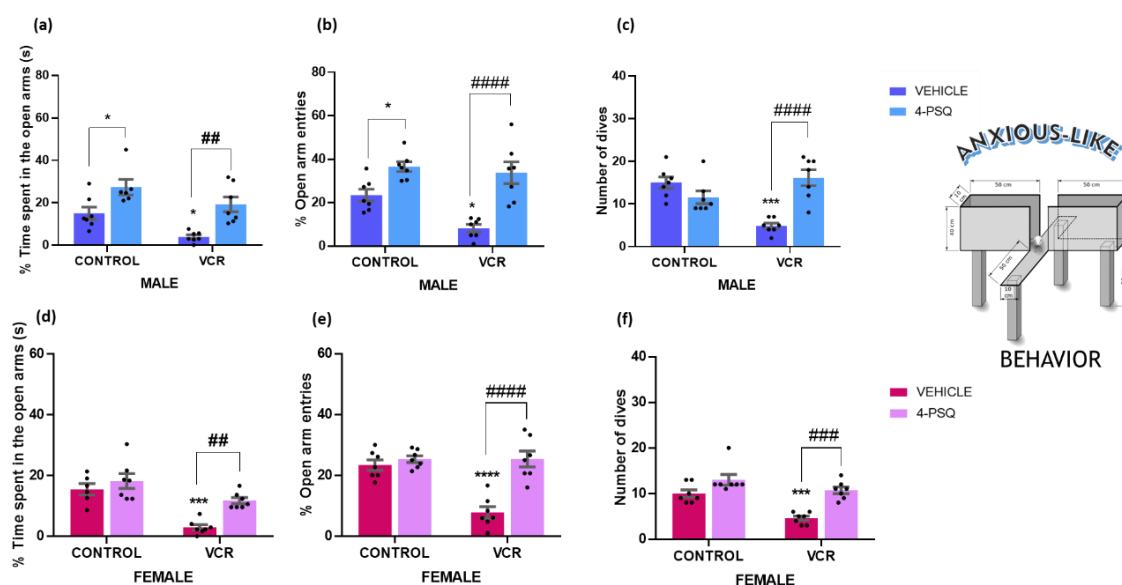


Fig. 4 - Effect of 7-chloro-4-(phenylselanyl) quinoline (4-PSQ) (1 mg.kg^{-1} , p.o.) and vincristine (VCR) (0.1 mg.kg^{-1} , i.p.) on time spent in open arms of male (a) and female (d) mice, entries into the open arms of male (b) and female (e) mice and dives of male (c) and female (f) mice in the elevated plus maze test. Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 7 animals per group. (*) $P < 0.05$, (***) $P < 0.001$ and (****) $P < 0.0001$ denote significance levels when compared with the control group; (##) $P < 0.01$; (###) $P < 0.001$ and (#####) $P < 0.0001$ denote significance levels compared with VCR groups. Two-way ANOVA followed by Tukey's test was used.

2.2. Biochemical Assays

2.2.1. Na^+ , K^+ - ATPase activity

Inhibition of the Na^+ , K^+ - ATPase enzyme activity is crucial in developing neurotoxicity induced by chemotherapy agents. In this context, the inhibitory potential of VCR on Na^+ , K^+ - ATPase activity is illustrated (Fig. 5). VCR effectively hindered Na^+ , K^+ - ATPase activity in the cerebral cortex (Fig. 5a, 78%), spinal

cord (Fig. 5b, 76%), and cerebellum (Fig. 5c, 56%) of male mice. Similarly, in female mice, VCR exerted inhibitory effects on Na^+ , K^+ - ATPase activity in the cerebral cortex (Fig. 5e, 47%), spinal cord (Fig. 5f, 46%), cerebellum (Fig. 5g, 51%), and hippocampus (Fig. 5h, 42%). Notably, no alterations were observed in the Na^+ , K^+ - ATPase activity in the hippocampus of male mice (Fig. 5d).

Conversely, 4-PSQ effectively counteracted the inhibition of Na^+ , K^+ - ATPase induced by VCR in the cerebral cortex, spinal cord, and cerebellum of male mice. In females, 4-PSQ normalized Na^+ , K^+ - ATPase activity solely in the cerebellum.

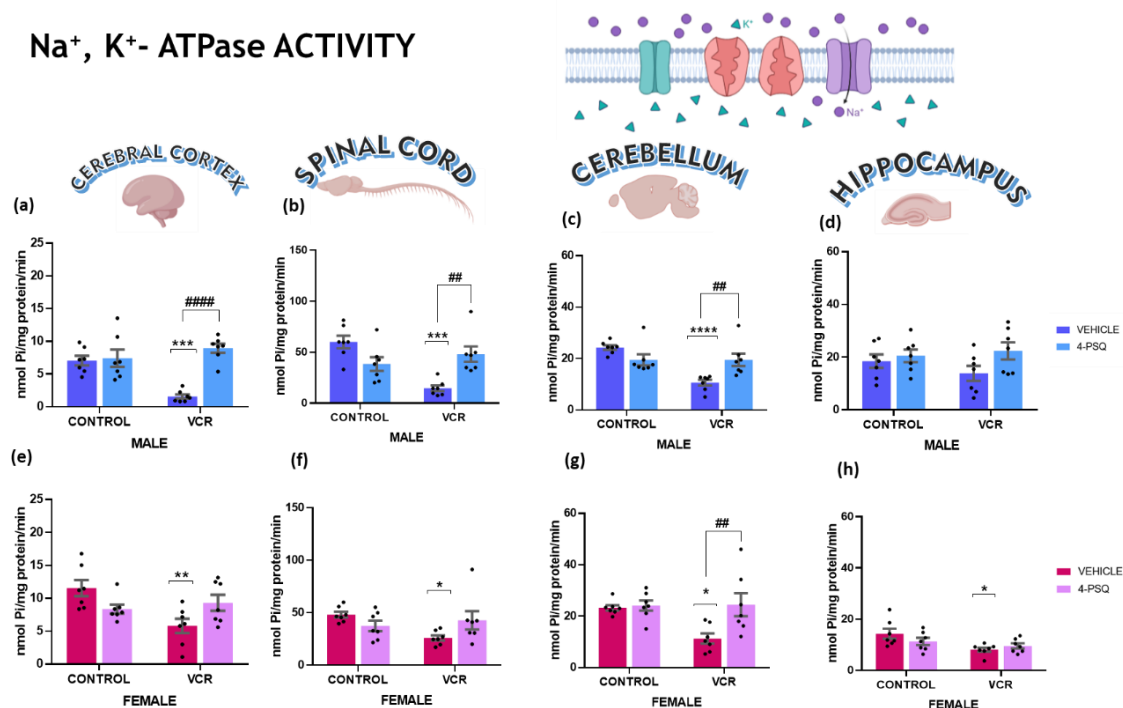


Fig. 5 - Effect of 7-chloro-4-(phenylselanyl) quinoline (4-PSQ) (1 mg.kg^{-1} , p.o.) and vincristine (VCR) (0.1 mg.kg^{-1} , i.p.) on Na^+ , K^+ - ATPase activity. Na^+ , K^+ - ATPase activity in the cerebral cortex of male (a) and female (e); in the spinal cord of male (b) and female (f); in the cerebellum of male (c) and female (g), and in the hippocampus of male (d) and female (h) mice. Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 7 animals per group. (*) $P < 0.05$, (**) $P <$

0.01, (***) $P < 0.001$, and (****) $P < 0.0001$ denote significance levels when compared with the control group. (##) $P < 0.01$ and (####) $P < 0.0001$ denotes significance levels compared with the VCR group. Two-way ANOVA followed by Tukey's test was used.

2.2.2. p21 mRNA expression levels

The p21, when altered, induces a phenotypic response related to changes in the cell cycle and can cause cellular damage from this deregulation. The gene expression of p21 was demonstrated in Fig. 6. The experimental data indicated that VCR increased the expression of p21 only in the cerebral cortex of female mice (Fig 6b, 50%). When VCR induced an increase in p21 expression, the compound 4-PSQ was able to normalize it. VCR and 4-PSQ did not affect p21 expression in the cerebral cortex and spinal cord of male mice nor in the spinal cord of female mice (Fig 6a, 6c, and 6d).

Levels of p21 mRNA expression

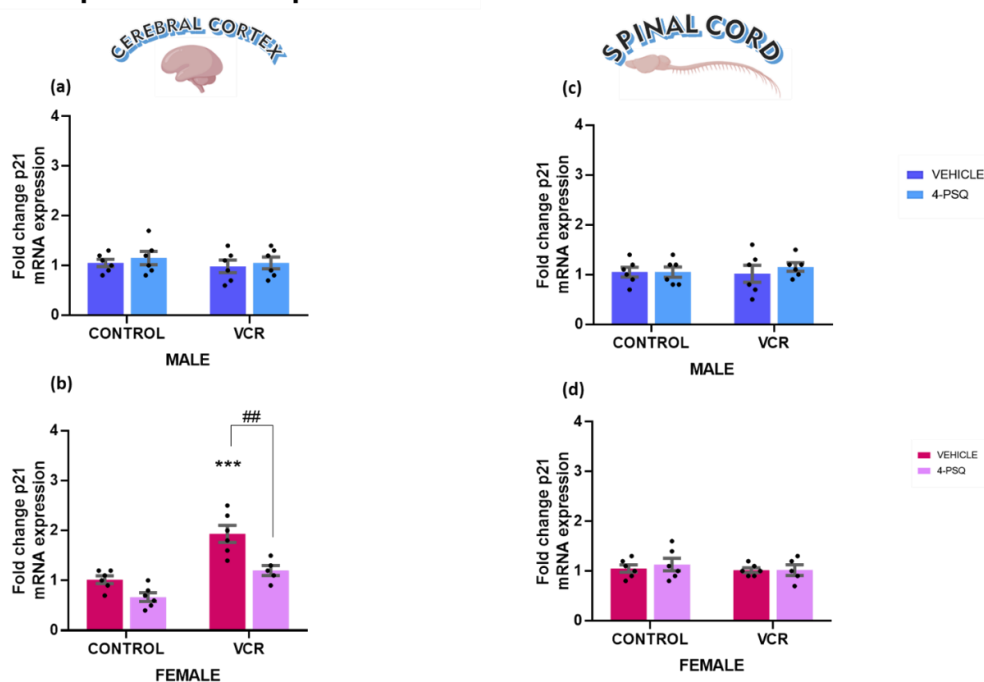


Fig. 6 - Effect of 7-chloro-4-(phenylselanyl) quinoline (4-PSQ) (1 mg.kg⁻¹, p.o.) and vincristine (VCR) (0.1 mg.kg⁻¹, i.p.) on protein 21 (p21) mRNA expression levels. The p21 gene expression in the cerebral cortex of male (a) and female (b); and in the spinal cord of male (c) and female (d) mice. Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 6 animals per group. (***) P < 0.001 denotes significance levels compared with the control group. (##) P < 0.01 denotes significance levels compared with the VCR group. Two-way ANOVA followed by Tukey's test was used.

2.2.2.1. NF κ B mRNA expression levels

Signaling through NF κ B is associated with neuroinflammation, activation of apoptosis pathways, impairing memory, and leading to emotional damage. The NF κ B gene expression observed in this study is demonstrated in Fig. 7. Our data demonstrated that VCR administration led to increased NF κ B gene expression in the cerebral cortex of male (Fig. 7a; 36%) and female (Fig. 7b; 42%) mice, and in the spinal cord of male (Fig. 7c; 57%) and female (Fig. 7d; 64%) mice. 4-PSQ regulated this gene expression, normalizing NF κ B to control levels in the cerebral cortex of males and the spinal cord of male and female mice.

Levels of NFκB mRNA expression

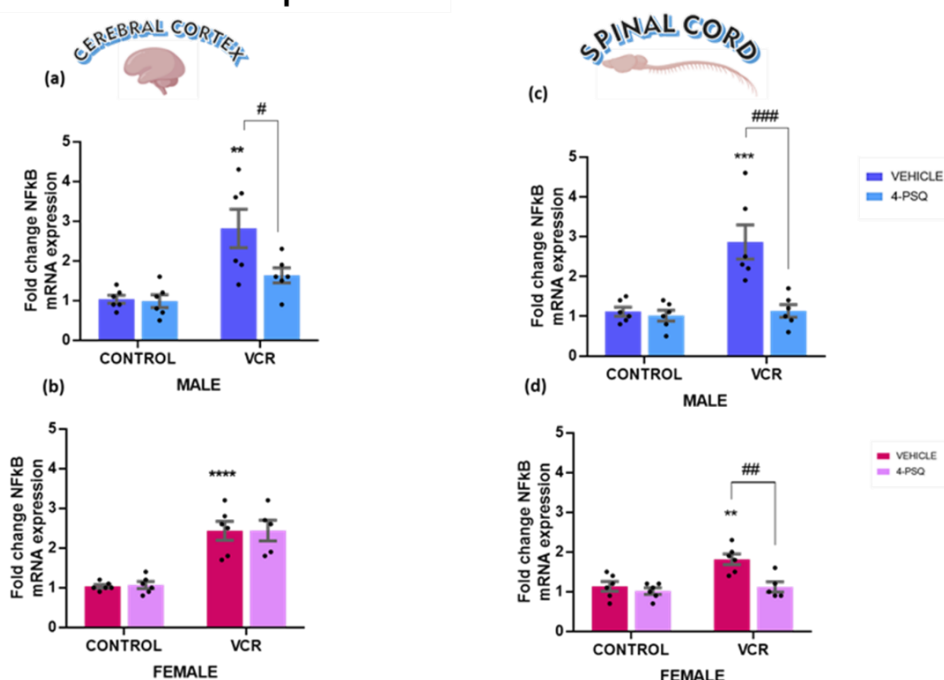


Fig. 7 - Effect of 7-chloro-4-(phenylselanyl) quinoline (4-PSQ) (1 mg.kg^{-1} , p.o.) and vincristine (VCR) (0.1 mg.kg^{-1} , i.p.) on levels of mRNA expression of nuclear factor kappa B (NFκB). NFκB gene expression in the cerebral cortex of male (a) and female (b), and in the spinal cord of male (c) and female (d) mice. Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 6 animals per group. (**) $P < 0.01$, (***) $P < 0.001$, and (****) $P < 0.0001$ denote significance levels compared with the control group. (#) $P < 0.05$, (##) $P < 0.01$, and (###) $P < 0.001$ denote significance levels compared with the VCR groups. Two-way ANOVA followed by Tukey's test was used.

2.3. Correlation between cerebral cortex analysis and behaviors

The heat graph (Fig. 8) demonstrates the correlation between tests and presents the correlation coefficient (r) of male (Fig. 8a) and female (Fig. 8b) mice. Values between $0.7 \leq r \leq 1$ were considered closest to a perfect positive correlation. Values between $-1 \leq r \leq -0.7$ were considered closer to a perfect negative correlation.

CORRELATION BETWEEN CEREBRAL CORTEX ANALYSIS AND BEHAVIORS

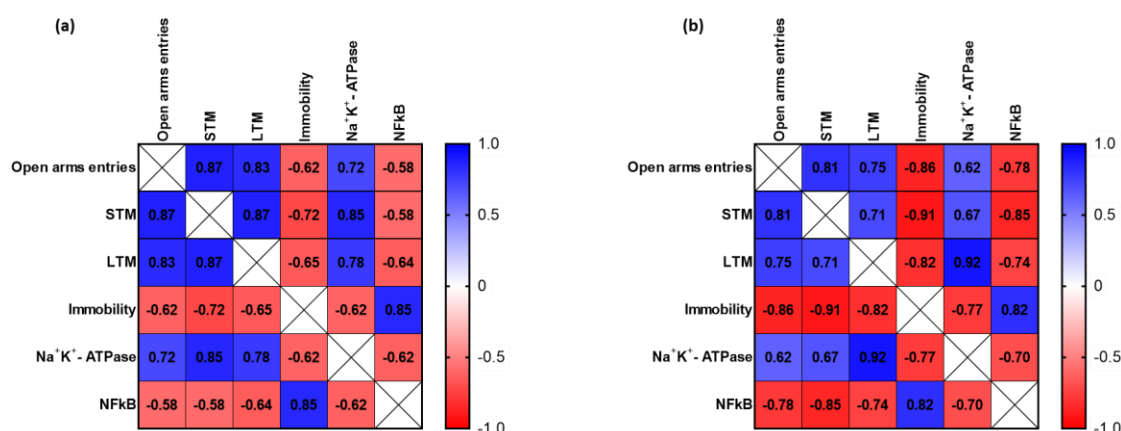


Fig. 8 - Correlation between emotional and cognitive behaviors with biochemical analyses in the cerebral cortex of male (a) and female (b) mice. Pearson's correlation coefficient (r) was indicated within the quadrants. Values of $r \cong 1$ indicate a positive correlation between the variables. Values of $r \cong -1$ indicate a negative correlation between the two variables. Exploratory preference for new objects was used as a parameter collected in the object recognition task to assess short-term (STM) and long-term (LTM) memory; the number of entries into the open arms was used as a measure of anxiety-like behavior in the elevated plus maze test, and immobility was used as a parameter in the tail suspension test.

In male mice, there was a positive correlation between the decrease in the exploratory preference of STM and LTM. There was also a positive correlation between the decrease in entries into the open arms and the reduction in exploratory preference (in STM and LTM). At the same time, inhibition of Na⁺, K⁺ - ATPase activity showed a positive correlation with the reduction in exploratory preference in STM and LTM. The inhibition of Na⁺, K⁺ - ATPase activity also positively correlated with reducing the number of entries into the open arms. The increase in immobility time showed a positive correlation with the increase in

NFκB mRNA expression. Still, in male mice, there was a negative correlation between the decrease in exploratory preference in the STM and the increase in general immobility time (indicating that the decrease in preference for the new object is related to the increase in general immobility). Table 1 (Supplementary material) presents P values demonstrating statistical significance for male mice.

Likewise, in female mice, statistical analysis demonstrated a positive correlation between the decrease in exploratory preference in STM and the decrease in exploratory preference in LTM. The reduction in exploratory preference in STM and LTM also showed a positive correlation with decreased entries into open arms. Inhibition of Na⁺ K⁺-ATPase positively correlates with decreased exploratory preference in LTM. Furthermore, increased NFκB expression was positively correlated with increased overall immobility time. A negative correlation was observed in the decrease in exploratory preference (both in STM and LTM) with the increase in general immobility; also, there was a negative correlation between the increase in the number of entries into the open arms and the increase in immobility. In parallel, increased expression of NFκB negatively correlated with a decrease in exploratory preference (in LTM and STM) and an increase in the number of entries into open arms.

The correlation coefficient also indicates a greater appeal for a correlation between the inhibition of the enzyme Na⁺, K⁺ -ATPase, and behavioral changes in male mice. At the same time, the increase in NFκB expression has a greater correlation with changes that can favor cognitive and emotional impairments in females. Table 2 (Supplementary material) presents P values that demonstrate the statistical significance for female mice.

3. Discussion

In this study, we observed for the first time the role of NF κ B signaling, p21 expression, and Na⁺, K⁺-ATPase activity in the development of emotional changes and cognitive deficits caused by VCR. Our findings indicate that VCR leads to cognitive and emotional disorders in male and female mice. We hypothesize that VCR inhibits Na⁺, K⁺-ATPase activity, promoting changes in neuronal depolarization, which results in cognitive deficits and emotional disturbances. Additionally, increased NF κ B expression suggests activation of neuroinflammatory and apoptotic pathways in VCR-exposed animals. The exclusive increase of p21 expression in the cerebral cortex of female mice may indicate greater impairment in emotional and cognitive processing, particularly in short-term memory. Notably, the selenium compound 4-PSQ reversed all the cognitive and emotional changes induced by VCR, suggesting its potential as a neuroprotective agent against VCR-induced neurotoxicity.

Chemotherapy-related cognitive decline, or "chemo-brain," affects 17-75% of patients, manifesting as memory impairment and cognitive dysfunction (Eide; Feng, 2020; Turcu-Stiolica *et al.*, 2022). In our study, VCR impaired short- and long-term memories in male and female mice, corroborating its neurotoxic effects. VCR-induced neurological damage leads to axonal degeneration and dysfunction in astrocytes, microglia, and neurons (Meléndez *et al.*, 2020). Our data support the hypothesis that VCR-induced cognitive impairments are linked to inhibiting Na⁺, K⁺-ATPase activity, and increased NF κ B expression. Memory consolidation, dependent on synaptic function, is altered by VCR (Magee; Grienberger, 2020a; Xu *et al.*, 2017a). Na⁺, K⁺-ATPase, crucial for synaptic functioning, is inhibited by VCR, preventing axonal depolarization, potentially due to reduced ATP affinity under oxidative stress conditions (Canta; Pozzi; Carozzi, 2015a; Joseph; Levine,

2006; Liu; Lilly; Shapiro, 2018a).

Our experimental data indicates that the VCR inhibits the Na^+ , K^+ pump, preventing axonal depolarization, which may be associated with the low affinity of ATP in these cells to provide the nerve impulse. The α and β subunits of Na^+ , K^+ - ATPase comprise around 24 thiols that are extremely sensitive to oxidative stress as they are targets of free radicals, and the VCR may also be interfering with the enzyme's activity due to oxidative stress (Cassol *et al.*, 2022a; Isaksen; Lykke-Hartmann, 2016a).

Furthermore, it has been hypothesized that in the cerebral cortex, where Na^+ , K^+ -ATPase activity is inhibited, explicit memory of visual stimuli reestablishes perceptual representations in visual areas (Steel *et al.*, 2021). The object recognition test is carried out with the rodent needing to explore new objects based on the experience of remembering the old object already explored (Gauthier; Tarr, 2016). Therefore, inhibited Na^+ , K^+ - ATPase activity can prevent the neurochemical perception of memories in the face of visual stimuli (Cassol *et al.*, 2022a).

The hippocampus, essential for spatial memory and the transition of short-term to long-term memory (Sekeres; Winocur; Moscovitch, 2018; Zhao, B. *et al.*, 2017), showed no alteration in Na^+ , K^+ -ATPase activity in male mice. Therefore, the impairment in Na^+ , K^+ - ATPase activity not caused in the hippocampus of male mice indicates that STM is not processed in the long term by the hippocampus through evocation by signal transduction initiated by the Na^+ , K^+ pump. In female mice, a hypothesis can be raised that VCR causes the inhibition of Na^+ , K^+ - ATPase and thus leads to damage in the transformation of STM through object recognition into LTM. Therefore, we can infer that the exposure of

male mice to VCR leads to impairment of memory consolidation through other pathways that are not dependent on Na^+ , K^+ - ATPase. One of the routes that may explain cognitive impairment is the increased expression of NF κ B in all tissues observed in our study.

Correlation analysis demonstrated the inhibition of Na^+ , K^+ - ATPase in the cerebral cortex as a mechanism directly related to emotional impairments (anxiety and depression) and cognitive deficits. It should be noted that this seems to be a mechanism more associated with damage to the central nervous system (CNS) of male mice. In other words, our correlation analysis reinforces this as a mechanism strongly affected by VCR. Male mice may be more susceptible to synaptic changes due to inhibiting the Na^+ , K^+ -ATPase enzyme. The cause of this action may be due to oxidative stress or directly influenced by the action of VCR by penetrating the blood-brain barrier (Mojarad-Jabali *et al.*, 2022; Wang *et al.*, 2010). However, it is postulated that the inhibition of Na^+ , K^+ -ATPase may be derived from the consolidation of oxidative stress since the increase in NF κ B expression may also occur as a result of this (Jin; Leng, 2023; Liu *et al.*, 2017a).

The general activity of Na^+ , K^+ - ATPase is crucial for multiple cellular functions, including maintaining resting membrane potential, regulating cell volume and pH, and driving secondary active transport, all linked to anxiety and depression (Dobretsov, 2005a). The $\alpha 2$ subunit specifically relates to emotional changes such as fear, anxiety, compulsivity, and hypoactivity (Isaksen; Lykke-Hartmann, 2016a). Excess extracellular K^+ and glutamate during intense neuronal activity, if not efficiently removed by astrocytes, can lead to widespread depolarization, depressing neuronal firing, and neurotransmitter release, contributing to depressive and anxiety-like behaviors (Lauritzen *et al.*, 2011a;

Pietrobon; Moskowitz, 2013a). Therefore, these studies corroborate the contributing role of Na^+ , K^+ - ATPase for the development of anxiety and depression in neurotoxic conditions, such as those induced by VCR.

NF κ B signaling is an alert for pathogenic and cellular danger signals, with a potential relationship between neuronal excitability processes and NF κ B accumulation (Albensi, 2019a; Kaltschmidt; Kaltschmidt, 2015). In other words, there may be a relationship between the inhibition of Na^+ , K^+ - ATPase, and the increase in NF κ B expression. Davis et al. (2005) reported that the inflammatory process, through the increase in nitric oxide (NO), can inhibit nuclear translocation and favor the accumulation of factors such as NF κ B. Inhibition of NF κ B translocation may reduce DNA binding capacity, which may inhibit nervous system excitability (Horie; Ma; Umezawa, 2015; Kanzaki *et al.*, 2021). Our analysis showed an inverse relationship between NF κ B and Na^+ , K^+ -ATPase, indicating that increased NF κ B expression typically accompanies decreased Na^+ , K^+ -ATPase activity.

The inflammatory process caused by NF κ B can initially promote the hyperproduction of pro-inflammatory cytokines, during the activation of inflammatory cascades, which can favor the formation of NO, generating the accumulation of NF κ B and impairing the nuclear translocation of this factor (Zheng *et al.*, 2023a). NF κ B accumulation can affect the immune response through changes in T cells, B cells, and dendritic cells (Mussbacher *et al.*, 2023a). Furthermore, the accumulation of NF κ B can promote abnormal cell survival, favoring uncontrolled cellular nutrition, which needs attention since dysfunctional cells will remain functioning (Albensi, 2019a). This point is in line with the results observed in this study by evaluating p21 expression. p21 acts as an inhibitor of

cyclin-dependent kinases (CDK), enzymes responsible for controlling the cell cycle. Since p21 was not altered by VCR in the cerebral cortex of males and in the spinal cord of male and female mice, it is likely that VCR (via NFκB) may not be acting as an inhibitor of CDKs. However, it is noteworthy that in the cerebral cortex of female mice, VCR increases p21 expression levels, indicating that NFκB may accumulate more in this tissue and influence neuroinflammation and abnormal cellular maintenance.

NFκB was also correlated with depressive-like and anxious-like behavior and cognitive impairment induced by VCR exposure. Mood disorders are characterized by decreased neurogenesis, alteration of synaptic structure, and synaptic transmission where NFκB acts (Caviedes *et al.*, 2017a; Li, W. *et al.*, 2021). Clarification about the potential of VCR to promote these comorbidities has not been indicated. Given these data, we found that NFκB is a key pathway for the emotional damage related to depression and anxiety that can be caused by VCR.

In the CNS, NFκB regulates learning and memory. The localization of NFκB in synaptosomes suggests a function of NFκB as a retrograde messenger (Kaltschmidt; Kaltschmidt, 2015; Meffert *et al.*, 2003). This mechanism may lead to the loss of axonal transport, already described as a target of the neurotoxic action of VCR (Starobova; Vetter, 2017b). Therefore, the accentuated expression of NFκB may be associated with cognitive loss in STM and LTM and promotion of axonal damage by VCR.

Concerning emotional damage, it is reported that the dysregulation of NFκB levels may be involved in the depression process. An example of this is the hyperacetylation of NFκB-p65, capable of inducing the positive regulation of the

metabotropic glutamate receptor mGlu2, an important target for the action of antidepressant drugs (Chiechio *et al.*, 2002; Law *et al.*, 2008). VCR in this context, through these common pathways, Na⁺, K⁺-ATPase/NFκB, can lead to emotional and cognitive dysregulation, promoting significant losses in male and female mice.

Regarding the effectiveness of 4-PSQ in reversing cognitive deficits and emotional losses, we can verify some key points in which the molecule may be helping therapeutically. One of the main points that are possibly linked to the neuroprotective potential of 4-PSQ is the anti-inflammatory property, which has been previously described and can be used to combat the neurotoxic action of VCR (de Oliveira *et al.*, 2022b; Paltian *et al.*, 2022b; Pinz *et al.*, 2016b; Silva *et al.*, 2017). We infer that 4-PSQ may be acting as a mediator to combat neuroinflammation, since this mechanism of 4-PSQ has already been reported as one of the main pharmacological targets of the compound, reducing the expression of inflammatory mediators (Paltian *et al.*, 2020b, 2022b). Furthermore, NFκB promotes the expression of pro-inflammatory cytokines such as interleukins (IL-33, IL-18, IL-1b), which can also be reversed by treatment with 4-PSQ (de Oliveira *et al.*, 2022b). This mechanism of anti-inflammatory 4-PSQ can be considered important for the reversal of cognitive impairment and depressive-like and anxiety-like behavior caused by VCR (de Oliveira *et al.*, 2022b; Rodrigues *et al.*, 2021a). Furthermore, in a study involving restraint stress, 4-PSQ normalized the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT) pathway, which is activated by neuroinflammatory processes that lead to neuronal dysregulation, impairing neuronal survival and neuroplasticity (de Oliveira *et al.*, 2022b).

Neuroplasticity is a function that is directly affected by neurotoxic agents, and that impairs memory recall. In this sense, VCR possibly led to losses in neuroplasticity, which may have promoted memory loss. Also, by regulating Na^+ , K^+ - ATPase, 4-PSQ can modulate neuronal excitability and regulate synapses, assisting in neuroplasticity and learning new memories (Barth *et al.*, 2019b; Rodrigues *et al.*, 2021a). 4-PSQ regulated Na^+ , K^+ - ATPase in models of anxiety, Alzheimer's, and peripheral neuropathy caused by oxaliplatin and paclitaxel (de Oliveira *et al.*, 2022b; Paltian *et al.*, 2020b, 2022b; Pinz *et al.*, 2018b; Reis *et al.*, 2020d).

Regarding the comparison of mechanisms between the sexes, our findings demonstrate equal development of psychiatric disorders (anxiety and depression), as well as cognitive deficits between male and female mice. In other words, there was no disparity in susceptibility to developing the emotional and cognitive behaviors assessed. However, we verified p21 as a specific and modified mechanism only in female mice exposed to VCR. Indeed, the relationship between p21 and progesterone, a female hormone, has already been reported (Kim *et al.*, 2013a). Progesterone regulates p21-activated kinase 4 (Pak4), which in pathological situations can cause the activation of inflammatory cascades, indicating a possible neuroinflammatory mechanism unique to female mice (Kim *et al.*, 2013a).

4. Conclusions

Our experimental data demonstrate, for the first time, the correlation between increased NF κ B expression and inhibition of Na^+ , K^+ - ATPase activity as a key mechanism for developing neurological damage promoted by VCR.

Furthermore, we are pioneers in assessing emotional damage caused by VCR. Our significant results reinforce the importance of clarifying the damage caused by VCR since it is expected to increase life expectancy in cancer survivors. We further propose 4-PSQ as an innovative molecule with relevant neuroprotective results capable of mitigating depressive, anxious, and memory-impairing behaviors in male and female mice.

5. Materials and Methods

5.2. Animals

The experiments used male and female *Swiss* mice (60 days). The animals were housed with free access to standard chow and water; humidity (20 - 80%) and temperature ($22\pm 2^{\circ}\text{C}$) were controlled respecting the rodents' light/dark cycle (12h/12h). All experiments were carried out following the Committee for the Care and Use of Experimental Animal Resources guidelines of the Federal University of Pelotas, Brazil (CEEAA 4506–2017).

5.3. Drugs

The compound 4-PSQ (Fig. 9) was synthesized and characterized by the Clean Organic Synthesis Laboratory (LASOL) of the Federal University of Pelotas. The chemical structure was characterized through nuclear magnetic resonance analysis (^1H and ^{13}C). The purity percentage of the compound 4-PSQ was verified by gas chromatography coupled with mass spectrometry (GC-MS), indicating 99.9% purity in the molecule (Duarte et al., 2017; Savegnago et al., 2013). VCR chemotherapeutic was purchased as sulfate from INTAS pharmaceuticals® (Batch: M2103904) and allocated at 4°C .

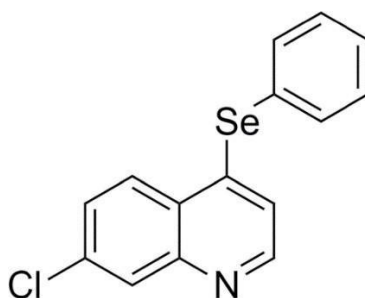


Fig. 9 - Chemical structure of 7-chloro-4-(phenylselanyl) quinoline (4-PSQ).

Due to its liposoluble property, 4-PSQ was prepared at 1 mg.kg⁻¹ in canola oil (10 mg.ml⁻¹; orally with gavage (p.o.)). The VCR was prepared at 0.1 mg/kg⁻¹ in 0.9% saline solution (10 mg.ml⁻¹; intraperitoneal (i.p.)) according to the recommended preparation method (Moschetti *et al.*, 2019b). All other reagents used in this study to perform biochemical techniques had analytical grades and were obtained from Sigma-Aldrich (St. Louis, MO, USA).

5.4. Experimental design

This study sought to investigate emotional and cognitive changes associated with VCR induction and the therapeutic potential of 4-PSQ. Subsequently, biochemical analyses were carried out to elucidate possible mechanisms related to the development of depressive-like, anxiety-like behavior and cognitive deficits in male and/or female mice.

Male and female Swiss mice were divided into four experimental groups: I) Control, II) VCR, III) 4-PSQ, and IV) VCR + 4-PSQ. VCR induction occurred from the experimental protocol's 1st to the 5th day. Groups II and IV of males and females received five injections of VCR (0.1 mg.ml⁻¹, i.p.). Groups I and III received 0.9% saline solution (10 ml.kg⁻¹; i.p.). From the 7th to the 16th day, the mice received treatment with the compound 4-PSQ or its vehicle. Groups III and IV received 4-PSQ (1 mg.kg⁻¹; p.o.); while groups I and II received the canola oil vehicle (10 ml.kg⁻¹; p.o.).

On days 12 and 13, the locomotor and exploratory capacities of the animals were observed, followed by cognitive assessment in the object recognition test. On day 14, depressive-like behavior was evaluated by the tail suspension test. On day 15, anxiety-like behavior was verified using the elevated plus maze test. Finally, on day 17 of the experimental protocol, all animals were euthanized, and brain structures were removed for biochemical analyses. The experimental design was summarized graphically in Fig. 10.

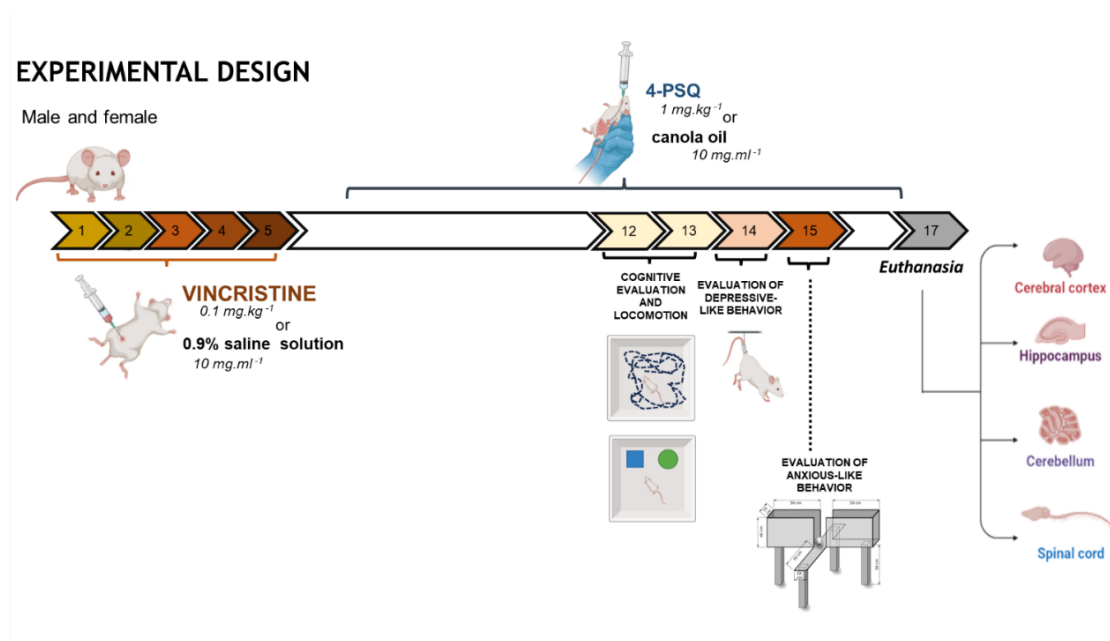


Fig. 10 - Experimental design scheme.

5.5. Behavior tests

5.5.1. Locomotor and exploratory abilities

On the 12th day of the experimental protocol, the open field test was conducted following the procedure described by Walsh and Cummins (1976). The open field apparatus, constructed from plywood, had walls 30 cm high. The floor of the open field measured 45 cm in length and 45 cm in width and was divided into 9 squares using masking tape markers (arranged in 3 rows of 3). During the test, each animal was placed at the center of the open field and

observed for 4 minutes to record their locomotion (the number of segments crossed with all four paws) and exploration (the number of times they reared with their hind limbs). After completing the test, the animals were allowed an additional 1 minute to adapt to the object recognition task. The locomotion data were expressed as the number of crossings, while the exploration data were described as the number of rearing.

5.5.2. Memory and cognition evaluation

The object recognition task was carried out on the 12th and 13th days of the experimental protocol, following the method previously described by Stangherlin et al. (Stangherlin; Rocha; Nogueira, 2009). This behavioral test is commonly used to assess animals' short-term memory (STM) and long-term memory (LTM).

After the habituation, the mice went through a training session. Each mouse was placed individually in the testing area with two identical objects, A1 and A2, for 5 minutes. The exploration was recorded when the mouse directed its nose within approximately 2 cm of the object, engaging in activities such as sniffing, touching, or looking at it. To assess STM, 1.5 hours after the training session, the mice were presented with a familiar object (A1) and a novel object (B). The exploration time was 5 minutes to measure learning and recognition memory.

Subsequently, LTM was evaluated 24 hours after the training session. The mice were allowed to explore a familiar object (A1) and a novel object (C) for 5 minutes, and the time spent exploring each object was recorded. The objects used in the experiment were positioned symmetrically within the testing area. Objects A1 and A2 were identical balls; object B was a cube, and object C was a

cylinder. These objects were made of plastic and measured 10 × 10 cm (length × height) with distinct color patterns (blue, red, and yellow). Between each trial, the arena and objects were cleaned with 30% ethanol to remove residues and odors. The data obtained from the experiment were expressed as percentages of exploratory preference, calculated as follows:

$$\text{Training: } (A2 / (A1 + A2)) \times 100$$

$$\text{STM: } (B / (A1 + B)) \times 100$$

$$\text{LTM: } (C / (A1 + C)) \times 100$$

5.5.3. Assessment of depressive-like behavior

The tail suspension test was conducted as described by Steru et al. (1985) on day 14 of the experimental protocol. The mice were suspended 50 cm above the ground by an adhesive tape placed approximately 1 cm from the tip of the animal's tail. Two parameters were evaluated during the behavioral test to assess the depressive-like response: the latency time (first episode of immobility) and the general immobility time. The test lasted 6 minutes in total. Mice were considered immobile only when passively hung and completely immobilized. Latency time and general immobility were recorded in the unit of seconds.

5.5.4. Assessment of anxious-like behavior

On the 15th day of the experimental protocol, the elevated plus maze test (EPM) was performed to measure rodent anxiety-like behavior, following the procedure described by Pellow et al. (1985). The EPM apparatus consisted of two open arms (16 × 5 cm) and two closed arms (16 × 5 × 10 cm) arranged at a 90° angle, all connected to a central platform (5 × 5 cm) elevated 50 cm from the floor. Each animal was individually placed in the maze's center, facing one of the open arms.

During a 5-minute session, the frequency of entries into the open and closed arms, the time spent in the open arm, and the number of head dips (leaning towards the edge) were recorded. The data were expressed as a percentage of entries (using all four paws) and time spent in the open arms relative to the total number of entries and time spent in both open and closed arms, respectively. The number of entries into the closed arms was also documented.

5.6. Biochemical Assays

Biochemical tests were carried out to investigate the mechanisms altered by VCR that led to the development of depressive-like and anxiety-like behaviors, as well as cognitive deficits. Here, the mechanistic action of VCR and 4-PSQ in relation to sex-dependent changes was observed to elucidate the possible predisposition to comorbidities among males and/or females.

We verified enzymatic damage to Na^+ , K^+ - ATPase, which can promote damage to neurochemical signaling and thus cause cognitive and emotional damage. The nervous system structures examined for oxidative damage and changes in Na^+ , K^+ - ATPase were the cerebral cortex, spinal cord, cerebellum, and hippocampus. Furthermore, the expression of NF κ B and p21 investigated damage to the cell cycle and promotion of the neuroinflammatory response in the cerebral cortex and spinal cord. The other structures (cerebellum and hippocampus) were not used for gene expression analysis because the sample volume was very low and did not meet the sample RNA extraction minimal requirements (<50 mg).

5.6.1. Tissue preparation

On the day of euthanasia, samples of the cerebral cortex, spinal cord,

cerebellum, and hippocampus were dissected. After separating the tissues, the samples were frozen and stored in an ultra-freezer (-80°C). For the biochemical assays, the samples were homogenized in a 50 mM Tris-HCl buffer with pH 7.4 and centrifuged at $900 \times g$ for 10 minutes to obtain the supernatant (S1).

5.6.2. Protein quantification

Protein concentration was determined spectrophotometrically at 595 nm using the Bradford method (1976a), with bovine serum albumin as a standard. The reaction mixture comprised S1 (50 μ L) and Coomassie Brilliant Blue (2.5 mL). It was incubated for 10 minutes. The protein level was expressed in milligrams of protein per milliliter and used for various biochemical analyses.

5.6.3. Na⁺, K⁺ - ATPase activity

To evaluate the activity of the Na⁺, K⁺ - ATPase enzyme, the system was prepared with 3 mM MgCl₂, 125 mM NaCl, 20 mM KCl, and 50 mM Tris/HCl (pH 7.4), along with an aliquot of S1, resulting in a final volume of 500 μ L. The reaction was initiated by adding ATP to a final concentration of 3.0 mM. Control samples were prepared under the same conditions but with the addition of 0.1 mM ouabain, a Na⁺, K⁺ pump inhibitor. Reactions were started by adding adenosine triphosphate (ATP) and stopped after 30 minutes of incubation by adding 10% trichloroacetic acid (TCA). The samples were further incubated at 37 °C for 30 minutes, and the incubation was halted by adding 10% TCA with 10 mM HgCl₂. Enzyme activity was calculated by measuring the difference in inorganic phosphate (Pi) levels between incubations performed in the absence and presence of ouabain.

The quantification of inorganic phosphate (Pi) released by ATPase enzymes was assessed using the method described by Fiske and Subbarow

(1925). Colorimetric reactions were analyzed spectrophotometrically at 650 nm. The results were expressed in nmol Pi/mg protein/min.

5.6.4. RNA Extraction and Quantitative RT-PCR

To evaluate the expression of p21 and NFκB, real-time RT-qPCR was performed. Total RNA was isolated from cerebral cortical and spinal cord clusters (n = 6) using TRIzol reagent (Invitrogen, Carlsbad, CA). The concentration and purity of the RNA were determined spectrophotometrically at a ratio of 260/280. Then, 1 µg of total RNA was reverse transcribed using the Applied Biosystems™ High Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA) in a 20 µL reaction according to the manufacturer's instructions. Real-time RT-qPCR quantified p21, NFκB, and β-actin mRNA levels and was performed in duplicate using the Applied Biosystems QuantiStudio 1. Non-template controls were used in each assay, producing no detectable signal during 40 amplification cycles. Target mRNA levels were normalized to β-actin levels using the $2^{-\Delta\Delta Ct}$ method (Livak; Schmittgen, 2001b).

5.7. Statistical analysis

The normality of the data was assessed using the Shapiro-Wilk normality test. Statistical analysis was conducted using GraphPad Prism 7.0 software (San Diego, CA, USA). No outliers were identified. Two-way ANOVA followed by Tukey's multiple comparisons test was employed for statistical analysis. Data were presented as mean ± standard error of the mean (S.E.M.). Statistical significance was defined as $P < 0.05$.

Pearson's correlation analysis was used to statistically verify the relationship between the development of depressive-like and anxious-like behaviors and cognitive deficit with changes in NFκB gene expression and Na⁺,

K⁺ - ATPase activity. The data chosen for statistical correlation analysis referred to the control and VCR groups of males and females. Values of $r \cong 1$ indicating a positive correlation between the variables were represented by blue. Values of $r \cong -1$, indicating a negative correlation between the two variables, were represented on the graph in red.

6. Declaration of authorship contribution

KPM and EAW conceived and designed the study. KPM, CCM, and VMER performed the biochemical and behavioral analyses. AQS and LDB were responsible for the PCR analysis. DA and ICO synthesized the compound 4-PSQ. KPM and EAW wrote the manuscript. EAW supervised the study. All authors approved the final version of the manuscript.

7. Acknowledgments

This study received financial support and scholarships from the following Brazilian agencies: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) (312747/2020-9, 406118/2021-3, 442284/2023-3), Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS) (PqG 21/2551-0001943-3, RITES 22/2551-0000389-3). This study was also financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) - Finance Code 001. This study also received financial assistance from L'ORÉAL-UNESCO-ABC for Women in Science. E.A.W. is recipient of CNPq fellowship.

8. References

AEBI, H. Catalase in vitro. **Methods in Enzymology**, [s. l.], v. 105, p. 121–126, 1984.

AKSENOV, M. Y.; MARKESBERY, W. R. Changes in thiol content and

expression of glutathione redox system genes in the hippocampus and cerebellum in Alzheimer's disease. **Neuroscience Letters**, [s. l.], v. 302, n. 2–3, p. 141–145, 2001.

ALAMRI, F. F. *et al.* Applicability of the grip strength and automated von Frey tactile sensitivity tests in the mouse photothrombotic model of stroke. **Behavioural Brain Research**, [s. l.], v. 336, n. August 2017, p. 250–255, 2018a.

ALAMRI, F. F. *et al.* Applicability of the grip strength and automated von Frey tactile sensitivity tests in the mouse photothrombotic model of stroke. **Behavioural Brain Research**, [s. l.], v. 336, n. August 2017, p. 250–255, 2018b. Disponível em: <http://dx.doi.org/10.1016/j.bbr.2017.09.008>.

ALBENSI, B. C. What Is Nuclear Factor Kappa B (NF- κ B) Doing in and to the Mitochondrion?. **Frontiers in Cell and Developmental Biology**, [s. l.], v. 7, 2019a.

ALBENSI, B. C. What Is Nuclear Factor Kappa B (NF- κ B) Doing in and to the Mitochondrion?. **Frontiers in Cell and Developmental Biology**, [s. l.], v. 7, 2019b. Disponível em: <https://www.frontiersin.org/article/10.3389/fcell.2019.00154/full>.

ALENEZI, S. K. The Ameliorative Effect of Thymoquinone on Vincristine-Induced Peripheral Neuropathy in Mice by Modulating Cellular Oxidative Stress and Cytokine. **Life**, [s. l.], v. 13, n. 1, p. 101, 2022.

ALENEZI, S. K. The Ameliorative Effect of Thymoquinone on Vincristine-Induced Peripheral Neuropathy in Mice by Modulating Cellular Oxidative Stress and Cytokine. **Life**, [s. l.], v. 13, n. 1, 2023a.

ALENEZI, S. K. The Ameliorative Effect of Thymoquinone on Vincristine-Induced Peripheral Neuropathy in Mice by Modulating Cellular Oxidative Stress and Cytokine. **Life**, [s. l.], v. 13, n. 1, 2023b.

ALWHAIBI, A. M. *et al.* Vincristine-Induced Neuropathy in Patients Diagnosed with Solid and Hematological Malignancies: The Role of Dose Rounding. **Journal of Clinical Medicine**, [s. l.], v. 12, n. 17, p. 5662, 2023.

AN, R. *et al.* Methylcobalamin Protects Melanocytes from H₂O₂-Induced Oxidative Stress by Activating the Nrf2/HO-1 Pathway. **Drug Design, Development and Therapy**, [s. l.], v. Volume 15, p. 4837–4848, 2021.

ANAND, K. J. S.; HICKEY, P. R. Pain and Its Effects in the Human Neonate and Fetus. **New England Journal of Medicine**, [s. l.], v. 317, n. 21, p. 1321–1329, 1987.

ANBALAGAN, M. *et al.* Post-translational modifications of nuclear receptors and human disease. **Nuclear receptor signaling**, [s. l.], v. 10, n. Figure 1, 2012.

ARETI, A. *et al.* Oxidative stress and nerve damage: Role in chemotherapy induced peripheral neuropathy. **Redox Biology**, [s. l.], v. 2, n. 1, p. 289–295, 2014.

BAE, E. H.; GREENWALD, M. K.; SCHWARTZ, A. G. Chemotherapy-Induced Peripheral Neuropathy: Mechanisms and Therapeutic Avenues. **Neurotherapeutics**, [s. l.], v. 18, n. 4, p. 2384–2396, 2021.

BAIG, M. A.; PANCHAL, S. S. Streptozotocin-Induced Diabetes Mellitus in Neonatal Rats: An Insight into its Applications to Induce Diabetic Complications. **Current Diabetes Reviews**, [s. l.], v. 16, n. 1, p. 26–39, 2019.

BAKER, D. W. History of The Joint Commission's Pain Standards. **JAMA**, [s. l.], v. 317, n. 11, p. 1117, 2017.

BARTH, A. *et al.* 7-Chloro-4-(Phenylselanyl) Quinoline with Memory Enhancer Action in Aging Rats: Modulation of Neuroplasticity, Acetylcholinesterase Activity, and Cholesterol Levels. **Molecular Neurobiology**, [s. l.], 2019a.

BARTH, A. *et al.* 7-Chloro-4-(Phenylselanyl) Quinoline with Memory Enhancer Action in Aging Rats: Modulation of Neuroplasticity, Acetylcholinesterase Activity, and Cholesterol Levels. **Molecular Neurobiology**, [s. l.], 2019b.

BARTLEY, E. J.; FILLINGIM, R. B. Sex differences in pain: a brief review of clinical and experimental findings. **British Journal of Anaesthesia**, [s. l.], v. 111, n. 1, p. 52–58, 2013.

BEJČEK, J. *et al.* Na⁺/K⁺-atpase revisited: On its mechanism of action, role in cancer, and activity modulation. **Molecules**, [s. l.], v. 26, n. 7, 2021.

BENJAMIN, R. S. *et al.* Chemotherapy for Bone Sarcomas in Adults: The MD Anderson Experience. **American Society of Clinical Oncology Educational Book**, [s. l.], n. 35, p. e656–e660, 2015.

BENNETT, M. I. *et al.* Prevalence and aetiology of neuropathic pain in cancer patients: A systematic review. **Pain**, [s. l.], v. 153, n. 2, p. 359–365, 2012.

BEYER, C.; KAROLCZAK, M. Estrogenic stimulation of neurite growth in midbrain dopaminergic neurons depends on cAMP/protein kinase A signalling. **Journal of Neuroscience Research**, [s. l.], v. 59, n. 1, p. 107–116, 2000a.

BEYER, C.; KAROLCZAK, M. Estrogenic stimulation of neurite growth in midbrain dopaminergic neurons depends on cAMP/protein kinase A signalling. **Journal of Neuroscience Research**, [s. l.], v. 59, n. 1, p. 107–116, 2000b.

BHATT, S. *et al.* 5-HT₃ Receptor Antagonism: A Potential Therapeutic Approach for the Treatment of Depression and other Disorders. **Current Neuropharmacology**, [s. l.], v. 19, n. 9, p. 1545–1559, 2020.

BILBERG, A. *et al.* High prevalence of widespread pain in women with early

rheumatoid arthritis. **Scandinavian Journal of Rheumatology**, [s. l.], v. 47, n. 6, p. 447–454, 2018. Disponível em: <https://doi.org/10.1080/03009742.2018.1447683>.

BLUETTE, C. T. *et al.* Behavioral, Histopathologic, and Molecular Biological Responses of Nanoparticle- and Solution-Based Formulations of Vincristine in Mice. **International Journal of Toxicology**, [s. l.], v. 40, n. 1, p. 40–51, 2021. Disponível em: <http://journals.sagepub.com/doi/10.1177/1091581820968255>.

BRADFORD, M. M. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. **Analytical biochemistry**, [s. l.], v. 72, n. 1–2, p. 248–254, 1976a.

BRADFORD, M. M. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. **Analytical biochemistry**, [s. l.], v. 72, n. 1–2, p. 248–254, 1976b. Disponível em: <https://www.sciencedirect.com/science/article/abs/pii/0003269776905273>.

BREIVIK, H. *et al.* Cancer-related pain: a pan-European survey of prevalence, treatment, and patient attitudes. **Annals of Oncology**, [s. l.], v. 20, n. 8, p. 1420–1433, 2009.

BRIGATTE, P. *et al.* Walker 256 Tumor-Bearing Rats as a Model to Study Cancer Pain. **The Journal of Pain**, [s. l.], v. 8, n. 5, p. 412–421, 2007.

BROWN, A. M.; ROSS, A.; BELSKY, J. A. Vincristine-Induced Autonomic Neuropathy Diagnosed via Quantitative Sudomotor Axon Reflex Sweat Test in an Adolescent Patient With Acute Leukemia. **Pediatric Blood & Cancer**, [s. l.], 2025.

BROZOVIĆ, G. Cancer Pain and Therapy. **Acta Clinica Croatica**, [s. l.], 2022.

BUJALSKA, M.; GUMUŁKA, S. W. Effect of cyclooxygenase and nitric oxide synthase inhibitors on vincristine induced hyperalgesia in rats. **Pharmacological Reports**, [s. l.], v. 60, n. 5, p. 735–741, 2008.

BURT, R. *et al.* Activated stromal cells transfer mitochondria to rescue acute lymphoblastic leukemia cells from oxidative stress. **Blood**, [s. l.], v. 134, n. 17, p. 1415–1429, 2019.

BUSCH, C. J.; BINDER, C. J. Malondialdehyde epitopes as mediators of sterile inflammation. **Biochimica et Biophysica Acta - Molecular and Cell Biology of Lipids**, [s. l.], v. 1862, n. 4, p. 398–406, 2017. Disponível em: <http://dx.doi.org/10.1016/j.bbalip.2016.06.016>.

CALIXTO-CAMPOS, C. *et al.* The Ehrlich Tumor Induces Pain-Like Behavior in Mice: A Novel Model of Cancer Pain for Pathophysiological Studies and Pharmacological Screening. **BioMed Research International**, [s. l.], v. 2013, p. 1–12, 2013.

CANTA, A.; POZZI, E.; CAROZZI, V. A. Mitochondrial dysfunction in chemotherapy-induced peripheral neuropathy (CIPN). **Toxics**, [s. l.], v. 3, n. 2, p. 198–223, 2015a.

CANTA, A.; POZZI, E.; CAROZZI, V. A. Mitochondrial dysfunction in chemotherapy-induced peripheral neuropathy (CIPN). **Toxics**, [s. l.], v. 3, n. 2, p. 198–223, 2015b.

CARACENI, A.; SHKODRA, M. Cancer Pain Assessment and Classification. **Cancers**, [s. l.], v. 11, n. 4, p. 510, 2019.

CASSOL, G. *et al.* A role of Na⁺, K⁺ -ATPase in spatial memory deficits and inflammatory/oxidative stress after recurrent concussion in adolescent rats. **Brain Research Bulletin**, [s. l.], v. 180, p. 1–11, 2022a.

CASSOL, G. *et al.* A role of Na⁺, K⁺ -ATPase in spatial memory deficits and inflammatory/oxidative stress after recurrent concussion in adolescent rats. **Brain Research Bulletin**, [s. l.], v. 180, p. 1–11, 2022b. Disponível em: <https://linkinghub.elsevier.com/retrieve/pii/S0361923021003543>.

CAVIEDES, A. *et al.* BDNF/NF-κB Signaling in the Neurobiology of Depression. **Current Pharmaceutical Design**, [s. l.], v. 23, n. 21, 2017a.

CAVIEDES, A. *et al.* BDNF/NF-κB Signaling in the Neurobiology of Depression. **Current Pharmaceutical Design**, [s. l.], v. 23, n. 21, 2017b. Disponível em: <http://www.eurekaselect.com/149163/article>.

CHANCAY, M. G.; GUENDSECHADZE, S. N.; BLANCO, I. Types of pain and their psychosocial impact in women with rheumatoid arthritis. **Women's Midlife Health**, [s. l.], v. 5, n. 1, p. 1–9, 2019.

CHANTAL, T. *et al.* ACTION OF VINCA ALKALOIDES ON CALCIUM MOVEMENTS THROUGH MITOCHONDRIAL MEMBRANE. **Pharmacological Research Communications**, [s. l.], v. 18, n. 6, p. 519–528, 1986.

CHEN, C. *et al.* Body weight, frailty, and chronic pain in older adults: A cross-sectional study. **BMC Geriatrics**, [s. l.], v. 19, n. 1, p. 1–10, 2019.

CHEN, X. *et al.* Current understanding of the molecular mechanisms of chemotherapy-induced peripheral neuropathy. **Frontiers in Molecular Neuroscience**, [s. l.], v. 17, 2024.

CHEN, S. P. *et al.* Involvement of hippocampal acetylcholinergic receptors in electroacupuncture analgesia in neuropathic pain rats. **Behavioral and Brain Functions**, [s. l.], v. 12, n. 1, p. 1–10, 2016.

CHEN, Q. M. Nrf2 for protection against oxidant generation and mitochondrial damage in cardiac injury. **Free Radical Biology and Medicine**, [s. l.], v. 179, p. 133–143, 2022.

CHEN, X.-J.; WANG, L.; SONG, X.-Y. Mitoquinone alleviates vincristine-induced neuropathic pain through inhibiting oxidative stress and apoptosis via the improvement of mitochondrial dysfunction. **Biomedicine & Pharmacotherapy**, [s. l.], v. 125, p. 110003, 2020.

CHENG, H. *et al.* Case report: Wallerian degeneration: The innate-immune response to adult-onset Still's disease peripheral nerve injury. **Frontiers in Neurology**, [s. l.], v. 13, 2022.

CHEON, J. H. *et al.* P-gp Inhibition by XL019, a JAK2 Inhibitor, Increases Apoptosis of Vincristine-treated Resistant KBV20C Cells with Increased p21 and pH2AX Expression. **Anticancer Research**, [s. l.], v. 37, n. 12, 2017a.

CHEON, J. H. *et al.* P-gp Inhibition by XL019, a JAK2 Inhibitor, Increases Apoptosis of Vincristine-treated Resistant KBV20C Cells with Increased p21 and pH2AX Expression. **Anticancer Research**, [s. l.], v. 37, n. 12, 2017b. Disponível em: <http://ar.iiarjournals.org/content/37/12/6761.abstract>.

CHIBA, T. *et al.* Vincristine increased spinal cord substance P levels in a peripheral neuropathy rat model. **Drug and Chemical Toxicology**, [s. l.], v. 45, n. 1, p. 393–397, 2022. Disponível em: <https://www.tandfonline.com/doi/full/10.1080/01480545.2019.1706547>.

CHIECHIO, S. *et al.* L-Acetylcarnitine Induces Analgesia by Selectively Up-Regulating mGlu2 Metabotropic Glutamate Receptors. **Molecular Pharmacology**, [s. l.], v. 61, n. 5, p. 989–996, 2002.

CHO, S.-H. *et al.* Anti-inflammatory activity of Echinosophora koreensis nakai root extract in lipopolysaccharides-stimulated RAW 264.7 cells and carrageenan-induced mouse paw edema model. **Journal of Ethnopharmacology**, [s. l.], v. 302, p. 115940, 2023.

CLARK, A. K.; MALCANGIO, M. Microglial signalling mechanisms: Cathepsin S and Fractalkine. **Experimental Neurology**, [s. l.], v. 234, n. 2, p. 283–292, 2012.

COBB, C. A.; COLE, M. P. Oxidative and nitrative stress in neurodegeneration. **Neurobiology of Disease**, [s. l.], v. 84, p. 4–21, 2015. Disponível em: <http://dx.doi.org/10.1016/j.nbd.2015.04.020>.

COLUZZI, F. *et al.* Pain management in childhood leukemia: Diagnosis and available analgesic treatments. **Cancers**, [s. l.], v. 12, n. 12, p. 1–13, 2020.

COLVIN, L. A. Chemotherapy-induced peripheral neuropathy: where are we now?. **Pain**, [s. l.], v. 160, n. 1, p. S1–S10, 2019.

COOK, K. M. *et al.* Experience of early-life pain in premature infants is associated with atypical cerebellar development and later neurodevelopmental deficits. **BMC Medicine**, [s. l.], v. 21, n. 1, p. 435, 2023.

COSTA, Y. M. *et al.* Reliability of the nociceptive blink reflex evoked by electrical stimulation of the trigeminal nerve in humans. **Clinical Oral Investigations**, [s. l.], v. 21, n. 8, p. 2453–2463, 2017.

COX, B. C. *et al.* Transport of multiple nicotinic acetylcholine receptors in the rat optic nerve: High densities of receptors containing $\alpha 6$ and $\beta 3$ subunits. **Journal of Neurochemistry**, [s. l.], v. 105, n. 5, p. 1924–1938, 2008.

CUREALL FRAMEWORK: WHO GLOBAL INITIATIVE FOR CHILDHOOD CANCER INCREASING ACCESS, ADVANCING QUALITY, SAVING LIVES. . [S. l.: s. n.], [s. d.].

DA MOTTA, K. P. *et al.* Insights into Vincristine-Induced Peripheral Neuropathy in Aged Rats: Wallerian Degeneration, Oxidative Damage, and Alterations in ATPase Enzymes. **ACS Chemical Neuroscience**, [s. l.], v. 15, n. 21, p. 3954–3969, 2024.

DA MOTTA, K. P. *et al.* The Antinociceptive Responses of MTDZ to Paclitaxel – Induced Peripheral Neuropathy and Acute Nociception in Mice : Behavioral , Pharmacological , and Biochemical Approaches. **Pharmaceuticals**, [s. l.], v. 16, n. 9, p. 1217, 2023.

DA ROCHA, V. M. E. *et al.* Structure-Activity Relationship of 7-Chloro-4-(Phenylselanyl) Quinoline: Novel Antinociceptive and Anti-Inflammatory Effects in Mice. **Chemistry & Biodiversity**, [s. l.], v. 22, n. 3, 2025.

DAGNINO, A. P. A.; CAMPOS, M. M. Chronic Pain in the Elderly: Mechanisms and Perspectives. **Frontiers in Human Neuroscience**, [s. l.], v. 16, p. 1–11, 2022.

DANG, X. *et al.* Alantolactone suppresses inflammation, apoptosis and oxidative stress in cigarette smoke-induced human bronchial epithelial cells through activation of Nrf2/HO-1 and inhibition of the NF- κ B pathways. **Respiratory Research**, [s. l.], v. 21, n. 1, p. 95, 2020.

DAVIS, R. L. *et al.* Effects of mechanistically distinct NF- κ B inhibitors on glial inducible nitric-oxide synthase expression. **Nitric Oxide**, [s. l.], v. 12, n. 4, p. 200–209, 2005.

DE FREITAS COUTO, S. *et al.* 7-chloro-4-(phenylselanyl) quinoline prevents dopamine depletion in a *Drosophila melanogaster* model of Parkinson's-like disease. **Journal of Trace Elements in Medicine and Biology**, [s. l.], v. 54, p. 232–243, 2019a. Disponível em: <https://linkinghub.elsevier.com/retrieve/pii/S0946672X1830405X>.

DE FREITAS COUTO, S. *et al.* 7-chloro-4-(phenylselanyl) quinoline prevents dopamine depletion in a *Drosophila melanogaster* model of Parkinson's-like disease. **Journal of Trace Elements in Medicine and Biology**, [s. l.], v. 54, p. 232–243, 2019b.

DE OLIVEIRA, R. L. *et al.* Prospecting for a quinoline containing selenium for comorbidities depression and memory impairment induced by restriction stress in mice. **Psychopharmacology**, [s. l.], v. 239, n. 1, p. 59–81, 2022a. Disponível em: <https://doi.org/10.1007/s00213-021-06039-8>.

DE OLIVEIRA, R. L. *et al.* Prospecting for a quinoline containing selenium for comorbidities depression and memory impairment induced by restriction stress in mice. **Psychopharmacology**, [s. l.], v. 239, n. 1, p. 59–81, 2022b.

DEL RIO, D.; STEWART, A. J.; PELLEGRINI, N. A review of recent studies on malondialdehyde as toxic molecule and biological marker of oxidative stress. **Nutrition, Metabolism and Cardiovascular Diseases**, [s. l.], v. 15, n. 4, p. 316–328, 2005.

DENG, G. Integrative Medicine Therapies for Pain Management in Cancer Patients. **The Cancer Journal**, [s. l.], v. 25, n. 5, p. 343–348, 2019.

DESFORGES, A. D. *et al.* Treatment and diagnosis of chemotherapy-induced peripheral neuropathy: An update. **Biomedicine & Pharmacotherapy**, [s. l.], v. 147, p. 112671, 2022.

DIOUF, B. *et al.* Association of an inherited genetic variant with vincristine-related peripheral neuropathy in children with acute lymphoblastic leukemia Critical revision of the manuscript for important intellectual content: Barthelemy Diouf; HHS Public Access. **Jama**, [s. l.], v. 313, n. 8, p. 815–823, 2015.

DOBRETISOV, M. Neuronal function and alpha3 isoform of the Na/K-ATPase. **Frontiers in Bioscience**, [s. l.], v. 10, n. 1–3, p. 2373, 2005a.

DOBRETISOV, M. Neuronal function and alpha3 isoform of the Na/K-ATPase. **Frontiers in Bioscience**, [s. l.], v. 10, n. 1–3, p. 2373, 2005b. Disponível em: <https://imrpess.com/journal/FBL/10/3/10.2741/1704>.

DOS SANTOS, L. M. *et al.* Methionine and methionine sulfoxide treatment induces M1/classical macrophage polarization and modulates oxidative stress and purinergic signaling parameters. **Molecular and Cellular Biochemistry**, [s. l.], v. 424, n. 1–2, p. 69–78, 2017.

DUARTE, L. F. B. *et al.* A simple method for the synthesis of 4-arylselanyl-7-chloroquinolines used as in vitro acetylcholinesterase inhibitors and in vivo memory improvement. **Tetrahedron Letters**, [s. l.], v. 58, n. 33, p. 3319–3322, 2017a.

DUARTE, L. F. B. *et al.* Organoselenium compounds from purines: Synthesis of 6-arylselanylpurines with antioxidant and anticholinesterase activities and memory improvement effect. **Bioorganic & Medicinal Chemistry**, [s. l.], v. 25, n. 24, p. 6718–6723, 2017b.

DUPUIS, L. L. *et al.* Anxiety, pain, and nausea during the treatment of standard-risk childhood acute lymphoblastic leukemia: A prospective, longitudinal study

from the Children's Oncology Group. **Cancer**, [s. l.], v. 122, n. 7, p. 1116–1125, 2016.

DZIECHCIAŻ, M.; BALICKA-ADAMIK, L.; FILIP, R. The problem of pain in old age. **Annals of agricultural and environmental medicine : AAEM**, [s. l.], v. . 1, n. 1, p. 35–38, 2013.

EDINOFF, A. N. *et al.* Selective Serotonin Reuptake Inhibitors and Adverse Effects: A Narrative Review. **Neurology International**, [s. l.], v. 13, n. 3, p. 387–401, 2021.

EDWARDS, R. R. *et al.* The role of psychosocial processes in the development and maintenance of chronic pain disorders. **Pain**, [s. l.], v. 176, n. 1, p. 70–92, 2017.

EIDE, S.; FENG, Z. P. Doxorubicin chemotherapy-induced “chemo-brain”: Meta-analysis. **European Journal of Pharmacology**, [s. l.], v. 881, n. July 2019, p. 173078, 2020.

EL HACHEM, G. *et al.* Advances in pain management for older patients with cancer. **ecancermedicalsecience**, [s. l.], v. 13, 2019.

ELDUFANI, J.; BLAISE, G. The role of acetylcholinesterase inhibitors such as neostigmine and rivastigmine on chronic pain and cognitive function in aging: A review of recent clinical applications. **Alzheimer's and Dementia: Translational Research and Clinical Interventions**, [s. l.], v. 5, p. 175–183, 2019.

ELLMAN, G. L. Tissue Sulfhydryl Groups. **Archives of biochemistry and biophysics**, [s. l.], v. 82, n. 1, p. 70–77, 1959.

ELTOKHY, A. K.; TOEMA, O.; EL-DEEB, O. S. The Correlation Between PINK-1/Parkin Mediated Mitophagy, Endoplasmic Reticulum Stress and Total Polyamines in Pediatric Bronchial Asthma: An Integrated Network of Pathways. **Molecular Biology Reports**, [s. l.], v. 49, n. 1, p. 227–235, 2022.

EVENEPOEL, M. *et al.* Pain Prevalence During Cancer Treatment: A Systematic Review and Meta-Analysis. **Journal of Pain and Symptom Management**, [s. l.], v. 63, n. 3, p. e317–e335, 2022.

FANE, M.; WEERARATNA, A. T. How the ageing microenvironment influences tumour progression. **Nature Reviews Cancer**, [s. l.], v. 20, n. 2, p. 89–106, 2020.

FANG, J. *et al.* Expression Dynamics of Heme Oxygenase-1 in Tumor Cells and the Host Contributes to the Progression of Tumors. **Journal of Personalized Medicine**, [s. l.], v. 11, n. 12, p. 1340, 2021.

FILIPPI-CHIELA, E. C. *et al.* Vincristine promotes differential levels of apoptosis, mitotic catastrophe, and senescence depending on the genetic

background of glioblastoma cells. **Toxicology in Vitro**, [s. l.], v. 85, p. 105472, 2022.

FISKE, B. C. H.; SUBBAROW, Y. The colorimetric determination of phosphorus. **The Journal of Biological Chemistry**, [s. l.], v. 66, n. september, p. 375–400, 1925a.

FISKE, B. C. H.; SUBBAROW, Y. The colorimetric determination of phosphorus. **The Journal of Biological Chemistry**, [s. l.], v. 66, n. september, p. 375–400, 1925b.

FITZMAURICE, C. *et al.* Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study Global Burden . **JAMA Oncology**, [s. l.], v. 3, n. 4, p. 524–548, 2017.

FLATTERS, S. J. L.; DOUGHERTY, P. M.; COLVIN, L. A. Clinical and preclinical perspectives on Chemotherapy-Induced Peripheral Neuropathy (CIPN): A narrative review. **British Journal of Anaesthesia**, [s. l.], v. 119, n. 4, p. 737–749, 2017.

FRANÇOIS, A. *et al.* The Low-Threshold Calcium Channel Cav3.2 Determines Low-Threshold Mechanoreceptor Function. **Cell Reports**, [s. l.], v. 10, n. 3, p. 370–382, 2015.

GAUTHIER, I.; TARR, M. J. Visual Object Recognition: Do We (Finally) Know More Now Than We Did?. **Annual Review of Vision Science**, [s. l.], v. 2, n. 1, p. 377–396, 2016.

GEŃGOTEK, A.; SKRZYDLEWSKA, E. Biological effect of protein modifications by lipid peroxidation products. **Chemistry and Physics of Lipids**, [s. l.], v. 221, n. February, p. 46–52, 2019.

GEŃGOTEK, A.; SKRZYDLEWSKA, E. Lipid peroxidation products' role in autophagy regulation. **Free Radical Biology and Medicine**, [s. l.], v. 212, p. 375–383, 2024.

GEISLER, S. Vincristine- and bortezomib-induced neuropathies – from bedside to bench and back. **Experimental Neurology**, [s. l.], v. 336, p. 113519, 2021a.

GEISLER, S. Vincristine- and bortezomib-induced neuropathies – from bedside to bench and back. **Experimental Neurology**, [s. l.], v. 336, p. 113519, 2021b. Disponível em: <https://doi.org/10.1016/j.expneurol.2020.113519>.

GEORGE, E. B.; GLASS, J. D.; GRIFFIN, J. W. Axotomy-induced axonal degeneration is mediated by calcium influx through ion-specific channels. **Journal of Neuroscience**, [s. l.], v. 15, n. 10, p. 6445–6452, 1995.

GILCHRIST, L. S.; MARAIS, L.; TANNER, L. Comparison of two chemotherapy-

induced peripheral neuropathy measurement approaches in children.

Supportive Care in Cancer, [s. l.], v. 22, n. 2, p. 359–366, 2014.

GILCHRIST, L.; TANNER, L. Gait Patterns in Children With Cancer and Vincristine Neuropathy. **Pediatric Physical Therapy**, [s. l.], v. 28, n. 1, p. 16–22, 2016.

GLOBAL CANCER BURDEN GROWING, AMIDST MOUNTING NEED FOR SERVICES. **Saudi medical journal**, [s. l.], v. 45, n. 3, p. 326–327, 2024.

GOESLING, J.; LIN, L. A.; CLAUW, D. J. Psychiatry and Pain Management: at the Intersection of Chronic Pain and Mental Health. **Current Psychiatry Reports**, [s. l.], v. 20, n. 2, 2018.

GOLCHIN, L. *et al.* Pistachio supplementation attenuates motor and cognition impairments induced by cisplatin or vincristine in rats. **Advanced Biomedical Research**, [s. l.], v. 4, n. 1, p. 92, 2015.

GOMBER, S.; DEWAN, P.; CHHONKER, D. Vincristine induced neurotoxicity in cancer patients. **Indian Journal of Pediatrics**, [s. l.], v. 77, n. 1, p. 97–100, 2010a.

GOMBER, S.; DEWAN, P.; CHHONKER, D. Vincristine induced neurotoxicity in cancer patients. **Indian Journal of Pediatrics**, [s. l.], v. 77, n. 1, p. 97–100, 2010b.

GÓMEZ, V. *et al.* Breast cancer–associated macrophages promote tumorigenesis by suppressing succinate dehydrogenase in tumor cells. **Science Signaling**, [s. l.], v. 13, n. 652, 2020.

GOUVEIA, D. N. *et al.* α -Terpineol reduces cancer pain via modulation of oxidative stress and inhibition of iNOS. **Biomedicine & Pharmacotherapy**, [s. l.], v. 105, p. 652–661, 2018.

GRANT, C. H. *et al.* Multimorbidity and analgesic-related harms: a systematic review. **British Journal of Anaesthesia**, [s. l.], v. 134, n. 6, p. 1717–1745, 2025.

GROTEN, C. J.; MACVICAR, B. A. Mitochondrial Ca^{2+} uptake by the MCU facilitates pyramidal neuron excitability and metabolism during action potential firing. **Communications Biology**, [s. l.], v. 5, n. 1, p. 900, 2022.

GU, C. *et al.* Cancer Cells Promote Immune Regulatory Function of Macrophages by Upregulating Scavenger Receptor MARCO Expression. **The Journal of Immunology**, [s. l.], v. 211, n. 1, p. 57–70, 2023.

GUHA, L.; SINGH, N.; KUMAR, H. Different Ways to Die: Cell Death Pathways and Their Association With Spinal Cord Injury. **Neurospine**, [s. l.], v. 20, n. 2, p. 430–448, 2023a.

GUHA, L.; SINGH, N.; KUMAR, H. Different Ways to Die: Cell Death Pathways and Their Association With Spinal Cord Injury. **Neurospine**, [s. l.], v. 20, n. 2, p. 430–448, 2023b.

HABIF, M. *et al.* Early Long-Term Memory Impairment and Changes in the Expression of Synaptic Plasticity-Associated Genes, in the McGill-R-Thy1-APP Rat Model of Alzheimer's-Like Brain Amyloidosis. **Frontiers in Aging Neuroscience**, [s. l.], v. 12, 2021. Disponível em: <https://www.frontiersin.org/articles/10.3389/fnagi.2020.585873/full>.

HABIG, W. H.; JAKOBY, M. J. P.; B., W. J. Glutathione S-Transferases: The first enzymatic step in mercapturic acid formation. **THE JOURNAL OF BIOLOGICAL CHEMISTRY**, [s. l.], v. 249, n. 22, p. 7130–7139, 1974.

HARRIS, J. C. *et al.* Sustained delivery of vincristine inside an orthotopic mouse sarcoma model decreases tumor growth. **Journal of Pediatric Surgery**, [s. l.], v. 51, n. 12, p. 2058–2062, 2016.

HASHMI, J. A.; DAVIS, K. D. Women experience greater heat pain adaptation and habituation than men. **Pain**, [s. l.], v. 145, n. 3, p. 350–357, 2009a.

HASHMI, J. A.; DAVIS, K. D. Women experience greater heat pain adaptation and habituation than men. **Pain**, [s. l.], v. 145, n. 3, p. 350–357, 2009b. Disponível em: <http://dx.doi.org/10.1016/j.pain.2009.07.002>.

HATHWAY, G. J. *et al.* Cancer Chemotherapy in Early Life Significantly Alters the Maturation of Pain Processing. **Neuroscience**, [s. l.], v. 387, p. 214–229, 2018.

HE, X.; SUN, J.; HUANG, X. Expression of caspase-3, Bax and Bcl-2 in hippocampus of rats with diabetes and subarachnoid hemorrhage. **Experimental and Therapeutic Medicine**, [s. l.], 2017.

HODAPP, J. W.; ALI, S.; DRENDEL, A. L. Bringing It All Together: A Review of the Challenges in Measuring Children's Satisfaction as a Key Component of Acute Pain Management. **Children**, [s. l.], v. 7, n. 11, p. 243, 2020.

HOLLIDAY, L. S. Vacuolar H⁺-ATPases (V-ATPases) as therapeutic targets: a brief review and recent developments. **Biotarget**, [s. l.], v. 1, n. 7, p. 18–18, 2017.

HONE, A. J.; MCINTOSH, J. M. **Nicotinic Acetylcholine Receptors in Neuropathic and Inflammatory Pain**. [S. l.: s. n.], 2018-. ISSN 1751553X.v. 592

HOOGEN, N. J. van den *et al.* Neonatal Plasticity of the Nociceptive System: Mechanisms, Effects, and Treatment of Repetitive Painful Procedures During NICU Admittance. **Current Pharmaceutical Design**, [s. l.], v. 23, n. 38, p. 5902–5910, 2018.

HORIE, K.; MA, J.; UMEZAWA, K. Inhibition of Canonical NF- κ B Nuclear Localization by (-)-DHMEQ via Impairment of DNA Binding. **Oncology Research Featuring Preclinical and Clinical Cancer Therapeutics**, [s. l.], v. 22, n. 2, p. 105–115, 2015.

HOU, Y. *et al.* Ageing as a risk factor for neurodegenerative disease. **Nature Reviews Neurology**, [s. l.], v. 15, n. 10, p. 565–581, 2019.

HUANG, Y. L. *et al.* Chronic pain and use of analgesics in the elderly: A nationwide population-based study. **Archives of Medical Science**, [s. l.], v. 16, n. 2, p. 627–634, 2020.

ISAKSEN, T. J.; LYKKE-HARTMANN, K. Insights into the Pathology of the α 2-Na⁺/K⁺-ATPase in Neurological Disorders; Lessons from Animal Models. **Frontiers in Physiology**, [s. l.], v. 7, 2016a.

ISAKSEN, T. J.; LYKKE-HARTMANN, K. Insights into the Pathology of the α 2-Na⁺/K⁺-ATPase in Neurological Disorders; Lessons from Animal Models. **Frontiers in Physiology**, [s. l.], v. 7, 2016b. Disponível em: <http://journal.frontiersin.org/Article/10.3389/fphys.2016.00161/abstract>.

JAGANJAC, M. *et al.* The relevance of pathophysiological alterations in redox signaling of 4-hydroxynonenal for pharmacological therapies of major stress-associated diseases. **Free Radical Biology and Medicine**, [s. l.], v. 157, p. 128–153, 2020.

JIANG, K.; SHI, Jinshan; SHI, Jing. Morin Alleviates Vincristine-Induced Neuropathic Pain via Nerve protective Effect and Inhibition of NF- κ B Pathway in Rats. **Cellular and Molecular Neurobiology**, [s. l.], v. 39, n. 6, p. 799–808, 2019a.

JIANG, K.; SHI, Jinshan; SHI, Jing. Morin Alleviates Vincristine-Induced Neuropathic Pain via Nerve protective Effect and Inhibition of NF- κ B Pathway in Rats. **Cellular and Molecular Neurobiology**, [s. l.], v. 39, n. 6, p. 799–808, 2019b. Disponível em: <https://doi.org/10.1007/s10571-019-00679-3>.

JIN, T.; LENG, B. Cynaropicrin Averts the Oxidative Stress and Neuroinflammation in Ischemic/Reperfusion Injury Through the Modulation of NF- κ B. **Applied Biochemistry and Biotechnology**, [s. l.], v. 195, n. 9, p. 5424–5438, 2023.

JOSEPH, E. K.; LEVINE, J. D. Mitochondrial electron transport in models of neuropathic and inflammatory pain. **Pain**, [s. l.], v. 121, n. 1–2, p. 105–114, 2006.

KAI, K. *et al.* Species and Sex Differences in Susceptibility to Olfactory Lesions Among the Mouse, Rat and Monkey Following an Intravenous Injection of Vincristine Sulphate. **Toxicologic Pathology**, [s. l.], v. 34, n. 3, p. 223–231, 2006.

KAKATKAR, S.; NARAYAN, A.; BALKRISHNAN, R. Prescription analgesic overuse in older adults: Can we mitigate this growing problem?. **AGING MEDICINE**, [s. l.], v. 5, n. 4, p. 294–296, 2022.

KALTSCHMIDT, B.; KALTSCHMIDT, C. NF-KappaB in Long-Term Memory and Structural Plasticity in the Adult Mammalian Brain. **Frontiers in Molecular Neuroscience**, [s. l.], v. 8, 2015.

KANG, L. *et al.* Oxaliplatin-induced peripheral neuropathy: clinical features, mechanisms, prevention and treatment. **Journal of Neurology**, [s. l.], n. 0123456789, 2020. Disponível em: <https://doi.org/10.1007/s00415-020-09942-w>.

KANZAKI, H. *et al.* Disabling the Nuclear Translocation of RelA/NF-κB by a Small Molecule Inhibits Triple-Negative Breast Cancer Growth. **Breast Cancer: Targets and Therapy**, [s. l.], v. Volume 13, p. 419–430, 2021.

KASAI, S. *et al.* Regulation of Nrf2 by Mitochondrial Reactive Oxygen Species in Physiology and Pathology. **Biomolecules**, [s. l.], v. 10, n. 2, p. 320, 2020.

KATSUYAMA, S. *et al.* Antinociceptive Effects of the Serotonin and Noradrenaline Reuptake Inhibitors Milnacipran and Duloxetine on Vincristine-Induced Neuropathic Pain Model in Mice. **ISRN Pain**, [s. l.], v. 2014, p. 1–7, 2014.

KAZARYAN, S. *et al.* Oxidative stress and histopathological changes in several organs of mice injected with biogenic silver nanoparticles. **Artificial Cells, Nanomedicine, and Biotechnology**, [s. l.], v. 50, n. 1, p. 331–342, 2022.

KESZTYÜS, D. *et al.* Use of Infrared Thermography in Medical Diagnosis, Screening, and Disease Monitoring: A Scoping Review. **Medicina**, [s. l.], v. 59, n. 12, p. 2139, 2023.

KHALILZADEH, M. *et al.* Aripiprazole prevents from development of vincristine-induced neuropathic nociception by limiting neural NOS overexpression and NF-κB hyperactivation. **Cancer Chemotherapy and Pharmacology**, [s. l.], v. 86, n. 3, p. 393–404, 2020a.

KHALILZADEH, M. *et al.* Aripiprazole prevents from development of vincristine-induced neuropathic nociception by limiting neural NOS overexpression and NF-κB hyperactivation. **Cancer Chemotherapy and Pharmacology**, [s. l.], v. 86, n. 3, p. 393–404, 2020b. Disponível em: <https://doi.org/10.1007/s00280-020-04127-8>.

KHIDR, H. Y. *et al.* Formoterol attenuated mitochondrial dysfunction in rotenone-induced Parkinson's disease in a rat model: Role of PINK-1/PARKIN and PI3K/Akt/CREB/BDNF/TrkB axis. **International Immunopharmacology**, [s. l.], v. 125, p. 111207, 2023.

KIGUCHI, N. *et al.* The critical role of invading peripheral macrophage-derived

interleukin-6 in vincristine-induced mechanical allodynia in mice. **European Journal of Pharmacology**, [s. l.], v. 592, n. 1–3, p. 87–92, 2008.

KIM, S. J. *et al.* Antitumor Effects of Selenium. **International Journal of Molecular Sciences**, [s. l.], v. 22, n. 21, p. 11844, 2021.

KIM, Y. S. *et al.* Assessment of pain in the elderly: A literature review. **National Medical Journal of India**, [s. l.], v. 30, n. 4, p. 203–207, 2017a.

KIM, Y. S. *et al.* Assessment of pain in the elderly: A literature review. **National Medical Journal of India**, [s. l.], v. 30, n. 4, p. 203–207, 2017b.

KIM, S. H. *et al.* Regulation of P21-Activated Kinase-4 by Progesterone and Tumor Necrosis Factor- α in Human Endometrium and Its Increased Expression in Advanced-Stage Endometriosis. **The Journal of Clinical Endocrinology & Metabolism**, [s. l.], v. 98, n. 2, p. E238–E248, 2013a.

KIM, S. H. *et al.* Regulation of P21-Activated Kinase-4 by Progesterone and Tumor Necrosis Factor- α in Human Endometrium and Its Increased Expression in Advanced-Stage Endometriosis. **The Journal of Clinical Endocrinology & Metabolism**, [s. l.], v. 98, n. 2, p. E238–E248, 2013b. Disponível em: <https://academic.oup.com/jcem/article-lookup/doi/10.1210/jc.2012-2969>.

KIM, J.; SHARMA, R. P. Calcium-mediated activation of c-Jun NH2-terminal kinase (JNK) and apoptosis in response to cadmium in murine macrophages. **Toxicological Sciences**, [s. l.], v. 81, n. 2, p. 518–527, 2004.

KINOSHITA, P. F. *et al.* The influence of Na⁺, K⁺-ATPase on glutamate signaling in neurodegenerative diseases and senescence. **Frontiers in Physiology**, [s. l.], v. 7, n. JUN, p. 1–19, 2016.

KINTOSSOU, A. K. *et al.* Early Life Nutrition Factors and Risk of Acute Leukemia in Children: Systematic Review and Meta-Analysis. **Nutrients**, [s. l.], v. 15, n. 17, p. 3775, 2023.

KOHNO, T. *et al.* Peripheral nerve injury alters excitatory synaptic transmission in lamina II of the rat dorsal horn. **Journal of Physiology**, [s. l.], v. 548, n. 1, p. 131–138, 2003.

KOSTIĆ, M.; MARJANOVIĆ, J.; DIVAC, V. Organoselenium transition metal complexes as promising candidates in medicine area. **JBIC Journal of Biological Inorganic Chemistry**, [s. l.], v. 29, n. 6, p. 555–571, 2024.

KREMER, M. *et al.* How to study anxiety and depression in rodent models of chronic pain?. **European Journal of Neuroscience**, [s. l.], v. 53, n. 1, p. 236–270, 2021.

KUPPUSAMY, P. *et al.* Targeting metabolic pathways alleviates bortezomib-induced neuropathic pain without compromising anticancer efficacy in a sex-specific manner. **Frontiers in Pain Research**, [s. l.], v. 5, 2024.

LAFORGIA, M. *et al.* Peripheral Neuropathy under Oncologic Therapies: A Literature Review on Pathogenetic Mechanisms. **International Journal of Molecular Sciences**, [s. l.], v. 22, n. 4, p. 1980, 2021.

LAURITZEN, M. *et al.* Clinical Relevance of Cortical Spreading Depression in Neurological Disorders: Migraine, Malignant Stroke, Subarachnoid and Intracranial Hemorrhage, and Traumatic Brain Injury. **Journal of Cerebral Blood Flow & Metabolism**, [s. l.], v. 31, n. 1, p. 17–35, 2011a.

LAURITZEN, M. *et al.* Clinical Relevance of Cortical Spreading Depression in Neurological Disorders: Migraine, Malignant Stroke, Subarachnoid and Intracranial Hemorrhage, and Traumatic Brain Injury. **Journal of Cerebral Blood Flow & Metabolism**, [s. l.], v. 31, n. 1, p. 17–35, 2011b. Disponível em: <http://journals.sagepub.com/doi/10.1038/jcbfm.2010.191>.

LAW, A. Y. S. *et al.* Histone deacetylase inhibitor-induced cellular apoptosis involves stanniocalcin-1 activation. **Experimental Cell Research**, [s. l.], v. 314, n. 16, p. 2975–2984, 2008.

LEE, S. J. *et al.* Fetal Pain. **JAMA**, [s. l.], v. 294, n. 8, p. 947, 2005.

LEE, J. Y. *et al.* The Antiallodynic Effect of Nefopam on Vincristine-Induced Neuropathy in Mice. **Journal of Pain Research**, [s. l.], v. Volume 13, p. 323–329, 2020. Disponível em: <https://www.dovepress.com/the-antiallodynic-effect-of-nefopam-on-vincristine-induced-neuropathy-peer-reviewed-article-JPR>.

LEE, B. Y.; HUR, E. M. A role of microtubules in oligodendrocyte differentiation. **International Journal of Molecular Sciences**, [s. l.], v. 21, n. 3, 2020.

LEGAKIS, L. P.; BIGBEE, J. W.; NEGUS, S. S. Lack of paclitaxel effects on intracranial Self-Stimulation in male and female rats: Comparison to mechanical sensitivity. **Behavioural Pharmacology**, [s. l.], v. 29, p. 290–298, 2018.

LEMOS, B. B. *et al.* ROLE OF 7-CHLORO-4- (PHENYLSELANYL) QUINOLINE IN THE TREATMENT. **Canadian physiology and pharmacology**, [s. l.], v. 99(4), n. 378–388, p. 1–50, 2021a.

LEMOS, B. B. *et al.* ROLE OF 7-CHLORO-4- (PHENYLSELANYL) QUINOLINE IN THE TREATMENT. **Canadian physiology and pharmacology**, [s. l.], v. 99(4), n. 378–388, p. 1–50, 2021b.

LI, H. *et al.* Adipocyte Fatty Acid-Binding Protein Promotes Palmitate-Induced Mitochondrial Dysfunction and Apoptosis in Macrophages. **Frontiers in Immunology**, [s. l.], v. 9, 2018.

LI, G. zhou *et al.* CaMKII and CaV3.2 T-type calcium channel mediate Connexin-43-dependent inflammation by activating astrocytes in vincristine-induced neuropathic pain. **Cell Biology and Toxicology**, [s. l.], p. 679–702, 2021a.

LI, G. zhou *et al.* CaMKII and Cav3.2 T-type calcium channel mediate Connexin-43-dependent inflammation by activating astrocytes in vincristine-induced neuropathic pain. **Cell Biology and Toxicology**, [s. l.], p. 679–702, 2021b.

LI, T. *et al.* Characterising vincristine-induced peripheral neuropathy in adults: symptom development and long-term persistent outcomes. **Supportive Care in Cancer**, [s. l.], v. 32, n. 5, p. 278, 2024.

LI, Y. *et al.* Dorsal root ganglion neurons become hyperexcitable and increase expression of voltage-gated T-type calcium channels (Cav3.2) in paclitaxel-induced peripheral neuropathy. **Pain**, [s. l.], v. 158, n. 3, p. 417–429, 2017.

LI, W. *et al.* Ibrutinib alleviates LPS-induced neuroinflammation and synaptic defects in a mouse model of depression. **Brain, Behavior, and Immunity**, [s. l.], v. 92, p. 10–24, 2021.

LI, G. zhou *et al.* Vincristine-induced peripheral neuropathy: A mini-review. **NeuroToxicology**, [s. l.], v. 81, p. 161–171, 2020a.

LI, G. zhou *et al.* Vincristine-induced peripheral neuropathy: A mini-review. **NeuroToxicology**, [s. l.], v. 81, p. 161–171, 2020b.

LIU, J. *et al.* Glutamatergic Neurons in the Amygdala Are Involved in Paclitaxel-Induced Pain and Anxiety. **Frontiers in Psychiatry**, [s. l.], v. 13, n. April, p. 1–11, 2022.

LIU, J. *et al.* Na/K-ATPase signaling and salt sensitivity: The role of oxidative stress. **Antioxidants**, [s. l.], v. 6, n. 1, p. 12–14, 2017a.

LIU, J. *et al.* Na/K-ATPase signaling and salt sensitivity: The role of oxidative stress. **Antioxidants**, [s. l.], v. 6, n. 1, p. 12–14, 2017b.

LIU, J.; LILLY, M. N.; SHAPIRO, J. I. Targeting Na/K-ATPase Signaling: A New Approach to Control Oxidative Stress. **Current Pharmaceutical Design**, [s. l.], v. 24, n. 3, p. 359–364, 2018a.

LIU, J.; LILLY, M. N.; SHAPIRO, J. I. Targeting Na/K-ATPase Signaling: A New Approach to Control Oxidative Stress. **Current Pharmaceutical Design**, [s. l.], v. 24, n. 3, p. 359–364, 2018b. Disponível em: <https://www.eurekaselect.com/158913/article>.

LIVAK, K. J.; SCHMITTGEN, T. D. Analysis of Relative Gene Expression Data Using Real-Time Quantitative PCR and the 2- $\Delta\Delta$ CT Method. **Methods**, [s. l.], v. 25, n. 4, p. 402–408, 2001a.

LIVAK, K. J.; SCHMITTGEN, T. D. Analysis of relative gene expression data using real-time quantitative PCR and the 2- $\Delta\Delta$ CT method. **Methods**, [s. l.], v. 25, n. 4, p. 402–408, 2001b.

LOWRY, Oliver H. *et al.* PROTEIN MEASUREMENT WITH THE FOLIN PHENOL REAGENT. **Journal of Biological Chemistry**, [s. l.], v. 193, n. 1, p. 265–275, 1951.

LUHMANN, H. J.; FUKUDA, A. Can we understand human brain development from experimental studies in rodents?. **Pediatrics International**, [s. l.], v. 62, n. 10, p. 1139–1144, 2020.

MACDONALD, A. D.; WOOLFE, G. Analgesic action of pethidine derivatives and related compounds. **British journal of pharmacology and chemotherapy**, [s. l.], v. 1, p. 4–14, 1946.

MADSEN, M. L. *et al.* Aspects of vincristine-induced neuropathy in hematologic malignancies: a systematic review. **Cancer Chemotherapy and Pharmacology**, [s. l.], v. 84, n. 3, p. 471–485, 2019. Disponível em: <https://doi.org/10.1007/s00280-019-03884-5>.

MAGEE, J. C.; GRIENBERGER, C. Synaptic Plasticity Forms and Functions. **Annual Review of Neuroscience**, [s. l.], v. 43, n. 1, p. 95–117, 2020a.

MAGEE, J. C.; GRIENBERGER, C. Synaptic Plasticity Forms and Functions. **Annual Review of Neuroscience**, [s. l.], v. 43, n. 1, p. 95–117, 2020b. Disponível em: <https://www.annualreviews.org/doi/10.1146/annurev-neuro-090919-022842>.

MALDONADO, L. A. G. *et al.* Influence of tumor cell-derived TGF- β on macrophage phenotype and macrophage-mediated tumor cell invasion. **The International Journal of Biochemistry & Cell Biology**, [s. l.], v. 153, p. 106330, 2022.

MALONEYHUSS, M. A. *et al.* Efficacy and toxicity of mustargen, vincristine, procarbazine and prednisone (MOPP) for the treatment of relapsed or resistant lymphoma in cats. **Journal of Feline Medicine and Surgery**, [s. l.], v. 22, n. 4, p. 299–304, 2020.

MARKOVIC, T. *et al.* Pain induces adaptations in ventral tegmental area dopamine neurons to drive anhedonia-like behavior. **Nature Neuroscience**, [s. l.], v. 24, n. 11, p. 1601–1613, 2021.

MASKO, M. *et al.* A novel approach to thermographic images analysis of equine thoracolumbar region: the effect of effort and rider's body weight on structural image complexity. **BMC Veterinary Research**, [s. l.], v. 17, n. 1, p. 99, 2021.

MCCALLUM, J. B. *et al.* Loss of T-type calcium current in sensory neurons of rats with neuropathic pain. **Anesthesiology**, [s. l.], v. 98, n. 1, p. 209–216, 2003.

MCILWAIN, K. L. *et al.* The use of behavioral test batteries: Effects of training history. **Physiology & Behavior**, [s. l.], v. 73, n. 5, p. 705–717, 2001.

MCKELVEY, R. *et al.* Neuropathic pain is constitutively suppressed in early life by anti-inflammatory neuroimmune regulation. **Journal of Neuroscience**, [s. l.], v. 35, n. 2, p. 457–466, 2015.

MEFFERT, M. K. *et al.* NF- κ B functions in synaptic signaling and behavior. **Nature Neuroscience**, [s. l.], v. 6, n. 10, p. 1072–1078, 2003.

MELÉNDEZ, D. M. *et al.* Spatial memory deficits after vincristine-induced lesions to the dorsal hippocampus. **PLoS ONE**, [s. l.], v. 15, n. 4, p. 1–16, 2020.

MESTDAGH, F.; STEYAERT, A.; LAVAND'HOMME, P. Cancer Pain Management: A Narrative Review of Current Concepts, Strategies, and Techniques. **Current Oncology**, [s. l.], v. 30, n. 7, p. 6838–6858, 2023.

MICLESCU, A. A. *et al.* Association between systemic inflammation and experimental pain sensitivity in subjects with pain and painless neuropathy after traumatic nerve injuries. **Scandinavian Journal of Pain**, [s. l.], v. 7, 2022.

MINJ, E.; UPADHAYAY, S.; MEHAN, S. Nrf2/HO-1 Signaling Activator Acetyl-11-keto-beta Boswellic Acid (AKBA)-Mediated Neuroprotection in Methyl Mercury-Induced Experimental Model of ALS. **Neurochemical Research**, [s. l.], v. 46, n. 11, p. 2867–2884, 2021.

MISRA, H. P.; FRIDOVICH, I. The role of superoxide anion in the autoxidation of epinephrine and a simple assay for superoxide dismutase. **Journal of Biological Chemistry**, [s. l.], v. 247, n. 10, p. 3170–3175, 1972.

MOJARAD-JABALI, S. *et al.* Comparison of three synthetic transferrin mimetic small peptides to promote the blood–brain barrier penetration of vincristine liposomes for improved glioma targeted therapy. **International Journal of Pharmaceutics**, [s. l.], v. 613, p. 121395, 2022.

MOK, C. C.; LOK, E. Y. C.; CHEUNG, E. F. C. Concurrent psychiatric disorders are associated with significantly poorer quality of life in patients with rheumatoid arthritis. **Scandinavian Journal of Rheumatology**, [s. l.], v. 41, n. 4, p. 253–259, 2012.

MONTAGUE, K. *et al.* A novel interaction between CX 3 CR 1 and CCR 2 signalling in monocytes constitutes an underlying mechanism for persistent vincristine-induced pain. **Journal of Neuroinflammation**, [s. l.], v. 15, n. 1, p. 1–15, 2018.

MONTAGUE-CARDOSO, K.; MALCANGIO, M. Changes in blood–spinal cord barrier permeability and neuroimmune interactions in the underlying mechanisms of chronic pain. **Pain Reports**, [s. l.], v. 6, n. 1, p. 1–7, 2021.

MORA, E. *et al.* Vincristine-induced peripheral neuropathy in pediatric cancer patients. **American Journal of Cancer Research**, [s. l.], v. 6, n. 11, p. 2416–2430, 2016.

MORTAZAVI, H. Balance training as a promising intervention for reducing the risk of fall in elderly patients with chemotherapy-induced peripheral neuropathy. **Journal of Cancer Research and Therapeutics**, [s. l.], v. 15, n. 5, p. 1192, 2019.

MOSCHETTI, G. *et al.* Prokineticin 2 promotes and sustains neuroinflammation in vincristine treated mice: Focus on pain and emotional like behavior. **Brain, Behavior, and Immunity**, [s. l.], v. 82, n. September, p. 422–431, 2019a.

MOSCHETTI, G. *et al.* Prokineticin 2 promotes and sustains neuroinflammation in vincristine treated mice: Focus on pain and emotional like behavior. **Brain, Behavior, and Immunity**, [s. l.], v. 82, n. September, p. 422–431, 2019b.

MOSELEY, A. E. *et al.* Deficiency in Na,K-ATPase α isoform genes alters spatial learning, motor activity, and anxiety in mice. **Journal of Neuroscience**, [s. l.], v. 27, n. 3, p. 616–626, 2007.

MOTTA, K. P. da *et al.* **7-Chloro-4- (phenylselanyl) quinoline reduces renal oxidative stress induced by oxaliplatin in mice.** [S. l.: s. n.], 2021a.

MOTTA, K. P. da *et al.* 7-Chloro-4- (phenylselanyl) quinoline reduces renal oxidative stress induced by oxaliplatin in mice. **Canadian physiology and pharmacology**, [s. l.], p. 1–37, 2021b.

MOTTA, K. P. da *et al.* 7-Chloro-4- (phenylselanyl) quinoline reduces renal oxidative stress induced by oxaliplatin in mice. **Canadian physiology and pharmacology**, [s. l.], p. 1–37, 2021c.

MOTTA, K. P. da *et al.* Target enzymes in oxaliplatin-induced peripheral neuropathy in Swiss mice: A new acetylcholinesterase inhibitor as therapeutic strategy. **Chemico-Biological Interactions**, [s. l.], v. 352, n. November 2021, p. 109772, 2022. Disponível em: <https://doi.org/10.1016/j.cbi.2021.109772>.

MOWLAVI, A. *et al.* Increased cutaneous nerve fibers in female specimens. **Plastic and Reconstructive Surgery**, [s. l.], v. 116, n. 5, p. 1407–1410, 2005.

MUSSBACHER, M. *et al.* NF- κ B in monocytes and macrophages – an inflammatory master regulator in multitasked immune cells. **Frontiers in Immunology**, [s. l.], v. 14, 2023a.

MUSSBACHER, M. *et al.* NF- κ B in monocytes and macrophages – an inflammatory master regulator in multitasked immune cells. **Frontiers in Immunology**, [s. l.], v. 14, 2023b. Disponível em: <https://www.frontiersin.org/articles/10.3389/fimmu.2023.1134661/full>.

NAGAI, J.; GOSHIMA, Y.; OHSHIMA, T. CRMP4 mediates MAG-induced inhibition of axonal outgrowth and protection against Vincristine-induced axonal degeneration. **Neuroscience Letters**, [s. l.], v. 519, n. 1, p. 56–61, 2012a. Disponível em: <http://dx.doi.org/10.1016/j.neulet.2012.05.020>.

NAGAI, J.; GOSHIMA, Y.; OHSHIMA, T. CRMP4 mediates MAG-induced inhibition of axonal outgrowth and protection against Vincristine-induced axonal degeneration. **Neuroscience Letters**, [s. l.], v. 519, n. 1, p. 56–61, 2012b.

NGO, V.; DUENNWALD, M. L. Nrf2 and Oxidative Stress: A General Overview of Mechanisms and Implications in Human Disease. **Antioxidants**, [s. l.], v. 11, n. 12, p. 2345, 2022.

NOGUEIRA, C. W.; ROCHA, J. B. T. Toxicology and pharmacology of selenium: Emphasis on synthetic organoselenium compounds. **Archives of Toxicology**, [s. l.], v. 85, n. 11, p. 1313–1359, 2011.

NOGUEIRA, C. W.; ZENI, G.; ROCHA, J. B. T. Organoselenium and organotellurium compounds: Toxicology and pharmacology. **Chemical Reviews**, [s. l.], v. 104, n. 12, p. 6255–6285, 2004.

NOVELLE, M. G.; CAMACHO-MORALES, A.; MARTÍNEZ DE MORENTIN, P. B. Editorial: Role of estrogens as key regulators of energy homeostasis. **Frontiers in Endocrinology**, [s. l.], v. 14, 2023.

OHKAWA, H.; OHISHI, N.; YAGI, K. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. **Analytical Biochemistry**, [s. l.], v. 95, n. 2, p. 351–358, 1979.

OLD, E. A. *et al.* Monocytes expressing CX3CR1 orchestrate the development of vincristine-induced pain. **Journal of Clinical Investigation**, [s. l.], v. 124, n. 5, p. 2023–2036, 2014a.

OLD, E. A. *et al.* Monocytes expressing CX3CR1 orchestrate the development of vincristine-induced pain. **Journal of Clinical Investigation**, [s. l.], v. 124, n. 5, p. 2023–2036, 2014b.

O'ROURKE, S. A.; SHANLEY, L. C.; DUNNE, A. The Nrf2-HO-1 system and inflammaging. **Frontiers in Immunology**, [s. l.], v. 15, 2024.

PAICE, J. A. *et al.* Management of Chronic Pain in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. **Journal of Clinical Oncology**, [s. l.], v. 34, n. 27, p. 3325–3345, 2016.

PALTIAN, J. J. *et al.* 7-chloro-4-(phenylselanyl) quinoline incorporation into polymeric nanocapsules improves its pharmacological action: Physicochemical, toxicological, and behavioral studies. **International Journal of Pharmaceutics**, [s. l.], v. 673, p. 125370, 2025.

PALTIAN, J. J. *et al.* 7-Chloro-4-(Phenylselanyl) Quinoline Is a Novel Multitarget Therapy to Combat Peripheral Neuropathy and Comorbidities Induced by Paclitaxel in Mice. **Molecular Neurobiology**, [s. l.], n. 0123456789, 2022a. Disponível em: <https://doi.org/10.1007/s12035-022-02991-4>.

PALTIAN, J. J. *et al.* 7-Chloro-4-(Phenylselenyl) Quinoline Is a Novel Multitarget Therapy to Combat Peripheral Neuropathy and Comorbidities Induced by Paclitaxel in Mice. **Molecular Neurobiology**, [s. l.], n. 0123456789, 2022b.

PALTIAN, J. J. *et al.* The anxiolytic effect of a promising quinoline containing selenium with the contribution of the serotonergic and GABAergic pathways: Modulation of parameters associated with anxiety in mice. **Behavioural Brain Research**, [s. l.], v. 393, n. June, p. 112797, 2020a. Disponível em: <https://doi.org/10.1016/j.bbr.2020.112797>.

PALTIAN, J. J. *et al.* The anxiolytic effect of a promising quinoline containing selenium with the contribution of the serotonergic and GABAergic pathways: Modulation of parameters associated with anxiety in mice. **Behavioural Brain Research**, [s. l.], v. 393, n. June, p. 112797, 2020b.

PATIL, M. J. *et al.* Ginger Constituent 6-Shogaol Attenuates Vincristine-Induced Activation of Mouse Gastroesophageal Vagal Afferent C-Fibers. **Molecules**, [s. l.], v. 27, n. 21, 2022.

PAUWELS, B. *et al.* Comparison of the sulforhodamine B assay and the clonogenic assay for in vitro chemoradiation studies. **Cancer Chemotherapy and Pharmacology**, [s. l.], v. 51, n. 3, p. 221–226, 2003.

PEDRA, N. S. *et al.* Impact of gallic acid on tumor suppression: Modulation of redox homeostasis and purinergic response in in vitro and a preclinical glioblastoma model. **The Journal of Nutritional Biochemistry**, [s. l.], v. 110, p. 109156, 2022.

PELLOW, S. *et al.* Validation of open : closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. **Journal of Neuroscience Methods**, [s. l.], v. 14, n. 3, p. 149–167, 1985.

PÉREZ-GONZÁLEZ, M. Z. *et al.* Anti-inflammatory, antioxidant, and acute toxicity of Brugmansia arborea extracts from wild plants and shoots obtained by indirect organogenesis. A thermographic assay to anti-inflammatory evaluation. **Biomedicine & Pharmacotherapy**, [s. l.], v. 186, p. 117972, 2025.

PIETROBON, D.; MOSKOWITZ, M. A. Pathophysiology of Migraine. **Annual Review of Physiology**, [s. l.], v. 75, n. 1, p. 365–391, 2013a.

PIETROBON, D.; MOSKOWITZ, M. A. Pathophysiology of Migraine. **Annual Review of Physiology**, [s. l.], v. 75, n. 1, p. 365–391, 2013b. Disponível em: <https://www.annualreviews.org/doi/10.1146/annurev-physiol-030212-183717>.

PINZ, M. *et al.* 4-Phenylselenyl-7-chloroquinoline, a new quinoline derivative containing selenium, has potential antinociceptive and anti-inflammatory actions. **European Journal of Pharmacology**, [s. l.], v. 780, p. 122–128, 2016a. Disponível em: <http://dx.doi.org/10.1016/j.ejphar.2016.03.039>.

PINZ, M. *et al.* 4-Phenylselenyl-7-chloroquinoline, a new quinoline derivative

containing selenium, has potential antinociceptive and anti-inflammatory actions. **European Journal of Pharmacology**, [s. l.], v. 780, p. 122–128, 2016b.

PINZ, M. P. *et al.* Current advances of pharmacological properties of 7-chloro-4-(phenylselenanyl) quinoline: Prevention of cognitive deficit and anxiety in Alzheimer's disease model. **Biomedicine and Pharmacotherapy**, [s. l.], v. 105, n. June, p. 1006–1014, 2018a. Disponível em: <https://doi.org/10.1016/j.biopha.2018.06.049>.

PINZ, M. P. *et al.* Current advances of pharmacological properties of 7-chloro-4-(phenylselenanyl) quinoline: Prevention of cognitive deficit and anxiety in Alzheimer's disease model. **Biomedicine and Pharmacotherapy**, [s. l.], v. 105, n. June, p. 1006–1014, 2018b.

PURSER, M. J.; JOHNSTON, D. L.; MCMILLAN, H. J. Chemotherapy-induced Peripheral Neuropathy Among Paediatric Oncology Patients. **Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques**, [s. l.], v. 41, n. 4, p. 442–447, 2014.

QUEIROZ, M. P. *et al.* Effect of Conjugated Linoleic Acid on Memory and Reflex Maturation in Rats Treated During Early Life. **Frontiers in Neuroscience**, [s. l.], v. 13, 2019.

QUEIROZ, K. F. F. da C.; DE CÁSSIA FERNANDES DE LIMA, R. Smart screening system for breast cancer: the use of thermographic images, evolutionary algorithms, and oversampling. **Biomedical Physics & Engineering Express**, [s. l.], v. 9, n. 5, p. 055027, 2023.

QUINES, C. B. *et al.* Involvement of the serotonergic system in the anxiolytic-like effect of 2-phenylethynyl butyltellurium in mice. **Behavioural Brain Research**, [s. l.], v. 277, p. 221–227, 2015.

QUINN, R. Comparing rat's to human's age: How old is my rat in people years? **Nutrition**, [s. l.], v. 21, n. 6, p. 775–777, 2005.

QUITON, R. L.; GREENSPAN, J. D. Sex differences in endogenous pain modulation by distracting and painful conditioning stimulation. **Pain**, [s. l.], p. 132–149, 2007.

RAASING, L. R. M. *et al.* Current View of Diagnosing Small Fiber Neuropathy. **Journal of Neuromuscular Diseases**, [s. l.], v. 8, n. 2, p. 185–207, 2021.

REIS, A. S. *et al.* 4-phenylselenanyl-7-chloroquinoline, a novel multitarget compound with anxiolytic activity: Contribution of the glutamatergic system. **Journal of Psychiatric Research**, [s. l.], v. 84, p. 191–199, 2017a.

REIS, A. S. *et al.* 4-phenylselenanyl-7-chloroquinoline, a novel multitarget compound with anxiolytic activity: Contribution of the glutamatergic system. **Journal of Psychiatric Research**, [s. l.], v. 84, p. 191–199, 2017b.

REIS, A. S. *et al.* 4-phenylselenyl-7-chloroquinoline, a novel multitarget compound with anxiolytic activity: Contribution of the glutamatergic system. **Journal of Psychiatric Research**, [s. l.], v. 84, p. 191–199, 2017c. Disponível em: <https://linkinghub.elsevier.com/retrieve/pii/S0022395616304976>.

REIS, A. S. *et al.* Advances in the Understanding of Oxaliplatin-Induced Peripheral Neuropathy in Mice: 7-Chloro-4-(Phenylselenyl) Quinoline as a Promising Therapeutic Agent. **Molecular Neurobiology**, [s. l.], v. 57, n. 12, p. 5219–5234, 2020a.

REIS, A. S. *et al.* Advances in the Understanding of Oxaliplatin-Induced Peripheral Neuropathy in Mice: 7-Chloro-4-(Phenylselenyl) Quinoline as a Promising Therapeutic Agent. **Molecular Neurobiology**, [s. l.], v. 57, n. 12, p. 5219–5234, 2020b.

REIS, A. S. *et al.* Interface of Aging and Acute Peripheral Neuropathy Induced by Oxaliplatin in Mice: Target-Directed Approaches for Na⁺, K⁺—ATPase, Oxidative Stress, and 7-Chloro-4-(phenylselenyl) quinoline Therapy. **Molecular Neurobiology**, [s. l.], v. 59, n. 3, p. 1766–1780, 2022. Disponível em: <https://doi.org/10.1007/s12035-021-02659-5>.

REIS, A. S. *et al.* Pharmacological modulation of Na⁺, K⁺-ATPase as a potential target for OXA-induced neurotoxicity: Correlation between anxiety and cognitive decline and beneficial effects of 7-chloro-4-(phenylselenyl) quinoline. **Brain Research Bulletin**, [s. l.], v. 162, n. June, p. 282–290, 2020c.

REIS, A. S. *et al.* Pharmacological modulation of Na⁺, K⁺-ATPase as a potential target for OXA-induced neurotoxicity: Correlation between anxiety and cognitive decline and beneficial effects of 7-chloro-4-(phenylselenyl) quinoline. **Brain Research Bulletin**, [s. l.], v. 162, n. June, p. 282–290, 2020d.

REIS, A. S. *et al.* Platinum Deposition in the Central Nervous System: A Novel Insight into Oxaliplatin-induced Peripheral Neuropathy in Young and Old Mice. **Molecular Neurobiology**, [s. l.], v. 62, n. 3, p. 3712–3729, 2025.

REZENDE, A. A. *et al.* Anti-Tumor Efficiency of Perillyl alcohol/ β -Cyclodextrin Inclusion Complexes in a Sarcoma S180-Induced Mice Model. **Pharmaceutics**, [s. l.], v. 13, n. 2, p. 245, 2021.

RODRIGUES, K. C. *et al.* The neurotherapeutic role of a selenium-functionalized quinoline in hypothalamic obese rats. **Psychopharmacology**, [s. l.], v. 238, n. 7, p. 1937–1951, 2021a.

RODRIGUES, K. C. *et al.* The neurotherapeutic role of a selenium-functionalized quinoline in hypothalamic obese rats. **Psychopharmacology**, [s. l.], v. 238, n. 7, p. 1937–1951, 2021b.

ROHN, T. T.; HINDS, T. R.; VINCENZI, F. F. Ion transport ATPases as targets for free radical damage. **Biochemical Pharmacology**, [s. l.], v. 46, n. 3, p. 525–

534, 1993.

RUAN, Y. *et al.* An effective and concise device for detecting cold allodynia in mice. **Scientific Reports**, [s. l.], v. 8, n. 1, 2018.

RUBIO, M. *et al.* The immunosuppressive effect of vincristine on allostimulatory potential of human dendritic cells interferes with their function and survival. **International Journal of Oncology**, [s. l.], 2004.

RUDNITSKAYA, E. A. *et al.* Features of Postnatal Hippocampal Development in a Rat Model of Sporadic Alzheimer's Disease. **Frontiers in Neuroscience**, [s. l.], v. 14, 2020.

RUHEE, R. T. *et al.* Organosulfur Compounds: A Review of Their Anti-inflammatory Effects in Human Health. **Frontiers in Nutrition**, [s. l.], v. 7, 2020.

SAGALAJEV, B. *et al.* Bidirectional amygdaloid control of neuropathic hypersensitivity mediated by descending serotonergic pathways acting on spinal 5-HT₃ and 5-HT_{1A} receptors. **Behavioural Brain Research**, [s. l.], v. 282, p. 14–24, 2015.

SAHRANAVARD, S. *et al.* Hydroethanolic extract of *Lavandula angustifolia* ameliorates vincristine-induced peripheral neuropathy in rats. **Research in Pharmaceutical Sciences**, [s. l.], v. 17, n. 3, p. 265, 2022. Disponível em: <https://journals.lww.com/10.4103/1735-5362.343080>.

SALAŁAT, K.; FILIPEK, B. Antinociceptive activity of transient receptor potential channel TRPV1, TRPA1, and TRPM8 antagonists in neurogenic and neuropathic pain models in mice. **Journal of Zhejiang University-SCIENCE B**, [s. l.], v. 16, n. 3, p. 167–178, 2015.

SAMPATHKUMAR, V. *et al.* Integration of signals from different cortical areas in higher order thalamic neurons. **Proceedings of the National Academy of Sciences**, [s. l.], v. 118, n. 30, 2021.

SANTOS, G. J. L. *et al.* *Himatanthus drasticus* (Apocynaceae) latex reduces oxidative stress and modulates CD4⁺, CD8⁺, FoxP3⁺ and HSP-60⁺ expressions in Sarcoma 180-bearing mice. **Journal of Ethnopharmacology**, [s. l.], v. 220, p. 159–168, 2018.

SAVEGNAGO, L. *et al.* Synthesis and antioxidant properties of novel quinoline-chalcogenium compounds. **Tetrahedron Letters**, [s. l.], v. 54, n. 1, p. 40–44, 2013a.

SAVEGNAGO, L. *et al.* Synthesis and antioxidant properties of novel quinoline-chalcogenium compounds. **Tetrahedron Letters**, [s. l.], v. 54, n. 1, p. 40–44, 2013b. Disponível em: <http://dx.doi.org/10.1016/j.tetlet.2012.10.067>.

SCHAPPACHER, K. A. *et al.* Neonatal vincristine administration modulates intrinsic neuronal excitability in the rat dorsal root ganglion and spinal dorsal

horn during adolescence. **Pain**, [s. l.], v. 160, n. 3, p. 645–657, 2019a.

SCHAPPACHER, K. A. *et al.* Neonatal vincristine administration modulates intrinsic neuronal excitability in the rat dorsal root ganglion and spinal dorsal horn during adolescence. **Pain**, [s. l.], v. 160, n. 3, p. 645–657, 2019b.

SCHAPPACHER, K. A. *et al.* Neonatal vincristine administration modulates intrinsic neuronal excitability in the rat dorsal root ganglion and spinal dorsal horn during adolescence. **Pain**, [s. l.], v. 160, n. 3, p. 645–657, 2019c.

SCHAPPACHER, K. A.; STYCZYNSKI, L.; BACCEI, M. L. **Early life vincristine exposure evokes mechanical pain hypersensitivity in the developing rat.** [S. l.: s. n.], 2017-. ISSN 18726623.v. 158

SEKERES, M. J.; WINOCUR, G.; MOSCOVITCH, M. The hippocampus and related neocortical structures in memory transformation. **Neuroscience Letters**, [s. l.], v. 680, p. 39–53, 2018.

SEMPLE, B. D. *et al.* Brain development in rodents and humans: Identifying benchmarks of maturation and vulnerability to injury across species. **Progress in Neurobiology**, [s. l.], v. 106–107, p. 1–16, 2013.

SENGUPTA, S. *et al.* Adverse Neonatal Outcomes Associated With Early-Term Birth. **JAMA Pediatrics**, [s. l.], v. 167, n. 11, p. 1053, 2013.

SHABANI, M. *et al.* Profound destructive effects of adolescent exposure to Vincristine accompanied with some sex differences in motor and memory performance. **Canadian Journal of Physiology and Pharmacology**, [s. l.], v. 90, n. 4, p. 379–386, 2012a.

SHABANI, M. *et al.* Profound destructive effects of adolescent exposure to Vincristine accompanied with some sex differences in motor and memory performance. **Canadian Journal of Physiology and Pharmacology**, [s. l.], v. 90, n. 4, p. 379–386, 2012b.

SHAO, Y. *et al.* Morin Regulates M1/M2 Microglial Polarization via NF- κ B p65 to Alleviate Vincristine-Induced Neuropathic Pain. **Drug Design, Development and Therapy**, [s. l.], v. Volume 18, p. 3143–3156, 2024.

SHAYESTEH, S. *et al.* Dapsone improves the vincristine-induced neuropathic nociception by modulating neuroinflammation and oxidative stress. **DARU, Journal of Pharmaceutical Sciences**, [s. l.], v. 30, n. 2, p. 303–310, 2022a.

SHAYESTEH, S. *et al.* Dapsone improves the vincristine-induced neuropathic nociception by modulating neuroinflammation and oxidative stress. **DARU, Journal of Pharmaceutical Sciences**, [s. l.], v. 30, n. 2, p. 303–310, 2022b. Disponível em: <https://doi.org/10.1007/s40199-022-00448-6>.

SHEN, Y. *et al.* Exogenous induction of HO-1 alleviates vincristine-induced neuropathic pain by reducing spinal glial activation in mice. **Neurobiology of**

Disease, [s. l.], v. 79, p. 100–110, 2015a.

SHEN, Y. *et al.* Exogenous induction of HO-1 alleviates vincristine-induced neuropathic pain by reducing spinal glial activation in mice. **Neurobiology of Disease**, [s. l.], v. 79, p. 100–110, 2015b. Disponível em: <http://dx.doi.org/10.1016/j.nbd.2015.04.012>.

SHINWARI, Z. *et al.* Vincristine and lomustine induce apoptosis and p21WAF1 up-regulation in medulloblastoma and normal human epithelial and fibroblast cells. **Journal of Neuro-Oncology**, [s. l.], v. 87, n. 2, p. 123–132, 2008.

SILVA, A. V. Associations between clinical signs and pathological findings in toxicity testing. **ALTEX**, [s. l.], 2020.

SILVA, V. D. G. *et al.* Further analysis of acute antinociceptive and anti-inflammatory actions of 4-phenylselenyl-7-chloroquinoline in mice. **Fundamental and Clinical Pharmacology**, [s. l.], v. 31, n. 5, p. 513–525, 2017a.

SILVA, V. D. G. *et al.* Further analysis of acute antinociceptive and anti-inflammatory actions of 4-phenylselenyl-7-chloroquinoline in mice. **Fundamental and Clinical Pharmacology**, [s. l.], v. 31, n. 5, p. 513–525, 2017b.

SIMÃO, D. A. da S. *et al.* Chemotherapy-induced peripheral neuropathy: review for clinical practice. **Revista Dor**, [s. l.], v. 16, n. 3, p. 215–220, 2015.

ŞİMŞEK, Ş.; OYMAK SOYSAL, A. N.; KAŞ ÖZDEMİR, A. Association between Pain Intensity, Pain Belief, and Coping Strategies in Older Adults. **Experimental Aging Research**, [s. l.], v. 49, n. 3, p. 244–251, 2023a. Disponível em: <https://doi.org/10.1080/0361073X.2022.2101304>.

ŞİMŞEK, Ş.; OYMAK SOYSAL, A. N.; KAŞ ÖZDEMİR, A. Association between Pain Intensity, Pain Belief, and Coping Strategies in Older Adults. **Experimental Aging Research**, [s. l.], v. 49, n. 3, p. 244–251, 2023b.

SINGH, G. *et al.* Bergapten Ameliorates Vincristine-Induced Peripheral Neuropathy by Inhibition of Inflammatory Cytokines and NFκB Signaling. research-article. **ACS Chemical Neuroscience**, [s. l.], v. 10, n. 6, p. 3008–3017, 2019a.

SINGH, G. *et al.* Bergapten Ameliorates Vincristine-Induced Peripheral Neuropathy by Inhibition of Inflammatory Cytokines and NFκB Signaling. research-article. **ACS Chemical Neuroscience**, [s. l.], v. 10, n. 6, p. 3008–3017, 2019b.

SMART, J. L.; DOBBING, J. Vulnerability of developing brain. II. Effects of early nutritional deprivation on reflex ontogeny and development of behaviour in the rat. **Brain Research**, [s. l.], v. 28, n. 1, p. 85–95, 1971.

SMITH, E. M. L. *et al.* Predictors of duloxetine response in patients with oxaliplatin-induced painful chemotherapy-induced peripheral neuropathy (CIPN): a secondary analysis of randomised controlled trial – CALGB/alliance 170601. **European Journal of Cancer Care**, [s. l.], v. 26, n. 2, 2017.

SNIJDERS, R. *et al.* Update on Prevalence of Pain in Patients with Cancer 2022: A Systematic Literature Review and Meta-Analysis. **Cancers**, [s. l.], v. 15, n. 3, p. 591, 2023.

SONG, B. *et al.* Inhibitory phosphorylation of GSK-3 by CaMKII couples depolarization to neuronal survival. **Journal of Biological Chemistry**, [s. l.], v. 285, n. 52, p. 41122–41134, 2010.

SORIANO, D. *et al.* Chemotherapy-induced neuropathy and pain in pediatric oncology patients: impact of combination therapies. **European Journal of Pediatrics**, [s. l.], v. 183, n. 9, p. 3749–3756, 2024.

SOYOCAK, A. *et al.* Tannic acid exhibits anti-inflammatory effects on formalin-induced paw edema model of inflammation in rats. **Human & Experimental Toxicology**, [s. l.], v. 38, n. 11, p. 1296–1301, 2019.

STANGHERLIN, E. C.; ROCHA, J. B. T.; NOGUEIRA, C. W. Diphenyl ditelluride impairs short-term memory and alters neurochemical parameters in young rats. **Pharmacology Biochemistry and Behavior**, [s. l.], v. 91, n. 3, p. 430–435, 2009.

STAROBOVA, H. *et al.* Minocycline prevents the development of mechanical allodynia in mouse models of vincristine-induced peripheral neuropathy. **Frontiers in Neuroscience**, [s. l.], v. 13, n. JUN, p. 1–10, 2019.

STAROBOVA, H.; VETTER, I. Pathophysiology of chemotherapy-induced peripheral neuropathy. **Frontiers in Molecular Neuroscience**, [s. l.], v. 10, n. May, p. 1–21, 2017a.

STAROBOVA, H.; VETTER, I. Pathophysiology of chemotherapy-induced peripheral neuropathy. **Frontiers in Molecular Neuroscience**, [s. l.], v. 10, n. May, p. 1–21, 2017b.

STEEL, A. *et al.* A network linking scene perception and spatial memory systems in posterior cerebral cortex. **Nature Communications**, [s. l.], v. 12, n. 1, p. 2632, 2021.

STERU, L. *et al.* The tail suspension test: A new method for screening antidepressants in mice. **Psychopharmacology**, [s. l.], v. 85, n. 3, p. 367–370, 1985.

STYCZYNSKI, L. M.; SCHAPPACHER, K. A.; BACCEI, M. L. Early life vincristine fails to prime developing pain pathways. **Neuroscience Letters**, [s. l.], v. 720, n. January, p. 134764, 2020. Disponível em: <https://doi.org/10.1016/j.neulet.2020.134764>.

SU, H. *et al.* Regulation of the Nrf2/HO-1 axis by mesenchymal stem cells-derived extracellular vesicles: implications for disease treatment. **Frontiers in Cell and Developmental Biology**, [s. l.], v. 12, 2024.

SU, Y.-C. *et al.* Survivors of Non-Hodgkin's Lymphoma: A Comparative Study on Patients With Vincristine-Induced Neuropathy and Their Quality of Life. **Journal of Nursing Research**, [s. l.], v. 33, n. 3, p. e393, 2025.

SUN, J. *et al.* Hemoprotein Bach1 regulates enhancer availability of heme oxygenase-1 gene. **The EMBO Journal**, [s. l.], v. 21, n. 19, p. 5216–5224, 2002.

SUN, G. *et al.* Temporal pain processing in the primary somatosensory cortex and anterior cingulate cortex. **Molecular Brain**, [s. l.], v. 16, n. 1, p. 3, 2023.

SUNG, J. Y. *et al.* Sensory axonal dysfunction in cervical radiculopathy. **Journal of Neurology, Neurosurgery and Psychiatry**, [s. l.], v. 86, n. 6, p. 640–645, 2015a.

SUNG, J. Y. *et al.* Sensory axonal dysfunction in cervical radiculopathy. **Journal of Neurology, Neurosurgery and Psychiatry**, [s. l.], v. 86, n. 6, p. 640–645, 2015b.

SWARM, R. A. *et al.* Adult Cancer Pain. **Journal of the National Comprehensive Cancer Network**, [s. l.], v. 11, n. 8, p. 992–1022, 2013.

SY, A. *et al.* Heterozygosity for CMT Type 4 Predicts a Severe Vincristine-induced Polyneuropathy Phenotype: A Case Report and Review of Literature. **Journal of Pediatric Hematology/Oncology**, [s. l.], v. 41, n. 1, p. E41–E43, 2019a.

SY, A. *et al.* Heterozygosity for CMT Type 4 Predicts a Severe Vincristine-induced Polyneuropathy Phenotype: A Case Report and Review of Literature. **Journal of Pediatric Hematology/Oncology**, [s. l.], v. 41, n. 1, p. E41–E43, 2019b.

TAKEDA, M.; TAKAHASHI, M.; MATSUMOTO, S. Suppression of neurokinin-1 receptor in trigeminal ganglia attenuates central sensitization following inflammation. **Journal of the Peripheral Nervous System**, [s. l.], v. 17, n. 2, p. 169–181, 2012.

TANTAWY, S. I. *et al.* Targeting MCL-1 protein to treat cancer: opportunities and challenges. **Frontiers in Oncology**, [s. l.], v. 13, 2023.

TAVES, S. *et al.* Microglia and Spinal Cord Synaptic Plasticity in Persistent Pain. **Neural Plasticity**, [s. l.], v. 2013, p. 1–10, 2013. Disponível em: <http://www.hindawi.com/journals/np/2013/753656/>.

TAY, N. *et al.* Chemotherapy-induced peripheral neuropathy in children and

adolescent cancer patients. **Frontiers in Molecular Biosciences**, [s. l.], v. 9, 2022.

TAY, S. Y. *et al.* Pediatric Oncology Patients With Vincristine-Induced Recurrent Laryngeal Nerve Palsy: Two Case Reports and a Brief Review of Literature. **Ear, Nose and Throat Journal**, [s. l.], v. 100, n. 10, p. NP459–NP463, 2021a.

TAY, S. Y. *et al.* Pediatric Oncology Patients With Vincristine-Induced Recurrent Laryngeal Nerve Palsy: Two Case Reports and a Brief Review of Literature. **Ear, Nose and Throat Journal**, [s. l.], v. 100, n. 10, p. NP459–NP463, 2021b.

TIMMINS, H. C. *et al.* The impact of obesity on neuropathy outcomes for paclitaxel- and oxaliplatin-treated cancer survivors. **Journal of Cancer Survivorship**, [s. l.], v. 16, n. 2, p. 223–232, 2022.

TINNIRELLO, A.; MAZZOLENI, S.; SANTI, C. Chronic Pain in the Elderly: Mechanisms and Perspectives. **Biomolecules**, [s. l.], v. 11, n. March, p. 1256, 2021.

TOWER, J.; POMATTO, L. C. D.; DAVIES, K. J. A. Sex differences in the response to oxidative and proteolytic stress. **Redox Biology**, [s. l.], v. 31, p. 101488, 2020.

TREDE, R. D. The International Association for the Study of Pain definition of pain: As valid in 2018 as in 1979, but in need of regularly updated footnotes. **Pain Reports**, [s. l.], v. 3, n. 2, p. 1–3, 2018.

TREVISAN, G. *et al.* Antinociceptive Effects of 14-Membered Cyclopeptide Alkaloids. **Journal of natural products**, [s. l.], v. 72, p. 608–612, 2009.

TRIARICO, S. *et al.* Vincristine-induced peripheral neuropathy (Vipn) in pediatric tumors: Mechanisms, risk factors, strategies of prevention and treatment. **International Journal of Molecular Sciences**, [s. l.], v. 22, n. 8, 2021a.

TRIARICO, S. *et al.* Vincristine-induced peripheral neuropathy (Vipn) in pediatric tumors: Mechanisms, risk factors, strategies of prevention and treatment. **International Journal of Molecular Sciences**, [s. l.], v. 22, n. 8, 2021b.

TRIARICO, S. *et al.* Vincristine-Induced Peripheral Neuropathy (VIPN) in Pediatric Tumors: Mechanisms, Risk Factors, Strategies of Prevention and Treatment. **International Journal of Molecular Sciences**, [s. l.], v. 22, n. 8, p. 4112, 2021c.

TUCKER, M. H.; TIWARI, P.; CARTER, B. S. The physiology, assessment, and treatment of neonatal pain. **Seminars in Fetal and Neonatal Medicine**, [s. l.], v. 28, n. 4, p. 101465, 2023.

TUMMALA, R. *et al.* Expression of Na,K-ATPase- β 1 subunit increases uptake

and sensitizes carcinoma cells to oxaliplatin. **Cancer Chemotherapy and Pharmacology**, [s. l.], v. 64, n. 6, p. 1187–1194, 2009.

TUNJUNGSARI, D. A.; GUNAWAN, P. I.; UGRASENA, I. D. G. RISK FACTORS OF VINCRISTINE-INDUCED PERIPHERAL NEUROPATHY IN ACUTE LYMPHOBLASTIC LEUKAEMIA CHILDREN. **The Journal of Medical Investigation**, [s. l.], v. 68, n. 3.4, p. 232–237, 2021.

TURCU-STIOLICA, A. *et al.* Diagnostic Accuracy of Machine-Learning Models on Predicting Chemo-Brain in Breast Cancer Survivors Previously Treated with Chemotherapy: A Meta-Analysis. **International Journal of Environmental Research and Public Health**, [s. l.], v. 19, n. 24, p. 16832, 2022.

UITTENBOOGAARD, A. *et al.* Pharmacogenomics of Vincristine-Induced Peripheral Neuropathy in Children with Cancer: A Systematic Review and Meta-Analysis. **Cancers**, [s. l.], v. 14, n. 3, p. 612, 2022.

UMANA, I. C. *et al.* **Nicotinic modulation of descending pain control circuitry**. [S. l.: s. n.], 2017-. ISSN 18726623.v. 158

VAN DE VELDE, M. E. *et al.* The association between vincristine-induced peripheral neuropathy and health-related quality of life in children with cancer. **Cancer Medicine**, [s. l.], v. 10, n. 22, p. 8172–8181, 2021.

VAN DE VELDE, M. E. *et al.* Vincristine-induced peripheral neuropathy in children with cancer: A systematic review. **Critical Reviews in Oncology/Hematology**, [s. l.], v. 114, p. 114–130, 2017a. Disponível em: <https://doi.org/10.1016/j.critrevonc.2017.04.004>.

VAN DE VELDE, M. E. *et al.* Vincristine-induced peripheral neuropathy in children with cancer: A systematic review. **Critical Reviews in Oncology/Hematology**, [s. l.], v. 114, p. 114–130, 2017b.

VAN DEN BEUKEN-VAN EVERDINGEN, M. H. J. *et al.* Prevalence of pain in patients with cancer: a systematic review of the past 40 years. **Annals of Oncology**, [s. l.], v. 18, n. 9, p. 1437–1449, 2007.

VEGA-AVELAIRA, D.; MOSS, A.; FITZGERALD, M. Age-related changes in the spinal cord microglial and astrocytic response profile to nerve injury. **Brain, Behavior, and Immunity**, [s. l.], v. 21, n. 5, p. 617–623, 2007.

VOGT, A. G. *et al.* Organoselenium group is critical for antioxidant activity of 7-chloro-4-phenylselenyl-quinoline. **Chemico-Biological Interactions**, [s. l.], v. 282, p. 7–12, 2018a. Disponível em: <https://doi.org/10.1016/j.cbi.2018.01.003>.

VOGT, A. G. *et al.* Organoselenium group is critical for antioxidant activity of 7-chloro-4-phenylselenyl-quinoline. **Chemico-Biological Interactions**, [s. l.], v. 282, p. 7–12, 2018b.

VOSS, G. T. *et al.* Therapeutic and technological potential of 7-chloro-4-

phenylselanyl quinoline for the treatment of atopic dermatitis-like skin lesions in mice. **Materials Science and Engineering C**, [s. l.], v. 84, n. August 2017, p. 90–98, 2017a. Disponível em: <https://doi.org/10.1016/j.msec.2017.11.026>.

VOSS, G. T. *et al.* Therapeutic and technological potential of 7-chloro-4-phenylselanyl quinoline for the treatment of atopic dermatitis-like skin lesions in mice. **Materials Science and Engineering C**, [s. l.], v. 84, n. August 2017, p. 90–98, 2017b.

WALKER, J. L. *et al.* Gait-stance duration as a measure of injury and recovery in the rat sciatic nerve model. **Journal of Neuroscience Methods**, [s. l.], v. 52, n. 1, p. 47–52, 1994.

WALSH, R. N.; CUMMINS, R. A. The open-field test: A critical review. **Psychological Bulletin**, [s. l.], v. 83, n. 3, p. 482–504, 1976.

WANG, F. *et al.* Influence of blood-brain barrier efflux pumps on the distribution of vincristine in brain and brain tumors. **Neuro-Oncology**, [s. l.], v. 12, n. 10, p. 1043–1049, 2010.

WANG, X. *et al.* Observation of Acetylcholinesterase in Stress-Induced Depression Phenotypes by Two-Photon Fluorescence Imaging in the Mouse Brain. **Journal of the American Chemical Society**, [s. l.], v. 141, n. 5, p. 2061–2068, 2019.

WANG, M. S. *et al.* Pathogenesis of axonal degeneration: Parallels between Wallerian degeneration and vincristine neuropathy. **Journal of Neuropathology and Experimental Neurology**, [s. l.], v. 59, n. 7, p. 599–606, 2000a.

WANG, M. S. *et al.* Pathogenesis of axonal degeneration: Parallels between Wallerian degeneration and vincristine neuropathy. **Journal of Neuropathology and Experimental Neurology**, [s. l.], v. 59, n. 7, p. 599–606, 2000b.

WANG, J. H. *et al.* Relationship between prescribed opioids, pain management satisfaction, and pain intensity in oncology outpatients. **Supportive Care in Cancer**, [s. l.], v. 30, n. 4, p. 3233–3240, 2022. Disponível em: <https://doi.org/10.1007/s00520-021-06722-8>.

WANG, L.; AHN, Y. J.; ASMIS, R. Sexual dimorphism in glutathione metabolism and glutathione-dependent responses. **Redox Biology**, [s. l.], v. 31, p. 101410, 2020.

WEEKS, J. C.; LEVINE, R. B. Steroid hormone effects on neurons subserving behavior. **Current Opinion in Neurobiology**, [s. l.], v. 5, n. 6, p. 809–815, 1995.

WHITE, D. *et al.* Targeting translation: A review of preclinical animal models in the development of treatments for chemotherapy-induced peripheral

neuropathy. **Journal of the Peripheral Nervous System**, [s. l.], v. 28, n. 2, p. 179–190, 2023.

WIESKOPF, J. S. *et al.* The nicotinic $\alpha 6$ subunit gene determines variability in chronic pain sensitivity via cross-inhibition of P2X2/3 receptors. **Science Translational Medicine**, [s. l.], v. 7, n. 287, 2015.

WILHELM, E. A. *et al.* Antioxidant effect of quinoline derivatives containing or not selenium: Relationship with antinociceptive action quinolines are antioxidant and antinociceptive. **Anais da Academia Brasileira de Ciencias**, [s. l.], v. 89, n. 1, p. 457–467, 2017.

WILLIAMS, M. D.; LASCELLES, B. D. X. Early Neonatal Pain—A Review of Clinical and Experimental Implications on Painful Conditions Later in Life. **Frontiers in Pediatrics**, [s. l.], v. 8, 2020a.

WILLIAMS, M. D.; LASCELLES, B. D. X. Early Neonatal Pain—A Review of Clinical and Experimental Implications on Painful Conditions Later in Life. **Frontiers in Pediatrics**, [s. l.], v. 8, 2020b.

WOLF, E. *et al.* Innate Conformational Dynamics Drive Binding Specificity in Anti-Apoptotic Proteins Mcl-1 and Bcl-2. **Biochemistry**, [s. l.], v. 62, n. 11, p. 1619–1630, 2023.

WOOLF, C. J. Pain modulation in the spinal cord. **Frontiers in Pain Research**, [s. l.], v. 3, 2022.

WOOLFE, G.; MACDONALD, A. D. The Evaluation of the analgesic action of pethidine hydrochloride (demerol). **Journal of Pharmacology and Experimental Therapeutics**, [s. l.], v. 80, n. 3, p. 300–307, 1944.

WORLD HEALTH ORGANIZATION (WHO). **Global cancer burden growing, amidst mounting need for services**. [S. l.: s. n.], 2024. Disponível em: : <https://www.who.int/news/item/01-02-2024-global-cancer-burden-growing-amidstmounting-need-for-services>. Acesso em: 14 jul. 2025.

XIAOHONG, G. *et al.* [Effects of glucocorticoid receptor agonists on hyperalgesia of rats with neuropathic pain and its mechanisms]. **Chinese Journal of Applied Physiology**, [s. l.], v. 38, n. 5, p. 470–474, 2022.

XU, T. *et al.* Epigenetic upregulation of CXCL12 expression mediates antitubulin chemotherapeutics-induced neuropathic pain. **Pain**, [s. l.], v. 158, n. 4, p. 637–648, 2017a.

XU, T. *et al.* Epigenetic upregulation of CXCL12 expression mediates antitubulin chemotherapeutics-induced neuropathic pain. **Pain**, [s. l.], v. 158, n. 4, p. 637–648, 2017b.

XU, J. *et al.* Longer versus Shorter Schedules of Vincristine, Irinotecan, and Temozolomide (VIT) for Relapsed or Refractory Ewing Sarcoma: A

Randomized Controlled Phase 2 Trial. **Clinical Cancer Research**, [s. l.], v. 29, n. 6, p. 1040–1046, 2023.

XUE, V. W. *et al.* Transforming Growth Factor- β : A Multifunctional Regulator of Cancer Immunity. **Cancers**, [s. l.], v. 12, n. 11, p. 3099, 2020.

YOHN, C. N.; GERGUES, M. M.; SAMUELS, B. A. The role of 5-HT receptors in depression Tim Bliss. **Molecular Brain**, [s. l.], v. 10, n. 1, p. 1–12, 2017.

YOON, S. Y.; OH, J. Neuropathic cancer pain: Prevalence, pathophysiology, and management. **Korean Journal of Internal Medicine**, [s. l.], v. 33, n. 6, p. 1058–1069, 2018.

ZAJĄCZKOWSKA, R. *et al.* Mechanisms of Chemotherapy-Induced Peripheral Neuropathy. **International Journal of Molecular Sciences**, [s. l.], v. 20, n. 6, p. 1451, 2019.

ŽARKOVIĆ, N. *et al.* Spontaneous Regression of Cancer: Revealing Granulocytes and Oxidative Stress as the Crucial Double-edge Sword. **Frontiers in Bioscience-Landmark**, [s. l.], v. 27, n. 4, 2022.

ZHAN, X.; LI, J.; ZHOU, T. Targeting Nrf2-Mediated Oxidative Stress Response Signaling Pathways as New Therapeutic Strategy for Pituitary Adenomas. **Frontiers in Pharmacology**, [s. l.], v. 12, 2021.

ZHANG, H. Cancer Pain Management—New Therapies. **Current Oncology Reports**, [s. l.], v. 24, n. 2, p. 223–226, 2022.

ZHANG, S. Chemotherapy-induced peripheral neuropathy and rehabilitation: A review. **Seminars in Oncology**, [s. l.], v. 48, n. 3, p. 193–207, 2021.

ZHAO, J. Y. *et al.* DNA methyltransferase DNMT3a contributes to neuropathic pain by repressing Kcna2 in primary afferent neurons. **Nature Communications**, [s. l.], v. 8, n. May 2016, p. 1–15, 2017.

ZHAO, B. *et al.* Supplementation of lycopene attenuates oxidative stress induced neuroinflammation and cognitive impairment via Nrf2/NF- κ B transcriptional pathway. **Food and Chemical Toxicology**, [s. l.], v. 109, p. 505–516, 2017a.

ZHAO, B. *et al.* Supplementation of lycopene attenuates oxidative stress induced neuroinflammation and cognitive impairment via Nrf2/NF- κ B transcriptional pathway. **Food and Chemical Toxicology**, [s. l.], v. 109, p. 505–516, 2017b. Disponível em: <https://doi.org/10.1016/j.fct.2017.09.050>.

ZHENG, S. *et al.* TNF- α Impairs Pericyte-Mediated Cerebral Microcirculation via the NF- κ B/iNOS Axis after Experimental Traumatic Brain Injury. **Journal of Neurotrauma**, [s. l.], v. 40, n. 3–4, p. 349–364, 2023a.

ZHENG, S. *et al.* TNF- α Impairs Pericyte-Mediated Cerebral Microcirculation via

the NF- κ B/iNOS Axis after Experimental Traumatic Brain Injury. **Journal of Neurotrauma**, [s. l.], v. 40, n. 3–4, p. 349–364, 2023b. Disponível em: <https://www.liebertpub.com/doi/10.1089/neu.2022.0016>.

ZHU, Y. *et al.* Inhibition of PINK1 senses ROS signaling to facilitate neuroblastoma cell pyroptosis. **Autophagy**, [s. l.], p. 1–20, 2025.

ZHU, M. *et al.* Na⁺/K⁺-ATPase-dependent autophagy protects brain against ischemic injury. **Signal Transduction and Targeted Therapy**, [s. l.], v. 5, n. 1, p. 55, 2020.

ZHU, S. *et al.* Roles of tumor-associated macrophages in tumor progression: implications on therapeutic strategies. **Experimental Hematology & Oncology**, [s. l.], v. 10, n. 1, p. 60, 2021.

ZHU, J. *et al.* The neuroprotective effect of oxytocin on vincristine-induced neurotoxicity in mice. **Toxicology Letters**, [s. l.], v. 340, p. 67–76, 2021. Disponível em: <https://linkinghub.elsevier.com/retrieve/pii/S0378427421000096>.

Legends

Fig. 1 - Chemical structure of 7-chloro-4-(phenylselanyl) quinoline (4-PSQ).

Fig. 2 - Experimental design scheme.

Fig. 3 - Effect of 7-chloro-4-(phenylselanyl) quinoline (4-PSQ) (1 mg.kg⁻¹, p.o.) and vincristine (VCR) (0.1 mg.kg⁻¹, i.p.) on the number of crossings of male (a) and female (c), and the number of rearings of male (b) and female (d) mice. Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 7 animals per group. Two-way ANOVA followed by Tukey's test was used.

Fig. 4 - Effect of 7-chloro-4-(phenylselanyl) quinoline (4-PSQ) (1 mg.kg⁻¹, p.o.) and vincristine (VCR) (0.1 mg.kg⁻¹, i.p.) on training of male (a) and female (d) mice; in the short term memory of male (b) and female (e) mice and in the long-term memory of male (c) and female (f) mice in the object recognition task. Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 7 animals per group. (***) $P < 0.001$ and (****) $P < 0.0001$ denote significance levels when compared with the control group; (##) $P < 0.01$ and (#####) $P < 0.0001$ denote significance levels compared with the VCR groups. Two-way ANOVA followed by Tukey's test

was used.

Fig. 5 - Effect of 7-chloro-4-(phenylselanyl) quinoline (4-PSQ) (1 mg.kg⁻¹, p.o.) and vincristine (VCR) (0.1 mg.kg⁻¹, i.p.) on male (a) and female (c) latency and immobility of male (b) and female (d) in the tail suspension test. Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 7 animals per group. (**) P < 0.01; (***) P < 0.001 and (****) P < 0.0001 denote significance levels when compared with the control group; (#) P < 0.05; (##) P < 0.01 and (####) P < 0.0001 denote significance levels compared with the VCR groups. Two-way ANOVA followed by Tukey's test was used.

Fig. 6 - Effect of 7-chloro-4-(phenylselanyl) quinoline (4-PSQ) (1 mg.kg⁻¹, p.o.) and vincristine (VCR) (0.1 mg.kg⁻¹, i.p.) on time spent in open arms of male (a) and female (d) mice, entries into the open arms of male (b) and female (e) mice and dives of male (c) and female (f) mice in the elevated plus maze test. Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 7 animals per group. (*) P < 0.05, (***) P < 0.001 and (****) P < 0.0001 denote significance levels when compared with the control group; (##) P < 0.01; (###) P < 0.001 and (####) P < 0.0001 denote significance levels compared with VCR groups. Two-way ANOVA followed by Tukey's test was used.

Fig. 7 - Effect of 7-chloro-4-(phenylselanyl) quinoline (4-PSQ) (1 mg.kg⁻¹, p.o.) and vincristine (VCR) (0.1 mg.kg⁻¹, i.p.) on Na⁺, K⁺ - ATPase activity. Na⁺, K⁺ - ATPase activity in the cerebral cortex of male (a) and female (e); in the spinal cord of male (b) and female (f); in the cerebellum of male (c) and female (g), and in the hippocampus of male (d) and female (h) mice. Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 7 animals per group. (*) P < 0.05, (**) P < 0.01, (***) P < 0.001, and (****) P < 0.0001 denote significance levels when

compared with the control group. (##) $P < 0.01$ and (####) $P < 0.0001$ denotes significance levels compared with the VCR group. Two-way ANOVA followed by Tukey's test was used.

Fig. 8 - Effect of 7-chloro-4-(phenylselanyl) quinoline (4-PSQ) (1 mg.kg^{-1} , p.o.) and vincristine (VCR) (0.1 mg.kg^{-1} , i.p.) on protein 21 (p21) mRNA expression levels. The p21 gene expression in the cerebral cortex of male (a) and female (b); and in the spinal cord of male (c) and female (d) mice. Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 6 animals per group. (***) $P < 0.001$ denotes significance levels compared with the control group. (##) $P < 0.01$ denotes significance levels compared with the VCR group. Two-way ANOVA followed by Tukey's test was used.

Fig. 9 - Effect of 7-chloro-4-(phenylselanyl) quinoline (4-PSQ) (1 mg.kg^{-1} , p.o.) and vincristine (VCR) (0.1 mg.kg^{-1} , i.p.) on levels of mRNA expression of nuclear factor kappa B (NFkB). NFkB gene expression in the cerebral cortex of male (a) and female (b), and in the spinal cord of male (c) and female (d) mice. Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 6 animals per group. (**) $P < 0.01$, (***) $P < 0.001$, and (****) $P < 0.0001$ denote significance levels compared with the control group. (#) $P < 0.05$, (##) $P < 0.01$, and (####) $P < 0.001$ denote significance levels compared with the VCR groups. Two-way ANOVA followed by Tukey's test was used.

Fig. 10 - Correlation between emotional and cognitive behaviors with biochemical analyses in the cerebral cortex of male (a) and female (b) mice. Pearson's correlation coefficient (r) was indicated within the quadrants. Values of $r \cong 1$ indicate a positive correlation between the variables. Values of $r \cong -1$ indicate a negative correlation between the two variables. Exploratory preference for new

objects was used as a parameter collected in the object recognition task to assess short-term (STM) and long-term (LTM) memory; the number of entries into the open arms was used as a measure of anxiety-like behavior in the elevated plus maze test, and immobility was used as a parameter in the tail suspension test.

Supplementary material

Correlation between NFκB Signaling and Na⁺, K⁺-ATPase Inhibition in Vincristine-Induced Emotional and Cognitive Comorbidities in Mice: Neuroprotective Potential of 4-PSQ

Ketlyn Pereira da Motta^a, Carolina Cristóvão Martins^a, Vanessa Macedo Esteves da Rocha^a, Diego Alves^b, Ingrid Cardoso Oliveira^b, André Quincozes dos Santos^c, Larissa Daniele Bobermin^c, Cristiane Luchese ^{a*}, Ethel Antunes Wilhelm^{a*}

Table 1. P-values from Pearson's correlation test between the number of entries into the open arms (anxious-like behavior), exploratory preference (memory assessment), and immobility time (depressive-like behavior) with biochemical changes in the cerebral cortex of mice males.

<i>Experimental groups</i>	<i>P-values</i>					
	Open arms entries	STM	LTM	Immobility	Na ⁺ , K ⁺ - ATPase	NFκB
Open arms entries		2.46 x10 ⁻⁴	0.001	0.032	0.013	0.062
STM	2.46 x10 ⁻⁴		2.43 x10 ⁻⁴	0.009	9.3x10 ⁻⁴	0.059
LTM	0.001	2.43 x10 ⁻⁴		0.021	0.005	0.034
Immobility	0.032	0.009	0.021		0.043	0.001
Na ⁺ , K ⁺ - ATPase	0.013	0.001	0.005	0.044		0.040
NFκB	0.062	0.059	0.034	0.001	0.040	

Abbreviations: Short-term memory (STM); Long-term memory (LTM); Nuclear factor kappa B (NFκB)

Table 2. P-values from Pearson's correlation test between the number of entries into the open arms (anxious-like behavior), exploratory preference (memory assessment), and immobility time (depressive-like behavior) with biochemical changes in the cerebral cortex of mice females.

<i>Experimental groups</i>	<i>P-values</i>					
	Open arms entries	STM	LTM	Immobility	Na ⁺ , K ⁺ -ATPase	NFκB
Open arms entries		0.002	0.004	3.27 x10 ⁻⁴	0.032	0.003
STM	0.002		0.009	3.75 x10 ⁻⁵	0.017	4.29 x10 ⁻⁴
LTM	0.005	0.010		0.001	2.34 x10 ⁻⁵	0.005
Immobility	3.27 x10 ⁻⁴	3.75 x10 ⁻⁵	0.001		0.003	0.001
Na ⁺ , K ⁺ -ATPase	0.033	0.017	2.00 x10 ⁻⁵	0.003		0.012
NFκB	0.003	4.29 x10 ⁻⁴	0.005	0.001	0.019	

Abbreviations: Short-term memory (STM); Long-term memory (LTM); Nuclear factor kappa B (NFκB)

4.3. Capítulo 3 – Manuscrito Científico 2

Dupla ação do 7-cloro-4-(fenilselanil)quinolina (4-PSQ): neuroproteção na neuropatia periférica induzida por vincristina e atividade antileucêmica

Nesta terceira etapa, continuamos a sequência de avaliar grupos possivelmente mais susceptíveis a NPIV, desta vez, avaliando o dimorfismo sexual como frente principal. Este manuscrito complementa o manuscrito 2, avaliando neurotoxicidade entre machos e fêmeas induzidos pela VCR, sendo esta parte voltada a compreensão da nocicepção. Sendo assim, o objetivo central do estudo foi avaliar a NPIV em camundongos machos e fêmeas que receberam VCR e o potencial efeito terapêutico do 4-PSQ perante a NPIV. Além disso, avaliamos outros mecanismos associados a NPIV que poderiam divergir entre os sexos como os danos oxidativos (por meio dos testes dos níveis de TBARS e NPSH e atividade da CAT); atividade da Ca^{2+} -ATPase; e expressão gênica de Nrf2 e HO-1. Instigados pelos promissores efeitos do 4-PSQ na NPIV avaliamos ainda o potencial efeito antitumoral do 4-PSQ e VCR numa linhagem de células leucêmicas humanas (HL-60).

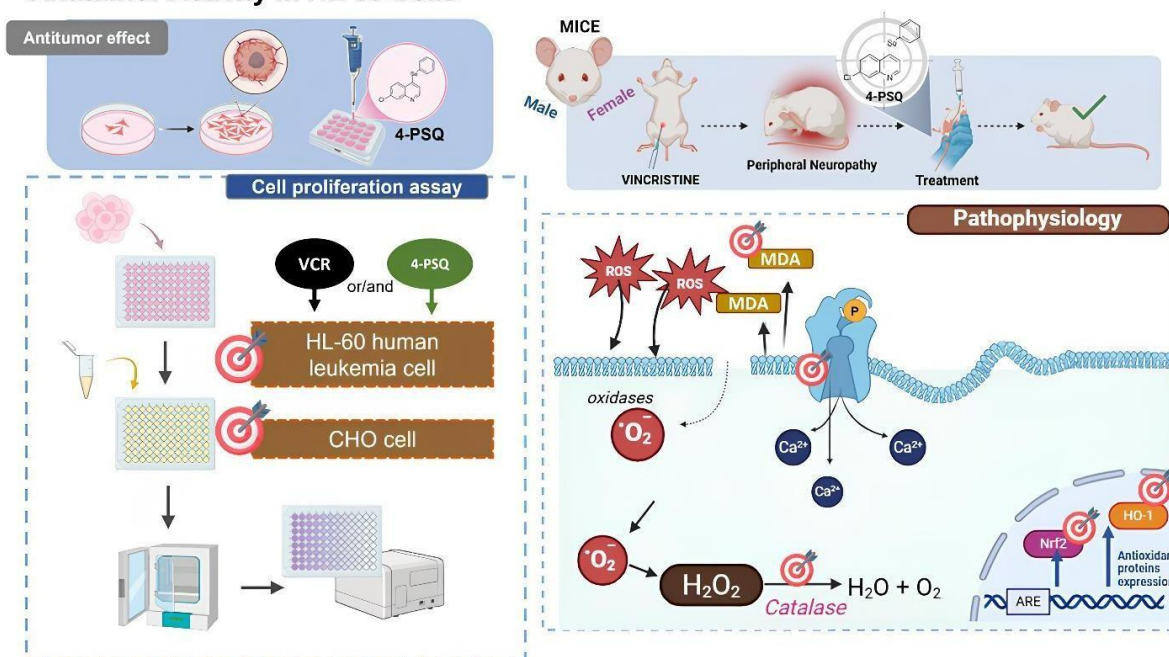
O conjunto de dados descritos a seguir, demonstraram a susceptibilidade de camundongos fêmeas em comparação a machos na NPIV. Paralelamente, verificamos que a NPIV apresenta alterações em mecanismos fisiopatológicos relacionados a: I) neuroinflamação (Nrf2 e HO-1); II) excitabilidade do sistema nervoso (Ca^{2+} -ATPase); e III) estresse oxidativo (níveis de TBARS e NPSH e atividade da CAT). A conexão entre essas três vias de ação da NPIV e a modulação neuroterapêutica da 4-PSQ culminou em uma descoberta que ajuda a entender como a VIPN pode ser efetivamente revertida na clínica oncológica.

Como etapa final do manuscrito, exploramos pela primeira vez, a atividade antitumoral da 4-PSQ em HL-60. O 4-PSQ demonstrou alta citotoxicidade contra células leucêmicas HL-60, com notável seletividade sobre células CHO (não tumorais). Embora nenhum efeito sinérgico tenha sido observado com o VCR, o 4-PSQ isoladamente demonstrou forte potencial como terapia adjuvante capaz de combater a leucemia e prevenir a neuropatia induzida por quimioterapia.

MANUSCRITO 2

Os resultados do Capítulo 3 da tese estão apresentados sob a forma de manuscrito científico, o qual se encontra assim organizado. Os itens Materiais e Métodos, Resultados, Discussão dos Resultados e Referências Bibliográficas encontram-se no próprio artigo. O manuscrito científico encontra-se submetido na revista *Biochemical Pharmacology*.

Dual Action of 4-PSQ: Antinociceptive Effects in Vincristine-Induced Neuropathy and Antitumor Activity in HL-60 Cells



Dual-Action 7-Chloro-4-(phenylselanyl)quinoline (4-PSQ): Neuroprotection in Vincristine-Induced Peripheral Neuropathy and Anti-Leukemic Activity

Ketlyn P. da Motta ^a, Vanessa M. E. da Rocha ^a, Carolina C. Martins ^a, Bruna S. Pacheco^b, Tiago Collares ^b, Fabiana K. Seixas ^b, Larissa Daniele Bobermin ^c, André Quincozes-Santos ^c, Maria Julia Mileto^d, Diego Alves ^d, and Ethel A. Wilhelm ^{a*}.

^a *Graduate Program in Biochemistry and Bioprospecting, Preclinical and Translational Research Group on Pain and Chronic Diseases, CCQFA – Federal University of Pelotas (UFPel), 96010-900, Pelotas, RS, Brazil.*

^b *Cellular and Molecular Oncology Research Group (GPO), CDTec, Federal University of Pelotas (UFPel), 96010-900, Pelotas, RS, Brazil.*

^c *Graduate Program in Biological Sciences: Biochemistry, Institute of Basic Health Sciences, Federal University of Rio Grande do Sul (UFRGS), 90035 -003, Porto Alegre, RS, Brazil.*

^d *Graduate Program in Chemistry, Clean Organic Synthesis Laboratory, CCQFA, UFPel, P.O., Box 354 - 96010-900, Pelotas, RS, Brazil.*

*Address for Correspondence:

Ethel Antunes Wilhelm; e-mail: ethelwilhelm@yahoo.com.br / Phone: +55-53-32757360

Graduate Program in Biochemistry and Bioprospecting (PPGBBio), Center for Chemical, Pharmaceutical and Food Sciences, Federal University of Pelotas (UFPel), Pelotas, Zip Code 96010-900, RS, Brazil.

Abstract

Vincristine (VCR) is a mainstay for hematologic malignancies, but its dose-limiting toxicity, VCR-induced peripheral neuropathy (VIPN), is highly prevalent and lacks effective treatment. Here, the therapeutic potential of 7-chloro-4-(phenylselanyl)quinoline (4-PSQ) was studied in a murine model of VIPN. Male and female mice were assigned to the Control, VCR, 4-PSQ, and VCR + 4-PSQ groups. VCR (0.1 mg/kg, i.p.) was administered for five consecutive days, and 4-PSQ (1 mg/kg, p.o.) was given on days 7 - 16. Mechanical and thermal hypersensitivities were assessed on days 0, 6, 11, and 16; tissues were collected on day 17 for biochemical and molecular analyses. VCR produced robust neuropathic pain phenotypes in both sexes, accompanied by increased lipid peroxidation (TBARS), elevated catalase (CAT) activity, depletion of non-protein sulfhydryl groups (NPSH), and Ca^{2+} -ATPase hyperactivity. VCR altered the expression of nuclear factor erythroid 2-related factor 2 (Nrf2) and heme oxygenase-1 (HO-1) in a sex- and region-dependent manner. 4-PSQ mitigated behavioral hypersensitivity and partially normalized redox and enzymatic disturbances, notably restoring Nrf2 expression in the female cerebral cortex and attenuating ATPase dysregulation. *In vitro*, 4-PSQ showed antitumor activity against HL-60 leukemia cells ($\text{IC}_{50} = 5.57 \mu\text{M}$) with substantially lower cytotoxicity in non-tumoral CHO cells ($\text{IC}_{50} = 68.29 \mu\text{M}$), indicating selectivity. When co-applied with VCR, 4-PSQ produced a modest attenuation of VCR potency in HL-60 cells. These data position 4-PSQ as a dual-profile candidate, combining neuroprotection with intrinsic antileukemic activity, whose use as an adjuvant to VCR-based regimens warrants further study with dosing and scheduling optimized to preserve antineoplastic efficacy.

Keywords: *antitumor activity, antinociception, leukemia, vincristine, Nrf2/HO-1 signaling pathway*

Introduction

Vincristine (VCR) is a widely used chemotherapeutic agent, routinely included in multi-agent treatment regimens for a broad range of malignancies, including solid tumors as well as hematologic and lymphatic cancers (Brown; Ross; Belsky, 2025; Madsen *et al.*, 2019; Tunjungsari; Gunawan; Ugrasena, 2021). Despite its clinical effectiveness, the extensive use of VCR is often accompanied by dose-limiting side effects, with neurotoxicity being the most significant (Geisler, 2021b; Li *et al.*, 2020a; Zhu, S. *et al.*, 2021). VCR-induced neurotoxicity primarily manifests as peripheral neuropathy, a debilitating and often irreversible condition that currently has no effective treatment options (Li *et al.*, 2020a; Mora *et al.*, 2016).

Nearly all patients exposed to VCR develop some degree of peripheral neuropathy, characterized by chronic pain, paresthesia, muscle weakness, foot and wrist drop, and areflexia (Alwhaibi *et al.*, 2023; Madsen *et al.*, 2019). The underlying pathophysiological mechanisms of VCR-induced peripheral neuropathy (VIPN), although not yet fully elucidated, are believed to involve multiple cellular pathways, including caspase-mediated neuronal apoptosis, dysregulation of intracellular calcium (Ca^{2+}) homeostasis, mitochondrial dysfunction (such as damage to mitochondrial DNA, altered electron transport chain activity, and membrane potential instability), and oxidative stress (Alenezi, 2023a; Diouf *et al.*, 2015; Li, G. zhou *et al.*, 2021a; Starobova; Vetter, 2017a).

Current pharmacological strategies for managing VIPN are largely limited to antidepressants and anxiolytics, which are not pain-directed and often provide suboptimal benefit (Desforges *et al.*, 2022; Zhang, 2021). The synthetic compound 7-chloro-4-(phenylselanyl)quinoline (4-PSQ) has shown robust

analgesic activity in preclinical models of chemotherapy-induced peripheral neuropathy, notably those triggered by paclitaxel and oxaliplatin, with efficacy attributed to combined antioxidant, anti-inflammatory, and neuroprotective actions that map onto key mechanisms of VIPN (Paltian *et al.*, 2022a; Reis *et al.*, 2020a, 2022, 2025). In paclitaxel-induced neuropathy, 4-PSQ reverses mechanical allodynia by limiting oxidative damage, modulating antioxidant enzymes, dampening neuroinflammatory mediators (NF- κ B, IL-1 β , TNF- α , iNOS), and restoring calcium homeostasis via Ca²⁺-ATPase regulation (19). In oxaliplatin models, it alleviates both acute and chronic nociception through the modulation of Na⁺,K⁺-ATPase and Mg²⁺-ATPase activities, alongside potent antioxidant effects (Reis *et al.*, 2020c, 2020a). Together, this capacity to counter oxidative stress while tuning neuronal excitability through ATPase regulation, particularly the Ca²⁺ pump, positions 4-PSQ as a compelling candidate to mitigate vincristine-induced neurotoxicity.

Given the lack of effective therapies for VIPN and its multifactorial pathophysiology, we evaluated the antinociceptive potential of 4-PSQ in a murine model of VCR-induced neuropathy. We paired longitudinal behavioral assessments with ex vivo analyses of central nervous system tissues to probe redox balance, ATPase function, and cytoprotective signaling. In view of vincristine's central role in hematologic malignancies, we also examined the anti-leukemic activity of 4-PSQ in vitro using the HL-60 cell line. We hypothesized that 4-PSQ could serve as an adjuvant candidate that mitigates VCR-induced neurotoxicity without compromising, and potentially enhancing, its antitumor efficacy, thereby informing the development of safer chemotherapy regimens.

Materials and Methods

Animals

Experiments were performed on 60-day-old male and female Swiss mice. Animals were maintained under controlled environmental conditions (temperature: $22 \pm 2^{\circ}\text{C}$; humidity: 20–80%) and a 12-hour light/dark cycle, with ad libitum access to standard food and water. All procedures were approved by the Institutional Animal Care and Use Committee of the Federal University of Pelotas, Brazil (protocol nº. CEEA 4506–2017), and conducted in accordance with established ethical guidelines.

Drugs

The compound 4-PSQ (Fig. 1) was synthesized and structurally characterized by the Clean Organic Synthesis Laboratory (LASOL) at the Federal University of Pelotas. Structural elucidation was performed using proton and carbon-13 nuclear magnetic resonance spectroscopy (^1H and ^{13}C NMR). Compound purity was assessed via gas chromatography–mass spectrometry (GC–MS), confirming a purity level of 99.9% (Duarte *et al.*, 2017b; Savegnago *et al.*, 2013b). VCR sulfate was obtained from INTAS Pharmaceuticals® (Batch No. M2103904) and stored at 4°C .

The 4-PSQ was formulated at a dose of 1 mg/kg in canola oil (10 mg/mL) and administered orally via gavage (p.o.), considering its lipophilic nature. VCR was prepared at a dose of 0.1 mg/kg in 0.9% saline (10 mg/mL) and administered intraperitoneally (i.p.), following established protocols. All additional reagents used for biochemical assays were of high analytical grade and procured from Sigma-Aldrich (St. Louis, MO, USA).

Experimental design

This study aimed to examine the therapeutic potential of 4-PSQ in VIPN, with a particular focus on gender-specific effects. To achieve this, biochemical analyses were also performed to explore potential mechanisms of neuropathy and neurotoxicity in male and female mice exposed to VCR. Male and female Swiss mice were randomly divided into four experimental groups: I) Control; II) VCR; III) 4-PSQ; and IV) VCR + 4-PSQ.

VCR administration occurred from day 1 to day 5 of the experimental protocol. Groups II and IV received five intraperitoneal injections of VCR (0.1 mg/mL), while Groups I and III received intraperitoneal injections of 0.9% saline (10 mg/mL). From day 7 to day 16, mice were treated with either 4-PSQ or its vehicle. Groups III and IV received 4-PSQ (1 mg/kg, orally), whereas Groups I and II received canola oil (10 mg/mL, orally) as the vehicle.

Mechanical hyperalgesia was measured on days 0, 6, 11, and 16 using a digital analgesimeter. Thermal sensitivity was tested on days 0, 6, and 16 with the hot plate test. On day 17, all animals were euthanized, and the cerebral cortex, spinal cord, cerebellum, and hippocampus were collected for biochemical and gene expression analyses. A graphical summary of the experimental design is shown in Fig. 2.

Behavior tests

Investigation of mechanical hyperalgesia

The mechanical sensitivity in mice was evaluated using the method described by Alamri et al. (2018a), on days 0, 6, 11, and 16 of the experimental protocol with some modifications. For this procedure, mice were individually

placed inside an acrylic box with wire grid floors in a quiet room. The test involved inducing a reflexive flexion of the hind paw using a handheld force transducer (digital analgesimeter, Insight, São Paulo, Brazil) with a polypropylene tip. The withdrawal threshold of the paw was measured by applying increasing pressure perpendicularly to the middle of the plantar surface of the hind paw until withdrawal occurred, and the pressure value was automatically recorded. The obtained data were statistically analyzed, and a line graph was plotted to assess the mechanical sensitivity during the experiment. The results were expressed as withdrawal threshold (g).

Investigation of thermal hyperalgesia

Thermal sensitivity in mice was measured using the method described by Woolfe and MacDonald (1946), with some modifications. The hot plate test, a behavioral model for assessing nociception response, was employed to observe reactions such as jumping and hind paw-licking in response to a thermal stimulus. The evaluation of thermal sensitivity was performed on days 0, 6, and 16 of the experiment. The mice were placed individually in an acrylic box on top of a heated metal plate maintained at $52 \pm 1^\circ\text{C}$. The time it took for nociceptive responses to occur was recorded as the latency. If there were significant decreases in paw withdrawal latency, it indicated heat hyperalgesia. To avoid harm to the animals' paws, the duration of time they spent on the plate was limited to 45 seconds. The data were expressed as latency (s).

Biochemical Assays

Biochemical assays were conducted to investigate the therapeutic mechanisms of 4-PSQ against VIPN in mice. Special attention was given to sex-dependent alterations, aiming to elucidate potential gender-related

predispositions to peripheral neuropathy.

Oxidative damage was the primary focus of the biochemical evaluations conducted on central nervous system structures. Lipid peroxidation levels were measured using the thiobarbituric acid reactive substances (TBARS) assay; non-protein oxidation was assessed by measuring NPSH levels; and changes in antioxidant defenses were determined through CAT activity. Additionally, enzymatic damage was evaluated by analyzing the activity of total ATPases and Ca^{2+} -ATPase.

Sex-specific differences in these parameters helped clarify how males and females differ in their susceptibility to VCR-induced oxidative damage in the brain. Additionally, gene expression analyses were conducted to measure the mRNA levels of key proteins involved in neurotoxic and oxidative stress responses, specifically Nrf2 and HO-1. The nervous system structures examined for oxidative damage and ATPase activity included the cerebral cortex, spinal cord, cerebellum, and hippocampus.

Tissue preparation

On the day of euthanasia, samples from the cerebral cortex, spinal cord, cerebellum, and hippocampus were dissected. The collected tissues were immediately frozen and stored at -80°C in an ultra-freezer. For biochemical assays, samples were homogenized in 50 mM Tris-HCl buffer (pH 7.4) and then centrifuged at $900 \times g$ for 10 minutes to obtain the supernatant (S1).

Involvement of Oxidative Stress

TBARS levels

TBARS levels were utilized as an indirect method to quantify the presence of malondialdehyde (MDA), one of the products formed during lipoperoxidation.

The measurement of TBARS levels followed the protocol described by Ohkawa et al. (1979). An aliquot of S1 was added to a reaction mixture containing thiobarbituric acid (0.8%), sodium dodecyl sulfate (8.1%), and acetic acid (pH 3.4), and then incubated at 95°C for 2 hours. The absorbance was measured at 532 nm using a spectrophotometer. The results were reported as nmol MDA/mg protein.

NPSH levels

NPSH levels were evaluated to directly quantify oxidative damage to thiols and indirectly measure reduced glutathione (GSH) levels. The determination of NPSH levels was performed using Ellman's method (1959). The S1 was mixed with 10% trichloroacetic acid (TCA) in a 1:1 volume ratio. After centrifugation at 900 x g for 10 minutes, the protein pellet was discarded, and the clear supernatant was used to assess the levels of free-thiol (SH) groups. An aliquot of the supernatant was added to a solution containing 1 M potassium phosphate buffer (pH 7.4) and 10 mM 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB). The color reaction was measured at 412 nm using a spectrophotometer. NPSH levels were expressed as nmol NPSH per gram of tissue.

CAT activity

CAT activity was measured spectrophotometrically following the method by Aebi (Aebi, 1984). The measurement involved monitoring the consumption of hydrogen peroxide (H₂O₂) in the presence of S1 at a wavelength of 240 nm. To start the enzymatic reaction, an aliquot of S1 (50 µL) and substrate (H₂O₂, 105 µL) were added to a medium containing 0.05 mM potassium phosphate buffer at pH 7.0. Enzymatic activity was expressed in units per milligram of protein (1 U decomposes 1 mM of H₂O₂ per minute at pH 7 and 25 °C).

ATPase activity

Total ATPase and Ca^{2+} -ATPase activities were evaluated according to the method described by Rohn (1993), with modifications as proposed by Trevisan (2009). Aliquots of the S1 fraction (50 μL) were incubated in a reaction medium containing all necessary substrates for ion pump activity: 30 mM Tris-HCl (pH 7.4), 50 mM NaCl, 5 mM KCl, 6 mM MgCl_2 , 4 mM CaCl_2 , and 3 mM ATP. To account for non-enzymatic substrate hydrolysis, control samples were prepared by adding TCA at the end of the reaction (Trevisan *et al.*, 2009).

Ca^{2+} -ATPase activity was determined by subtracting the enzymatic activity measured without Ca^{2+} from that measured with Ca^{2+} . Total ATPase activity was evaluated using incubation media containing all substrates. Enzymatic reactions were initiated by adding ATP and stopped after 30 minutes with 10% TCA. Samples were then incubated at 37 °C for 30 minutes, and the reaction was halted by adding 10% TCA with 10 mM HgCl_2 . Enzyme activity was calculated based on the difference in inorganic phosphate (Pi) levels between incubations performed in the presence and absence of ouabain.

The amount of Pi released by ATPase activity was quantified using the colorimetric method described by Fiske and Subbarow (1925b), with absorbance read spectrophotometrically at 650 nm. Results were expressed as nmol Pi/mg protein/min.

Protein quantification

Protein concentration was measured spectrophotometrically at 595 nm using the Bradford assay, with bovine serum albumin (BSA) as the standard. The reaction mixture included 50 μL of the S1 fraction and 2.5 mL of Coomassie Brilliant Blue reagent. After a 10-minute incubation, absorbance was measured,

and protein concentrations were expressed as mg/mL. These values were used to normalize the biochemical analyses.

RNA Extraction and Quantitative RT-PCR

To evaluate the expression of Nrf2 and HO-1, real-time RT-qPCR was performed. Total RNA was isolated from cerebral cortical and spinal cord clusters (n = 6) using TRIzol reagent (Invitrogen, Carlsbad, CA). The concentration and purity of the RNA were determined spectrophotometrically at a ratio of 260/280. Then, 1 µg of total RNA was reverse transcribed using the Applied Biosystems™ High Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA) in a 20 µL reaction according to the manufacturer's instructions. Real-time RT-qPCR quantified Nrf2, HO-1, and β-actin mRNA levels and was performed in duplicate using the Applied Biosystems QuantiStudio 1. Non-template controls were used in each assay, producing no detectable signal during 40 amplification cycles. Target mRNA levels were normalized to β-actin levels using the $2^{-\Delta\Delta C_t}$ method (Livak; Schmittgen, 2001b).

Evaluation of Antiproliferative Effects of 4-PSQ and VCR in HL-60 Human Leukemia Cells

In vitro determination of cytotoxicity

Cell culture

This study was performed using cancer cells HL-60 (human promyelocytic leukemia) and non-tumoral CHO cells, all obtained from Rio de Janeiro Cell Bank (PABCAM, Federal University of Rio de Janeiro, Brazil). The HL-60 cells were cultured in RPMI-1640 medium, while the CHO cells were cultured in DMEM medium. All culture media were supplemented with fetal bovine serum in a final

concentration of 10%, 1% of Penicillin/Streptomycin, and 1% of Amphotericin B. The cultivation conditions were also the same for all lineages, being 37 °C and 5% of CO₂ in a humidified atmosphere incubator.

Cell proliferation assay (MTT)

Cytotoxicity was estimated via the MTT cytotoxic assay using the cell lines: HL-60 (1×10^5 viable cells per well) and CHO (2×10^4 viable cells per well), which were incubated in the wells of a 96-well plate containing the appropriate medium. The plates were then cultured for 24 h (except for the suspended line HL-60 which received treatment immediately after plating) at 37 °C under the conditions of 5% CO₂ and 95% humidity, followed by treatment of HL-60 and CHO cells with different concentrations of 4-PSQ (2, 5, 20, 60, 100 and 120 μ M) and VCR (0.5, 1, 5, 25, 50 and 100 nM). Moreover, the HL-60 cells were also exposed to the combination of 4-PSQ + VCR at the same concentrations described above. The exposure time was 48 h. Two controls were used in the assay: a negative control containing untreated cells and a control containing the vehicle for solubilizing extracts (DMSO, 0.5%, data not shown). After incubation, the medium was removed and 100 μ L of MTT solution (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) (5 mg/mL) was added to each well, followed by 3 h of incubation. Afterward, the medium was removed again, and 100 μ L of DMSO was added to each well to solubilize the formazan crystals. The reduction of MTT to formazan, which is in direct proportion to the number of living cells, was examined in a microplate reader (Thermo Plate TP-Reader) at 492 nm. The results were expressed as the percentage of viable cells relative to the untreated cells. All observations were validated in a minimum of three independent experiments. All experiments were performed in triplicate. The percent inhibition

of cellular growth was determined as follows: inhibitory rate = $(1 - \text{Abs}_{492\text{treated cells}} / \text{Abs}_{492\text{control cells}}) \times 100$. The IC₅₀ value (50% inhibition of cell growth) was calculated using GraphPad Prism 8.0.

Statistical analysis

Statistical analysis was conducted using GraphPad Prism 8.0 software (San Diego, CA, USA). A two-way ANOVA followed by Tukey's multiple comparisons test was used for statistical analysis of all assays, except for cellular analysis. Comparison analysis of differences between sexes was performed using Student's t-test. Data were presented as mean $\pm$ standard error of the mean (S.E.M.). Evaluation of MTT results was performed using two-way analysis of variance (ANOVA) followed by the Bonferroni post hoc test. Main effects were reported only when the second-highest-order interaction was not statistically significant. Statistical significance was defined as $P < 0.05$.

Results

Behavior tests

Investigation of mechanical hyperalgesia

The VIPN frequently results in heightened mechanical sensitivity. The nociceptive responses to mechanical stimuli in male (Fig. 3a) and female (Fig. 3b) mice subjected to VCR and 4-PSQ are depicted graphically. Initially, we confirmed the absence of pre-sensitization in male and female mice through the baseline test. One day after the final chemotherapy session, we observed the onset of mechanical sensitivity in the VCR group of both male and female mice, persisting until the 16th day of the experimental protocol. In male mice receiving VCR, a reduction in the paw withdrawal threshold was observed on days 6 (53%), 11 (46%), and 16 (45%). Similarly, in female mice exposed to VCR, a decrease

in the paw withdrawal threshold was noted on days 6 (46%), 11 (42%), and 16 (49%). As demonstrated in Fig. 3c, no significant differences were observed between male and female mice on any of the days analyzed.

The treatment with 4-PSQ, initiated after confirming mechanical sensitivity on day 6, effectively reversed mechanical hypernociception in both male and female mice. On days 11 and 16, 4-PSQ normalized the sensitivity induced by VCR to control levels in both male and female mice.

Investigation of thermal hyperalgesia

The VIPN commonly leads to heightened heat sensitivity. The graphical representation of nociceptive responses to thermal stimuli in male (Fig. 4a) and female (Fig. 4b) mice under the influence of VCR and 4-PSQ is provided. To begin with, we confirmed the absence of pre-sensitization in male and female mice through baseline testing. One day after the final chemotherapy session, thermal sensitivity was observed in both male and female mice of the VCR group, persisting until the 16th day of the experimental protocol. In male mice treated with VCR, there was a reduction in latency time on days 6 (42%), 11 (31%), and 16 (21%). Similarly, in female mice subjected to VCR, latency time decreased on days 6 (37%), 11 (46%), and 16 (38%).

Upon initiating treatment with 4-PSQ after confirming thermal sensitivity on day 6, heat hypernociception was effectively reversed in both male and female mice. On days 11 and 16, 4-PSQ normalized the thermal sensitivity induced by VCR in both male and female mice to levels seen in the control group.

Statistical analysis between males and females demonstrated (Fig. 4c) that female mice receiving VCR developed an exacerbation of thermal sensitivity

on days 11 (37%) and 16 (25%) of the experimental protocol compared to males receiving VCR.

Involvement of Oxidative Stress

TBARS levels

Lipid peroxidation levels can indicate potential damage to macromolecules resulting from VCR induction. The MDA is the primary product of lipid peroxidation, indirectly quantified and assessed through the TBARS test. Figure 5 illustrates the TBARS levels in male and female mice. The VCR caused an elevation in TBARS levels in the spinal cord (Fig. 5b, 149%) and cerebellum (Fig. 5c, 41%) of male mice, but not in female mice. However, VCR didn't induce changes in TBARS levels in the cerebral cortex of both males and females, as well as in the spinal cord and cerebellum of females.

Remarkably, the compound 4-PSQ was able to restore the elevated TBARS levels caused by VCR in the spinal cord (Fig. 5b) and cerebellum (Fig. 5c) of male mice. The effect of VCR seemed to be gender-specific, mainly affecting males, and 4-PSQ showed its ability to counteract the changes in lipid peroxidation.

NPSH levels

NPSH compounds are sensitive to oxidative stress because of their sulfur group, yet they have important roles in the body. Treatments with VCR and 4-PSQ, either alone or together, showed no change in NPSH levels (Fig. 6). The NPSH content stayed the same in the cerebral cortex (Fig. 6a, 10d), spinal cord (Fig. 6b, 6e), and cerebellum (Fig. 6c, 10f) of both male and female mice. No differences were seen between males and females.

CAT activity

The CAT enzyme has significant antioxidant activity against oxidative stress. The activity of CAT is shown in Fig. 7. VCR exposure increased CAT activity in the cerebral cortex (Fig. 7a, 55%) and spinal cord (Fig. 7b, 145%) of males; and in the cerebral cortex (Fig. 7c, 150%) and spinal cord (Fig. 7d, 153%) of females. No differences were observed between male and female mice that received VCR.

The 4-PSQ was able to normalize CAT enzyme activity to control levels in both male and female mice when combined with VCR. Specifically, in the cerebral cortex of males (Fig. 7a) and females (Fig. 7d), and in the spinal cord of males (Fig. 7b) and females (Fig. 7e), where VCR increased enzymatic activity, 4-PSQ reversed this hyperactivation. In the cerebellum of both male and female mice, no changes in CAT enzymatic activity were observed due to the effects of VCR or 4-PSQ.

ATPase activity

The total ATPase assay aims to detect potential changes in the electrochemical gradient. As shown in Fig. 8, noticeable variations in total ATPase activity were observed after administering the VCR chemotherapy drug. VCR induction led to increased total ATPase activity in the cerebral cortex (Fig. 8a, 21%) and hippocampus (Fig. 8d, 84%) of male mice. In females, VCR caused elevated total ATPase activity in the cerebral cortex (Fig. 8e, 55%), spinal cord (Fig. 8f, 37%), and cerebellum (Fig. 8g, 32%).

However, VCR induction did not alter the activity of total ATPases in the

spinal cord (Fig. 8b) and cerebellum (Fig. 8c) of males, nor in the hippocampus of females (Fig. 8h). Treatment with 4-PSQ failed to reverse the increased total ATPase activity in the hippocampus of male mice exposed to VCR (Fig. 8d).

Overall, treatment with 4-PSQ was ineffective in counteracting the increase in ATPase activity induced by VCR. The heightened enzymatic activity of total ATPases, especially in the cerebral cortex (Fig. 8a) and hippocampus (Fig. 8d) of males, and in the cerebral cortex (Fig. 8e), spinal cord (Fig. 8f), and cerebellum (Fig. 8g) of females, was not reversed by 4-PSQ.

Regarding the activity of the Ca^{2+} - ATPase enzyme, we observed an increase across all evaluated brain tissues in both males and females (Fig. 9). VCR exposure caused elevated Ca^{2+} - ATPase activity in the cerebral cortex (Fig. 9a, 115%), spinal cord (Fig. 9b, 170%), cerebellum (Fig. 9c, 152%), and hippocampus (Fig. 9d, 576%) in male mice. Similarly, in females, VCR exposure led to higher Ca^{2+} - ATPase activity in the cerebral cortex (Fig. 9e, 217%), spinal cord (Fig. 9f, 213%), cerebellum (Fig. 9g, 92%), and hippocampus (Fig. 9h, 103%).

Remarkably, compound 4-PSQ was able to restore the Ca^{2+} - ATPase enzymatic activity that had been affected by VCR, except in the cerebral cortex of male mice. Notably emphasizing the effect of 4-PSQ, its action was evident in regulating Ca^{2+} - ATPase activity against the impact of VCR in the cerebral cortex (Fig. 9e) of females, as well as in the spinal cord of males and females (Fig. 9b and 13f, respectively), the cerebellum of males and females (Fig. 9c and 13g, respectively), and the hippocampus of males and females (Fig. 9d and 13h, respectively).

Nrf2 expression

To explore the potential role of Nrf2 in the pathophysiological mechanisms underlying VIPN and the therapeutic potential of 4-PSQ, we measured the mRNA expression levels of this transcription factor in the cerebral cortex (Fig. 10 a,b) and spinal cord (Fig. 10 c, d) of mice after VCR exposure. Nrf2 expression was reduced in the cerebral cortex of female (Fig. 10b; 32%) mice treated with VCR. In the spinal cord, VCR increased Nrf2 expression in male (Fig. 10c; 144%) and female (Fig. 10d; 94%) mice. Conversely, treatment with 4-PSQ restored Nrf2 expression in the cerebral cortex and spinal cord of female mice affected by VCR. Neither VCR nor 4-PSQ caused changes in Nrf2 expression in the cerebral cortex of male mice.

HO-1 expression

Since HO-1 is a downstream target of Nrf2 and plays a key role in the cellular antioxidant response, we next examined its mRNA expression in the cerebral cortex (Fig. 11 a,b) and spinal cord (Fig. 11 c,d) of VCR-induced and 4-PSQ-treated mice. VCR treatment resulted in a decrease in HO-1 expression only in the cerebral cortex (Fig. 11a; 47%) of male mice. Treatment with 4-PSQ in the same cerebral cortex tissue restored HO-1 expression in males. No changes were observed in the cerebral cortex of female mice or in the spinal cords of male and female mice when exposed to VCR and/or 4-PSQ.

Biochemical differences between males and females

Involvement of Oxidative Stress

We performed a statistical analysis using the t-test to assess potential

differences between males and females. In the biochemical tests that evaluated analyses associated with oxidative stress, we observed significant sex-related differences in TBARS (Fig. 12a) and NPSH (Fig. 12b) levels.

In the spinal cord TBARS test, we found that female mice receiving VCR showed a decrease (43%) in TBARS levels compared to males exposed to VCR. Meanwhile, in the VCR + 4-PSQ group, female mice showed an increase (104%) in TBARS levels compared to the same group of males. In the NPSH level test, we observed a significant depletion in females compared to their corresponding male groups in the control (44%), VCR (36%), and VCR + 4-PSQ (45%) groups, as well as in the spinal cord.

ATPases activity

Statistical analysis using the t-test demonstrated significant sex-related differences in the Ca^{2+} -ATPase (Fig. 13a and 13b) and total ATPase (Fig. 13c) tests. In the Ca^{2+} -ATPase test, we found that female mice receiving VCR and VCR+4-PSQ showed Ca^{2+} -ATPase inhibition compared to the same groups receiving the same treatment in males. Ca^{2+} -ATPase inhibition in the spinal cord of mice receiving VCR was 60% in males versus females, while in the VCR+4-PSQ group, it was 69%. In the cerebellum, the corresponding difference between males and females receiving only VCR was 61%, while the difference between the groups receiving VCR and 4-PSQ was 65%.

In the total ATPase test, we observed significant differences only in the cerebellum (Fig 13c). It was observed that female mice receiving VCR and VCR+4-PSQ presented an inhibition of total ATPases compared to the same groups that received the same treatment in males. The corresponding difference

between males and females that received only VCR was 29%, while between the groups that associated VCR + 4-PSQ, there was a difference of 39%.

Evaluation of Antiproliferative Effects of 4-PSQ and VCR in HL-60 Human

The cytotoxic potential of 4-PSQ was assessed in the acute promyelocytic leukemia cell line HL-60 and the non-tumoral cell line CHO. Cytotoxicity was determined using the MTT assay after 48 h of exposure to 4-PSQ (2 - 120 μ M) or VCR (0.5 - 100 nM). In HL-60 cells, both treatments induced a concentration-dependent reduction in cell viability (Fig. 14A and 14B). The IC₅₀ values were 5.57 ± 2.71 μ M for 4-PSQ in HL-60 cells and 2.51 ± 1.19 nM for VCR in CHO cells (Table 1). When 4-PSQ was combined with VCR at the specified concentrations, a change in VCR potency was observed, with the IC₅₀ increasing from 2.51 ± 1.19 nM (single treatment) to 11.89 ± 5.87 nM (combined, Fig. 14C). Although this increase indicates a reduction in VCR potency, the compound maintained significant antitumor activity in the nanomolar range.

Table 1. IC₅₀ (median inhibitory concentration) values of 4-PSQ, Vincristine, and 4-PSQ + Vincristine on leukemia HL-60 and CHO cell lines after 48 h of exposure.

Treatment	IC ₅₀	
	HL-60	CHO
4-PSQ (μ M)	5.57 ± 2.71	68.29 ± 7.26
Vincristine (nM)	2.51 ± 1.19 nM	n.d.
4-PSQ + Vincristine (nM)	11.89 ± 5.87 nM*	-

Data are expressed as mean $\pm$ standard error of the mean (SEM) of three independent experiments performed in triplicate.

* Vincristine treatment concentration.

n.d.: not detected (absence of cytotoxicity at the concentrations tested).

- not evaluated

4-PSQ and VCR were also tested on the non-tumoral CHO cell line (**Fig. 15**). For 4-PSQ, the maximum inhibition was 69%, with a significantly higher IC_{50} value ($68.29 \pm 7.26 \mu M$) compared to that in the HL-60 tumor cell line ($5.57 \pm 2.71 \mu M$). As for VCR, the maximum inhibition of cell growth was 15%. These results suggest that both compounds have a strong preference for the tumor cell line over non-tumoral cells.

Discussion

VIPN is a severe and debilitating condition. 4-PSQ, on the other hand, is an analgesic with effective effects against chronic pain, already proven in preclinical analyses. This study demonstrated, for the first time, the potential of 4-PSQ in reversing VIPN in male and female mice. We found, as a pioneer, that VIPN presents alterations in pathophysiological mechanisms related to: (I) neuroinflammation (Nrf2 and HO-1); (II) nervous system excitability (ATPase activity); and (III) oxidative stress (TBARs and NPSH levels, and CAT activity). The connection between these three pathways of VIPN action and the neurotherapeutic modulation of 4-PSQ culminated in a discovery that helps understand how VIPN can be effectively reversed in the oncology clinic. Furthermore, for the first time, we investigated the antitumor activity of 4-PSQ in human leukemia cell culture, yielding interesting results in conjunction with VCR, as well as in isolation. Therefore, 4-PSQ, in addition to its promising effects on VIPN, also represents a compound with antitumor potential, which represents a clinical advantage in the oncology setting.

The VCR triggered both mechanical and thermal hypernociception,

starting one day after the last chemotherapy session and lasting until the 16th day of the experimental protocol in male and female mice. However, we observed that female mice exposed to VCR show a continued nociceptive response to heat, whereas males seem to decrease their thermal sensitivity. Reports of cell damage and neuropathic susceptibility in female rats treated with VCR have already been documented (Kai *et al.*, 2006). The connection between estrogen and female susceptibility to VCR-induced nociception has been emphasized, as estrogen is known to regulate neural proliferation, survival, and synapse formation (Beyer; Karolczak, 2000b; Kai *et al.*, 2006; Weeks; Levine, 1995). In this context, it is suggested that the prolonged thermal nociception seen in VCR-treated females could be indirectly related to hormonal disruptions.

The 4-PSQ effectively reverses both mechanical and thermal nociception caused by VCR in both males and females. Its ability to influence the nervous system and regulate pathways involved in producing painful sensations, such as glutamatergic and nitrergic pathways, helps decrease nociception (Reis *et al.*, 2017c; Silva *et al.*, 2017b). Additionally, 4-PSQ's capacity to boost synaptic plasticity by increasing levels of neural cell adhesion molecule (NCAM) and polysialyltransferase in rats has been previously shown (Barth *et al.*, 2019a). As a result, the synaptic alterations induced by VCR that led to nociception may be modulated by 4-PSQ. Furthermore, the effect of 4-PSQ on cell adhesion molecules responsible for regulating synaptic function could be a key factor in reversing VCR-induced nociception in females.

VIPN has been strongly linked to increased oxidative stress, which contributes to neuronal damage and pain hypersensitivity. Our findings showed lipid peroxidation only in the spinal cord and cerebellum of male mice exposed to

VCR. From this, we infer that lipid peroxidation might be a VCR-induced effect that is more specific to male mice. MDA is associated with the pro-inflammatory action of molecules, leading to the stimulation of Th17 and Th12 lymphocytes, as well as the activation of NF κ B and TNF α (Del Rio; Stewart; Pellegrini, 2005; Gęgotek; Skrzydlewska, 2019). Therefore, we suggest that VCR may trigger lipid peroxidation and neuroinflammation by releasing MDA in the spinal cord and cerebellum of male mice. The 4-PSQ, on the other hand, was able to reverse lipid peroxidation caused by VCR in male mice. Notably, 4-PSQ is well-known for its antioxidant ability to protect macromolecules like proteins and lipids (Gęgotek; Skrzydlewska, 2024; Lemos *et al.*, 2021b).

Reduced levels of NPSH, a key component of the cellular redox defense system, contribute to increased oxidative stress in spinal and cortical circuits, thus facilitating central sensitization and exacerbating pain processing. In our study, NPSH levels remained unchanged by VCR and 4-PSQ. NPSH compounds, including N-acetylcysteine, cysteine, and GSH, are highly sensitive to oxidative stress. However, VCR did not lead to depletion of this parameter in males or females. The unchanged NPSH may be associated with a compensatory mechanism, as VCR can induce oxidative stress locally or through pathways not directly dependent on NPSH depletion. This was verified in our study, as CAT activity and TBARS levels were altered, while NPSH levels remained unchanged.

Still in this line of oxidative damage, antioxidant defenses are an important part of combating oxidative stress because they suffer disruptions in homeostasis due to the high concentration of reactive species. Among the antioxidant defenses is the enzyme CAT. In this context, we have discovered that VCR induction led to an elevation in CAT activity in the cerebral cortex and spinal cord

of male and female mice. The excessive activation of CAT in this context is intrinsic to the increase in hydrogen peroxide, its substrate of action. The increase in hydrogen peroxide in the cortex and spinal cord of mice receiving VCR characterizes a state of oxidative damage at target sites involved in the pain response. Redox alterations can compromise synaptic plasticity and affect cortical circuits that modulate the pain experience, interfering with the balance between inhibitory and excitatory mechanisms in the cerebral cortex (a region involved in sensory integration and conscious pain perception) and the spinal cord (responsible for receiving peripheral signals and integrating excitatory and inhibitory information) (Sun *et al.*, 2023; Woolf, 2022). Thus, these redox dysfunctions demonstrated by CAT in conjunction with NPSH and TBARS demonstrate an alteration in the amplification of pain perception and a failure in endogenous analgesia mechanisms associated with VIPN.

Consistent with the previous findings, ATPase enzymes, which are membrane-bound enzymes, regulate the exchange of ions by pumps, influence cellular excitability, and therefore, control the release of neurotransmitters into the synaptic cleft (Sung *et al.*, 2015b). Our study showed that VCR induction caused an increase in overall ATPase activity in various tissues of both males and females. The analysis suggests that VCR generally enhances ATPase activity, leading to increased cellular excitability through ion exchange. The rise in ATPase activity is probably linked to an increase in the Ca^{2+} pump, as the activity of the Ca^{2+} -ATPase enzyme was also elevated due to VCR treatment (Canta; Pozzi; Carozzi, 2015b; Starobova; Vetter, 2017a).

A previous study has already shown that VCR causes a significant increase in calcium transients in nodose ganglia neurons (Patil *et al.*, 2022). It is

well known that VCR-induced damage to peripheral neurons is directly connected to changes in calcium balance. First, VCR decreases calcium uptake by mitochondria, leading to a buildup of calcium ions inside the cell (Starobova; Vetter, 2017a). The changes in calcium caused by VCR trigger a rise in reactive species, disrupt glial function, and activate apoptotic pathways (Starobova; Vetter, 2017a).

In fact, the increase in ionic pumps, as indicated by the elevated total ATPase activity in certain brain tissues and the overall rise in Ca^{2+} -ATPase activity, aligns with VCR's mechanism of action. Additionally, it is implied that the increased Ca^{2+} -ATPase and CAT activity may show a link between changes in calcium homeostasis and the rise of reactive species caused by VCR. We also emphasize that the simultaneous increase in the activity of Ca^{2+} -ATPase and CAT enzymes in the cerebral cortex, spinal cord, and cerebellum reflects a shared mechanism of VCR action in both males and females.

Furthermore, it's important to emphasize that VCR's detrimental impact on calcium ion exchange leads to a neuroinflammatory process: positive regulation of the expression of the chemokine receptor (CXC), resulting in an increase in lymphocytes, monocytes, and pro-inflammatory factors like $\text{TNF-}\alpha$ and $\text{IL-1}\beta$ (Miclescu *et al.*, 2022; Xu *et al.*, 2017a). Additionally, VCR activates microglia by augmenting CXC expression, subsequently leading to the production of $\text{IL-1}\beta$ and $\text{TNF-}\alpha$ through the Mitogen-Activated Protein (MAP) signaling pathway (Clark; Malcangio, 2012).

The selectivity of 4-PSQ in modulating ATPase ion pumps has been previously demonstrated in various experimental models (Paltian *et al.*, 2022a; Reis *et al.*, 2022; Rodrigues *et al.*, 2021b). When considering the overall balance

of ATPase activity, we did not observe a significant reversal of enzymatic activity caused by the compound 4-PSQ against the effects of VCR. However, in the assessment of Ca^{2+} -ATPase activity, we found that 4-PSQ restored enzymatic activity in all tissues except the cerebral cortex of male mice. The selectivity of 4-PSQ for the Ca^{2+} -ATPase enzyme is a key point to highlight in efforts to reduce VIPN. This specific action of 4-PSQ is likely due to the compound's liposolubility, which increases membrane permeability and helps modulate membrane enzymes like ATPases.

Given that these are two key proteins in oxidatively stressful situations, such as those induced by VCR, we evaluated the expression of Nrf2 and HO-1. Both Nrf2 and HO-1, when expressed, favor a cascade of events that culminate in neuroinflammation, oxidation, and even apoptosis (Dang *et al.*, 2020; O'Rourke; Shanley; Dunne, 2024). The Nrf2/HO-1 pathway has been intrinsically associated with neuroprotection because Nrf2 is a transcription factor that, when activated, induces the expression of genes that encode protective proteins, including HO-1 (in healthy situations)[50,52,53]. HO-1, in turn, plays an important role in the removal of toxic heme and in the production of antioxidant compounds.

Nrf2 activation occurs in the presence of Nrf2 activators, including reactive oxygen species (ROS), which modify cysteine residues in KEAP1, allowing the release and stabilization of Nrf2 (Kasai *et al.*, 2020). In the present study, VCR significantly suppressed the expression of the Nrf2 gene in the cerebral cortex of female mice, while it induced an overexpression in the spinal cord of both sexes. The expression of Nrf2 observed in this study is the Nrf2 present in the cell nucleus, which is not activated, since Nrf2 is only activated after migrating to the cytoplasm. Therefore, the decrease in Nrf2 expression in the cerebral cortex of

females can be explained by the possible migration of Nrf2 to the cytoplasm(Chen, 2022). The overexpression of Nrf2 in males and females in the spinal cord may be related to the oxidative stress itself, which favors the activation of Mitogen-Activated Protein Kinase (MAPK) / phosphoinositide 3-kinase/protein kinase B (PI3K-Akt) / protein kinase c (PKC), leading to the activation of transcription factors and an increase in the Nfe2l2 gene, which sequentially activates the expression of Nrf2 (Zhan; Li; Zhou, 2021). In summary, the imbalance between Nrf2 activation and expression is a typical response caused by oxidative stress.

In this line, we found that VCR selectively decreased HO-1 gene expression in the cerebral cortex of male mice, while no significant changes were seen in the spinal cord of either sex or in the female cortex. Interestingly, the cerebral cortex of males was the only tissue not affected in the evaluation of Nrf2 expression. The disconnect between the direct activation pathway of Nrf2/HO-1 can be explained by incomplete or dysfunctional activation of Nrf2 after expression (Ngo; Duennwald, 2022; Su *et al.*, 2024). Malfunction of the Nrf2/HO-1 pathway is often linked to increased Nrf2 mRNA levels, with impaired translocation to the nucleus or inefficient DNA binding (ARE)(Su *et al.*, 2024; Sun *et al.*, 2002). Other factors that might cause the disconnect include repressive factors like Bach1, post-transcriptional regulation of the HMOX1 gene, or differences in the timing or sensitivity of this tissue's transcriptional response to Nrf2-mediated antioxidant signaling(Sun *et al.*, 2002).

Regarding the single alteration of HO-1 in the cerebral cortex of males that was not modified by Nrf2, this is one of the most relevant findings of this study. This data demonstrates an adaptive failure in the Nrf2/HO-1 pathway common in

neurotoxicity, which is a key point in VIPN in males. Except for Nrf2 expression in the spinal cord of males, 4-PSQ was able to repair the nuances in the alterations of the Nrf2/HO-1 pathway, indicating that the therapeutic action of 4-PSQ may be associated with its antioxidant action previously reported.

Our findings provide novel insights into the sex-related biochemical alterations induced by VCR and its modulation by 4-PSQ in mice. The observed differences in oxidative stress markers and ATPase activity between males and females highlight the importance of considering sex as a biological variable in preclinical studies of chemotherapy-induced neurotoxicity.

The decrease in TBARS levels in the spinal cord of females exposed to VCR, contrasted with males, suggests a differential modulation of lipid peroxidation pathways between sexes. Interestingly, in the VCR+4-PSQ group, females exhibited a pronounced increase in TBARS levels, which may indicate a distinct redox imbalance under combined treatment. Previous reports have demonstrated that VCR induces oxidative damage through the generation of ROS, mitochondrial dysfunction, and impaired antioxidant defenses (Chen; Wang; Song, 2020; Shayesteh *et al.*, 2022b). Moreover, sex-specific responses to oxidative stress have been described, where estrogen-dependent mechanisms may either protect against or exacerbate redox imbalance depending on the cellular context (Tower; Pomatto; Davies, 2020). Thus, the divergent TBARS responses observed here may reflect an interplay between VCR-induced oxidative stress, 4-PSQ's modulatory effects, and sex-specific redox regulation.

Regarding NPSH levels, our data revealed a consistent depletion in females across all experimental groups in the spinal cord. The more pronounced depletion in females could indicate an intrinsic vulnerability of female mice to

VCR-induced oxidative stress, potentially associated with sex-specific regulation of GSH synthesis and turnover. This is in line with studies reporting lower GSH availability and reduced activity of glutathione-dependent enzymes in female rodents under stress conditions (Wang; Ahn; Asmis, 2020).

In addition to oxidative stress, we observed significant sex-related differences in Ca^{2+} -ATPase and total ATPase activities. Both in the spinal cord and cerebellum, females showed stronger inhibition of Ca^{2+} -ATPase after VCR and VCR+4-PSQ treatment compared to males. Our results suggest that female mice may be more susceptible to Ca^{2+} dysregulation under VCR treatment, possibly due to differences in estrogen-mediated calcium signaling and ATPase regulation (Novelle; Camacho-Morales; Martínez De Morentin, 2023).

Furthermore, the inhibition of total ATPases observed in the cerebellum of females reinforces the idea that sex-dependent metabolic vulnerability may exacerbate VCR-induced neurotoxicity. Considering that cerebellar circuits are involved in motor coordination, these findings may help explain sex-related differences in VCR-induced ataxia and motor impairment observed in clinical and preclinical studies (Starobova; Vetter, 2017a).

Collectively, our results highlight that female may present a heightened susceptibility to oxidative stress and bioenergetic dysfunction under VCR treatment, which could be partly explained by hormonal modulation, antioxidant system regulation, and mitochondrial function. Importantly, the interaction of 4-PSQ with these pathways seems to diverge between sexes, reinforcing the need for sex-specific analyses when evaluating novel adjuvants against chemotherapy-induced neurotoxicity.

In vitro results showed that 4-PSQ has inherent antitumor activity against

HL-60 leukemia cells, with a dose-dependent cytotoxic effect and an IC_{50} in the micromolar range ($5.57 \mu M$). Although not as potent as VCR (IC_{50} : $2.51 nM$), 4-PSQ's ability to decrease leukemic cell viability confirms its potential to inhibit tumor growth. This is especially meaningful given the compound's dual profile, exhibiting both antitumoral and antinociceptive properties. The identification of these effects supports further investigation of 4-PSQ as an adjunct agent in leukemia treatment protocols, particularly in strategies aimed at reducing VIPN without losing antitumor efficiency.

Although combining VCR and 4-PSQ did not significantly boost cytotoxic effects in HL-60 cells compared to each compound alone, the dual pharmacological profile of 4-PSQ remains highly important. Its inherent antitumor activity, along with its proven neuroprotective and antioxidant benefits *in vivo*, indicates that 4-PSQ could be a valuable addition to chemotherapy protocols. While VCR is very effective against leukemic cells, its use is limited by the risk of irreversible neurotoxicity. In this context, 4-PSQ stands out as a promising candidate that may help reduce VCR-induced damage to the central nervous system. This potential supports further research into 4-PSQ not only as a cytotoxic agent but also as a neuroprotective compound that could improve the tolerability and safety of chemotherapy treatments.

To further investigate the selectivity of 4-PSQ and VCR, both compounds were evaluated in the non-tumorigenic CHO cell line. The IC_{50} for 4-PSQ was $68.29 \pm 7.26 \mu M$, significantly higher than that observed in the HL-60 leukemia cells ($5.57 \pm 2.71 \mu M$), suggesting a marked preferential cytotoxicity toward tumor cells. Notably, VCR did not reach 50% inhibition in CHO cells at the tested concentrations, further confirming its tumor-selective profile. These findings

support the therapeutic relevance of 4-PSQ, which, despite being less potent than VCR, demonstrated selective antitumor activity. This tumor-versus-normal cell differential response is particularly promising for minimizing off-target toxicity. It supports the rationale for 4-PSQ as a complementary agent in leukemia treatment, especially considering its additional neuroprotective potential. The IC_{50} value is nearly 12-fold higher in CHO cells compared to HL-60 cells, suggesting a favorable therapeutic index, minimizing potential harm to healthy tissues. Moreover, organoselenium compounds, including phenylselenanyl derivatives, are increasingly recognized for their dual antitumor and redox-modulating properties, with several studies highlighting their ability to induce apoptosis and modulate oxidative stress-related pathways in cancer cells (via ROS generation, caspase activation, and mitochondrial dysfunction)(Kim *et al.*, 2021; Kostić; Marjanović; Divac, 2024; Nogueira; Rocha, 2011; Nogueira; Zeni; Rocha, 2004) . In this context, 4-PSQ emerges as a promising candidate not only for its direct cytotoxic effect against leukemic cells but also for its neuroprotective profile, as evidenced in the *in vivo* VIPN model. The combination of these properties positions 4-PSQ as a novel adjuvant strategy that could enhance leukemia treatment efficacy while reducing chemotherapy-induced peripheral neuropathy, a major limitation of VCR-based regimens.

Conclusions

This study demonstrated that 4-PSQ exhibits both neuroprotective and antitumoral properties, effectively reversing VCR-induced mechanical and thermal hyperalgesia in male and female mice. 4-PSQ modulated oxidative stress markers, restored Ca^{2+} -ATPase activity, and regulated Nrf2 gene expression in a sex- and region-specific manner. While VCR selectively reduced HO-1

expression in the male cortex, 4-PSQ did not reverse this change, possibly due to regulatory factors like Bach1. Notably, female mice exhibited greater susceptibility to alterations in total ATPase and Ca^{2+} -ATPase activities, as well as pronounced differences in TBARS and NPSH levels compared to males; these unprecedented findings highlight novel sex-dependent vulnerabilities to VCR-induced neurotoxicity, which may be partly linked to estrogen-mediated modulation of redox balance and calcium homeostasis. *In vitro*, 4-PSQ showed high cytotoxicity against HL-60 leukemia cells with notable selectivity over non-tumoral CHO cells. Although no synergistic effect was observed with VCR, 4-PSQ alone displayed strong potential as an adjuvant therapy capable of targeting leukemia and preventing chemotherapy-induced neuropathy.

Acknowledgments

This study received financial support and scholarships from the following Brazilian agencies: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) (312747/2020-9, 406118/2021-3, 442284/2023-3, 403846/2025-0, 304038/2025-3), Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS) (21/2551-0001943-3, 22/2551-0000389-3, 23/2551-0001861-6; 24/2551-0001948-0). This study was also financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) - Finance Code 001. EAW, TC, FKS, AQS and DA are recipients of CNPq fellowship. This study also received financial assistance from L'ORÉAL-UNESCO-ABC for Women in Science.

Author contributions

KPM conceived and designed the study. KPM and VMER performed biochemical and behavioral analyses. BSP, TC, and FKS were responsible for *in vitro* analyses. LDB and AQS were responsible for gene expression analysis. MJM and DA were responsible for the synthesis of compound 4-PSQ. KPM and EAW wrote the manuscript. EAW supervised the study. All authors approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used GPTchat (OpenAI, 2025) to improve readability and language. After using this tool, the authors have reviewed and edited the content as necessary and take full responsibility for the content of the publication.

References

- AEBI, H. Catalase in vitro. **Methods in Enzymology**, [s. l.], v. 105, p. 121–126, 1984.
- AKSENOV, M. Y.; MARKESBERY, W. R. Changes in thiol content and expression of glutathione redox system genes in the hippocampus and cerebellum in Alzheimer's disease. **Neuroscience Letters**, [s. l.], v. 302, n. 2–3, p. 141–145, 2001.
- ALAMRI, F. F. *et al.* Applicability of the grip strength and automated von Frey tactile sensitivity tests in the mouse photothrombotic model of stroke.

Behavioural Brain Research, [s. l.], v. 336, n. August 2017, p. 250–255, 2018a.

ALAMRI, F. F. *et al.* Applicability of the grip strength and automated von Frey tactile sensitivity tests in the mouse photothrombotic model of stroke. **Behavioural Brain Research**, [s. l.], v. 336, n. August 2017, p. 250–255, 2018b. Disponível em: <http://dx.doi.org/10.1016/j.bbr.2017.09.008>.

ALBENSI, B. C. What Is Nuclear Factor Kappa B (NF- κ B) Doing in and to the Mitochondrion?. **Frontiers in Cell and Developmental Biology**, [s. l.], v. 7, 2019a.

ALBENSI, B. C. What Is Nuclear Factor Kappa B (NF- κ B) Doing in and to the Mitochondrion?. **Frontiers in Cell and Developmental Biology**, [s. l.], v. 7, 2019b. Disponível em: <https://www.frontiersin.org/article/10.3389/fcell.2019.00154/full>.

ALENEZI, S. K. The Ameliorative Effect of Thymoquinone on Vincristine-Induced Peripheral Neuropathy in Mice by Modulating Cellular Oxidative Stress and Cytokine. **Life**, [s. l.], v. 13, n. 1, p. 101, 2022.

ALENEZI, S. K. The Ameliorative Effect of Thymoquinone on Vincristine-Induced Peripheral Neuropathy in Mice by Modulating Cellular Oxidative Stress and Cytokine. **Life**, [s. l.], v. 13, n. 1, 2023a.

ALENEZI, S. K. The Ameliorative Effect of Thymoquinone on Vincristine-Induced Peripheral Neuropathy in Mice by Modulating Cellular Oxidative Stress and Cytokine. **Life**, [s. l.], v. 13, n. 1, 2023b.

ALWHAIBI, A. M. *et al.* Vincristine-Induced Neuropathy in Patients Diagnosed with Solid and Hematological Malignancies: The Role of Dose Rounding. **Journal of Clinical Medicine**, [s. l.], v. 12, n. 17, p. 5662, 2023.

AN, R. *et al.* Methylcobalamin Protects Melanocytes from H₂O₂-Induced Oxidative Stress by Activating the Nrf2/HO-1 Pathway. **Drug Design, Development and Therapy**, [s. l.], v. Volume 15, p. 4837–4848, 2021.

ANAND, K. J. S.; HICKEY, P. R. Pain and Its Effects in the Human Neonate and Fetus. **New England Journal of Medicine**, [s. l.], v. 317, n. 21, p. 1321–1329, 1987.

ANBALAGAN, M. *et al.* Post-translational modifications of nuclear receptors and human disease. **Nuclear receptor signaling**, [s. l.], v. 10, n. Figure 1, 2012.

ARETI, A. *et al.* Oxidative stress and nerve damage: Role in chemotherapy induced peripheral neuropathy. **Redox Biology**, [s. l.], v. 2, n. 1, p. 289–295, 2014.

BAE, E. H.; GREENWALD, M. K.; SCHWARTZ, A. G. Chemotherapy-Induced Peripheral Neuropathy: Mechanisms and Therapeutic Avenues. **Neurotherapeutics**, [s. l.], v. 18, n. 4, p. 2384–2396, 2021.

BAIG, M. A.; PANCHAL, S. S. Streptozotocin-Induced Diabetes Mellitus in Neonatal Rats: An Insight into its Applications to Induce Diabetic Complications. **Current Diabetes Reviews**, [s. l.], v. 16, n. 1, p. 26–39, 2019.

BAKER, D. W. History of The Joint Commission's Pain Standards. **JAMA**, [s. l.], v. 317, n. 11, p. 1117, 2017.

BARTH, A. *et al.* 7-Chloro-4-(Phenylselanyl) Quinoline with Memory Enhancer Action in Aging Rats: Modulation of Neuroplasticity, Acetylcholinesterase Activity, and Cholesterol Levels. **Molecular Neurobiology**, [s. l.], 2019a.

BARTH, A. *et al.* 7-Chloro-4-(Phenylselanyl) Quinoline with Memory Enhancer Action in Aging Rats: Modulation of Neuroplasticity, Acetylcholinesterase Activity, and Cholesterol Levels. **Molecular Neurobiology**, [s. l.], 2019b.

BARTLEY, E. J.; FILLINGIM, R. B. Sex differences in pain: a brief review of clinical and experimental findings. **British Journal of Anaesthesia**, [s. l.], v. 111, n. 1, p. 52–58, 2013.

BEJČEK, J. *et al.* Na⁺/K⁺-atpase revisited: On its mechanism of action, role in cancer, and activity modulation. **Molecules**, [s. l.], v. 26, n. 7, 2021.

BENJAMIN, R. S. *et al.* Chemotherapy for Bone Sarcomas in Adults: The MD Anderson Experience. **American Society of Clinical Oncology Educational Book**, [s. l.], n. 35, p. e656–e660, 2015.

BENNETT, M. I. *et al.* Prevalence and aetiology of neuropathic pain in cancer patients: A systematic review. **Pain**, [s. l.], v. 153, n. 2, p. 359–365, 2012.

BEYER, C.; KAROLCZAK, M. Estrogenic stimulation of neurite growth in midbrain dopaminergic neurons depends on cAMP/protein kinase A signalling. **Journal of Neuroscience Research**, [s. l.], v. 59, n. 1, p. 107–116, 2000a.

BEYER, C.; KAROLCZAK, M. Estrogenic stimulation of neurite growth in midbrain dopaminergic neurons depends on cAMP/protein kinase A signalling. **Journal of Neuroscience Research**, [s. l.], v. 59, n. 1, p. 107–116, 2000b.

BHATT, S. *et al.* 5-HT₃ Receptor Antagonism: A Potential Therapeutic Approach for the Treatment of Depression and other Disorders. **Current Neuropharmacology**, [s. l.], v. 19, n. 9, p. 1545–1559, 2020.

BILBERG, A. *et al.* High prevalence of widespread pain in women with early rheumatoid arthritis. **Scandinavian Journal of Rheumatology**, [s. l.], v. 47, n. 6, p. 447–454, 2018. Disponível em: <https://doi.org/10.1080/03009742.2018.1447683>.

BLUETTE, C. T. *et al.* Behavioral, Histopathologic, and Molecular Biological Responses of Nanoparticle- and Solution-Based Formulations of Vincristine in Mice. **International Journal of Toxicology**, [s. l.], v. 40, n. 1, p. 40–51, 2021.

Disponível em: <http://journals.sagepub.com/doi/10.1177/1091581820968255>.

BRADFORD, M. M. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. **Analytical biochemistry**, [s. l.], v. 72, n. 1–2, p. 248–254, 1976a.

BRADFORD, M. M. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. **Analytical biochemistry**, [s. l.], v. 72, n. 1–2, p. 248–254, 1976b. Disponível em: <https://www.sciencedirect.com/science/article/abs/pii/0003269776905273>.

BREIVIK, H. *et al.* Cancer-related pain: a pan-European survey of prevalence, treatment, and patient attitudes. **Annals of Oncology**, [s. l.], v. 20, n. 8, p. 1420–1433, 2009.

BRIGATTE, P. *et al.* Walker 256 Tumor-Bearing Rats as a Model to Study Cancer Pain. **The Journal of Pain**, [s. l.], v. 8, n. 5, p. 412–421, 2007.

BROWN, A. M.; ROSS, A.; BELSKY, J. A. Vincristine-Induced Autonomic Neuropathy Diagnosed via Quantitative Sudomotor Axon Reflex Sweat Test in an Adolescent Patient With Acute Leukemia. **Pediatric Blood & Cancer**, [s. l.], 2025.

BROZOVIĆ, G. Cancer Pain and Therapy. **Acta Clinica Croatica**, [s. l.], 2022.

BUJALSKA, M.; GUMUŁKA, S. W. Effect of cyclooxygenase and nitric oxide synthase inhibitors on vincristine induced hyperalgesia in rats. **Pharmacological Reports**, [s. l.], v. 60, n. 5, p. 735–741, 2008.

BURT, R. *et al.* Activated stromal cells transfer mitochondria to rescue acute lymphoblastic leukemia cells from oxidative stress. **Blood**, [s. l.], v. 134, n. 17, p. 1415–1429, 2019.

BUSCH, C. J.; BINDER, C. J. Malondialdehyde epitopes as mediators of sterile inflammation. **Biochimica et Biophysica Acta - Molecular and Cell Biology of Lipids**, [s. l.], v. 1862, n. 4, p. 398–406, 2017. Disponível em: <http://dx.doi.org/10.1016/j.bbalip.2016.06.016>.

CALIXTO-CAMPOS, C. *et al.* The Ehrlich Tumor Induces Pain-Like Behavior in Mice: A Novel Model of Cancer Pain for Pathophysiological Studies and Pharmacological Screening. **BioMed Research International**, [s. l.], v. 2013, p. 1–12, 2013.

CANTA, A.; POZZI, E.; CAROZZI, V. A. Mitochondrial dysfunction in chemotherapy-induced peripheral neuropathy (CIPN). **Toxics**, [s. l.], v. 3, n. 2, p. 198–223, 2015a.

CANTA, A.; POZZI, E.; CAROZZI, V. A. Mitochondrial dysfunction in chemotherapy-induced peripheral neuropathy (CIPN). **Toxics**, [s. l.], v. 3, n. 2, p. 198–223, 2015b.

CARACENI, A.; SHKODRA, M. Cancer Pain Assessment and Classification. **Cancers**, [s. l.], v. 11, n. 4, p. 510, 2019.

CASSOL, G. *et al.* A role of Na⁺, K⁺ -ATPase in spatial memory deficits and inflammatory/oxidative stress after recurrent concussion in adolescent rats. **Brain Research Bulletin**, [s. l.], v. 180, p. 1–11, 2022a.

CASSOL, G. *et al.* A role of Na⁺, K⁺ -ATPase in spatial memory deficits and inflammatory/oxidative stress after recurrent concussion in adolescent rats. **Brain Research Bulletin**, [s. l.], v. 180, p. 1–11, 2022b. Disponível em: <https://linkinghub.elsevier.com/retrieve/pii/S0361923021003543>.

CAVIEDES, A. *et al.* BDNF/NF-κB Signaling in the Neurobiology of Depression. **Current Pharmaceutical Design**, [s. l.], v. 23, n. 21, 2017a.

CAVIEDES, A. *et al.* BDNF/NF-κB Signaling in the Neurobiology of Depression. **Current Pharmaceutical Design**, [s. l.], v. 23, n. 21, 2017b. Disponível em: <http://www.eurekaselect.com/149163/article>.

CHANCAY, M. G.; GUENDSECHADZE, S. N.; BLANCO, I. Types of pain and their psychosocial impact in women with rheumatoid arthritis. **Women's Midlife Health**, [s. l.], v. 5, n. 1, p. 1–9, 2019.

CHANTAL, T. *et al.* ACTION OF VINCA ALKALOIDES ON CALCIUM MOVEMENTS THROUGH MITOCHONDRIAL MEMBRANE. **Pharmacological Research Communications**, [s. l.], v. 18, n. 6, p. 519–528, 1986.

CHEN, C. *et al.* Body weight, frailty, and chronic pain in older adults: A cross-sectional study. **BMC Geriatrics**, [s. l.], v. 19, n. 1, p. 1–10, 2019.

CHEN, X. *et al.* Current understanding of the molecular mechanisms of chemotherapy-induced peripheral neuropathy. **Frontiers in Molecular Neuroscience**, [s. l.], v. 17, 2024.

CHEN, S. P. *et al.* Involvement of hippocampal acetylcholinergic receptors in electroacupuncture analgesia in neuropathic pain rats. **Behavioral and Brain Functions**, [s. l.], v. 12, n. 1, p. 1–10, 2016.

CHEN, Q. M. Nrf2 for protection against oxidant generation and mitochondrial damage in cardiac injury. **Free Radical Biology and Medicine**, [s. l.], v. 179, p. 133–143, 2022.

CHEN, X.-J.; WANG, L.; SONG, X.-Y. Mitoquinone alleviates vincristine-induced neuropathic pain through inhibiting oxidative stress and apoptosis via the improvement of mitochondrial dysfunction. **Biomedicine & Pharmacotherapy**, [s. l.], v. 125, p. 110003, 2020.

CHENG, H. *et al.* Case report: Wallerian degeneration: The innate-immune response to adult-onset Still's disease peripheral nerve injury. **Frontiers in**

Neurology, [s. l.], v. 13, 2022.

CHEON, J. H. *et al.* P-gp Inhibition by XL019, a JAK2 Inhibitor, Increases Apoptosis of Vincristine-treated Resistant KBV20C Cells with Increased p21 and pH2AX Expression. **Anticancer Research**, [s. l.], v. 37, n. 12, 2017a.

CHEON, J. H. *et al.* P-gp Inhibition by XL019, a JAK2 Inhibitor, Increases Apoptosis of Vincristine-treated Resistant KBV20C Cells with Increased p21 and pH2AX Expression. **Anticancer Research**, [s. l.], v. 37, n. 12, 2017b. Disponível em: <http://ar.iiajournals.org/content/37/12/6761.abstract>.

CHIBA, T. *et al.* Vincristine increased spinal cord substance P levels in a peripheral neuropathy rat model. **Drug and Chemical Toxicology**, [s. l.], v. 45, n. 1, p. 393–397, 2022. Disponível em: <https://www.tandfonline.com/doi/full/10.1080/01480545.2019.1706547>.

CHIECHIO, S. *et al.* L-Acetylcarnitine Induces Analgesia by Selectively Up-Regulating mGlu2 Metabotropic Glutamate Receptors. **Molecular Pharmacology**, [s. l.], v. 61, n. 5, p. 989–996, 2002.

CHO, S.-H. *et al.* Anti-inflammatory activity of Echinosophora koreensis nakai root extract in lipopolysaccharides-stimulated RAW 264.7 cells and carrageenan-induced mouse paw edema model. **Journal of Ethnopharmacology**, [s. l.], v. 302, p. 115940, 2023.

CLARK, A. K.; MALCANGIO, M. Microglial signalling mechanisms: Cathepsin S and Fractalkine. **Experimental Neurology**, [s. l.], v. 234, n. 2, p. 283–292, 2012.

COBB, C. A.; COLE, M. P. Oxidative and nitrate stress in neurodegeneration. **Neurobiology of Disease**, [s. l.], v. 84, p. 4–21, 2015. Disponível em: <http://dx.doi.org/10.1016/j.nbd.2015.04.020>.

COLUZZI, F. *et al.* Pain management in childhood leukemia: Diagnosis and available analgesic treatments. **Cancers**, [s. l.], v. 12, n. 12, p. 1–13, 2020.

COLVIN, L. A. Chemotherapy-induced peripheral neuropathy: where are we now?. **Pain**, [s. l.], v. 160, n. 1, p. S1–S10, 2019.

COOK, K. M. *et al.* Experience of early-life pain in premature infants is associated with atypical cerebellar development and later neurodevelopmental deficits. **BMC Medicine**, [s. l.], v. 21, n. 1, p. 435, 2023.

COSTA, Y. M. *et al.* Reliability of the nociceptive blink reflex evoked by electrical stimulation of the trigeminal nerve in humans. **Clinical Oral Investigations**, [s. l.], v. 21, n. 8, p. 2453–2463, 2017.

COX, B. C. *et al.* Transport of multiple nicotinic acetylcholine receptors in the rat optic nerve: High densities of receptors containing $\alpha 6$ and $\beta 3$ subunits. **Journal of Neurochemistry**, [s. l.], v. 105, n. 5, p. 1924–1938, 2008.

CUREALL FRAMEWORK: WHO GLOBAL INITIATIVE FOR CHILDHOOD CANCER INCREASING ACCESS, ADVANCING QUALITY, SAVING LIVES. . [s. l.: s. n.], [s. d.].

DA MOTTA, K. P. *et al.* Insights into Vincristine-Induced Peripheral Neuropathy in Aged Rats: Wallerian Degeneration, Oxidative Damage, and Alterations in ATPase Enzymes. **ACS Chemical Neuroscience**, [s. l.], v. 15, n. 21, p. 3954–3969, 2024.

DA MOTTA, K. P. *et al.* The Antinociceptive Responses of MTDZ to Paclitaxel – Induced Peripheral Neuropathy and Acute Nociception in Mice : Behavioral , Pharmacological , and Biochemical Approaches. **Pharmaceuticals**, [s. l.], v. 16, n. 9, p. 1217, 2023.

DA ROCHA, V. M. E. *et al.* Structure-Activity Relationship of 7-Chloro-4-(Phenylselanyl) Quinoline: Novel Antinociceptive and Anti-Inflammatory Effects in Mice. **Chemistry & Biodiversity**, [s. l.], v. 22, n. 3, 2025.

DAGNINO, A. P. A.; CAMPOS, M. M. Chronic Pain in the Elderly: Mechanisms and Perspectives. **Frontiers in Human Neuroscience**, [s. l.], v. 16, p. 1–11, 2022.

DANG, X. *et al.* Alantolactone suppresses inflammation, apoptosis and oxidative stress in cigarette smoke-induced human bronchial epithelial cells through activation of Nrf2/HO-1 and inhibition of the NF- κ B pathways. **Respiratory Research**, [s. l.], v. 21, n. 1, p. 95, 2020.

DAVIS, R. L. *et al.* Effects of mechanistically distinct NF- κ B inhibitors on glial inducible nitric-oxide synthase expression. **Nitric Oxide**, [s. l.], v. 12, n. 4, p. 200–209, 2005.

DE FREITAS COUTO, S. *et al.* 7-chloro-4-(phenylselanyl) quinoline prevents dopamine depletion in a *Drosophila melanogaster* model of Parkinson's-like disease. **Journal of Trace Elements in Medicine and Biology**, [s. l.], v. 54, p. 232–243, 2019a. Disponível em: <https://linkinghub.elsevier.com/retrieve/pii/S0946672X1830405X>.

DE FREITAS COUTO, S. *et al.* 7-chloro-4-(phenylselanyl) quinoline prevents dopamine depletion in a *Drosophila melanogaster* model of Parkinson's-like disease. **Journal of Trace Elements in Medicine and Biology**, [s. l.], v. 54, p. 232–243, 2019b.

DE OLIVEIRA, R. L. *et al.* Prospecting for a quinoline containing selenium for comorbidities depression and memory impairment induced by restriction stress in mice. **Psychopharmacology**, [s. l.], v. 239, n. 1, p. 59–81, 2022a. Disponível em: <https://doi.org/10.1007/s00213-021-06039-8>.

DE OLIVEIRA, R. L. *et al.* Prospecting for a quinoline containing selenium for comorbidities depression and memory impairment induced by restriction stress in mice. **Psychopharmacology**, [s. l.], v. 239, n. 1, p. 59–81, 2022b.

DEL RIO, D.; STEWART, A. J.; PELLEGRINI, N. A review of recent studies on malondialdehyde as toxic molecule and biological marker of oxidative stress. **Nutrition, Metabolism and Cardiovascular Diseases**, [s. l.], v. 15, n. 4, p. 316–328, 2005.

DENG, G. Integrative Medicine Therapies for Pain Management in Cancer Patients. **The Cancer Journal**, [s. l.], v. 25, n. 5, p. 343–348, 2019.

DESFORGES, A. D. *et al.* Treatment and diagnosis of chemotherapy-induced peripheral neuropathy: An update. **Biomedicine & Pharmacotherapy**, [s. l.], v. 147, p. 112671, 2022.

DIOUF, B. *et al.* Association of an inherited genetic variant with vincristine-related peripheral neuropathy in children with acute lymphoblastic leukemia Critical revision of the manuscript for important intellectual content: Barthelemy Diouf; HHS Public Access. **Jama**, [s. l.], v. 313, n. 8, p. 815–823, 2015.

DOBRETISOV, M. Neuronal function and alpha3 isoform of the Na/K-ATPase. **Frontiers in Bioscience**, [s. l.], v. 10, n. 1–3, p. 2373, 2005a.

DOBRETISOV, M. Neuronal function and alpha3 isoform of the Na/K-ATPase. **Frontiers in Bioscience**, [s. l.], v. 10, n. 1–3, p. 2373, 2005b. Disponível em: <https://imrpess.com/journal/FBL/10/3/10.2741/1704>.

DOS SANTOS, L. M. *et al.* Methionine and methionine sulfoxide treatment induces M1/classical macrophage polarization and modulates oxidative stress and purinergic signaling parameters. **Molecular and Cellular Biochemistry**, [s. l.], v. 424, n. 1–2, p. 69–78, 2017.

DUARTE, L. F. B. *et al.* A simple method for the synthesis of 4-arylselanyl-7-chloroquinolines used as in vitro acetylcholinesterase inhibitors and in vivo memory improvement. **Tetrahedron Letters**, [s. l.], v. 58, n. 33, p. 3319–3322, 2017a.

DUARTE, L. F. B. *et al.* Organoselenium compounds from purines: Synthesis of 6-arylselanylpurines with antioxidant and anticholinesterase activities and memory improvement effect. **Bioorganic & Medicinal Chemistry**, [s. l.], v. 25, n. 24, p. 6718–6723, 2017b.

DUPUIS, L. L. *et al.* Anxiety, pain, and nausea during the treatment of standard-risk childhood acute lymphoblastic leukemia: A prospective, longitudinal study from the Children's Oncology Group. **Cancer**, [s. l.], v. 122, n. 7, p. 1116–1125, 2016.

DZIECHCIAŻ, M.; BALICKA-ADAMIK, L.; FILIP, R. The problem of pain in old age. **Annals of agricultural and environmental medicine : AAEM**, [s. l.], v. 1, n. 1, p. 35–38, 2013.

EDINOFF, A. N. *et al.* Selective Serotonin Reuptake Inhibitors and Adverse

Effects: A Narrative Review. **Neurology International**, [s. l.], v. 13, n. 3, p. 387–401, 2021.

EDWARDS, R. R. *et al.* The role of psychosocial processes in the development and maintenance of chronic pain disorders. **Pain**, [s. l.], v. 176, n. 1, p. 70–92, 2017.

EIDE, S.; FENG, Z. P. Doxorubicin chemotherapy-induced “chemo-brain”: Meta-analysis. **European Journal of Pharmacology**, [s. l.], v. 881, n. July 2019, p. 173078, 2020.

EL HACHEM, G. *et al.* Advances in pain management for older patients with cancer. **ecancermedicalscience**, [s. l.], v. 13, 2019.

ELDUFANI, J.; BLAISE, G. The role of acetylcholinesterase inhibitors such as neostigmine and rivastigmine on chronic pain and cognitive function in aging: A review of recent clinical applications. **Alzheimer's and Dementia: Translational Research and Clinical Interventions**, [s. l.], v. 5, p. 175–183, 2019.

ELLMAN, G. L. Tissue Sulfhydryl Groups. **Archives of biochemistry and biophysics**, [s. l.], v. 82, n. 1, p. 70–77, 1959.

ELTOKHY, A. K.; TOEMA, O.; EL-DEEB, O. S. The Correlation Between PINK-1/Parkin Mediated Mitophagy, Endoplasmic Reticulum Stress and Total Polyamines in Pediatric Bronchial Asthma: An Integrated Network of Pathways. **Molecular Biology Reports**, [s. l.], v. 49, n. 1, p. 227–235, 2022.

EVENEPOEL, M. *et al.* Pain Prevalence During Cancer Treatment: A Systematic Review and Meta-Analysis. **Journal of Pain and Symptom Management**, [s. l.], v. 63, n. 3, p. e317–e335, 2022.

FANE, M.; WEERARATNA, A. T. How the ageing microenvironment influences tumour progression. **Nature Reviews Cancer**, [s. l.], v. 20, n. 2, p. 89–106, 2020.

FANG, J. *et al.* Expression Dynamics of Heme Oxygenase-1 in Tumor Cells and the Host Contributes to the Progression of Tumors. **Journal of Personalized Medicine**, [s. l.], v. 11, n. 12, p. 1340, 2021.

FILIPPI-CHIELA, E. C. *et al.* Vincristine promotes differential levels of apoptosis, mitotic catastrophe, and senescence depending on the genetic background of glioblastoma cells. **Toxicology in Vitro**, [s. l.], v. 85, p. 105472, 2022.

FISKE, B. C. H.; SUBBAROW, Y. The colorimetric determination of phosphorus. **The Journal of Biological Chemistry**, [s. l.], v. 66, n. september, p. 375–400, 1925a.

FISKE, B. C. H.; SUBBAROW, Y. The colorimetric determination of phosphorus. **The Journal of Biological Chemistry**, [s. l.], v. 66, n. september, p. 375–400, 1925b.

FITZMAURICE, C. *et al.* Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study Global Burden . **JAMA Oncology**, [s. l.], v. 3, n. 4, p. 524–548, 2017.

FLATTERS, S. J. L.; DOUGHERTY, P. M.; COLVIN, L. A. Clinical and preclinical perspectives on Chemotherapy-Induced Peripheral Neuropathy (CIPN): A narrative review. **British Journal of Anaesthesia**, [s. l.], v. 119, n. 4, p. 737–749, 2017.

FRANÇOIS, A. *et al.* The Low-Threshold Calcium Channel Cav3.2 Determines Low-Threshold Mechanoreceptor Function. **Cell Reports**, [s. l.], v. 10, n. 3, p. 370–382, 2015.

GAUTHIER, I.; TARR, M. J. Visual Object Recognition: Do We (Finally) Know More Now Than We Did?. **Annual Review of Vision Science**, [s. l.], v. 2, n. 1, p. 377–396, 2016.

GEŖGOTEK, A.; SKRZYDLEWSKA, E. Biological effect of protein modifications by lipid peroxidation products. **Chemistry and Physics of Lipids**, [s. l.], v. 221, n. February, p. 46–52, 2019.

GEŖGOTEK, A.; SKRZYDLEWSKA, E. Lipid peroxidation products' role in autophagy regulation. **Free Radical Biology and Medicine**, [s. l.], v. 212, p. 375–383, 2024.

GEISLER, S. Vincristine- and bortezomib-induced neuropathies – from bedside to bench and back. **Experimental Neurology**, [s. l.], v. 336, p. 113519, 2021a.

GEISLER, S. Vincristine- and bortezomib-induced neuropathies – from bedside to bench and back. **Experimental Neurology**, [s. l.], v. 336, p. 113519, 2021b. Disponível em: <https://doi.org/10.1016/j.expneurol.2020.113519>.

GEORGE, E. B.; GLASS, J. D.; GRIFFIN, J. W. Axotomy-induced axonal degeneration is mediated by calcium influx through ion-specific channels. **Journal of Neuroscience**, [s. l.], v. 15, n. 10, p. 6445–6452, 1995.

GILCHRIST, L. S.; MARAIS, L.; TANNER, L. Comparison of two chemotherapy-induced peripheral neuropathy measurement approaches in children. **Supportive Care in Cancer**, [s. l.], v. 22, n. 2, p. 359–366, 2014.

GILCHRIST, L.; TANNER, L. Gait Patterns in Children With Cancer and Vincristine Neuropathy. **Pediatric Physical Therapy**, [s. l.], v. 28, n. 1, p. 16–22, 2016.

GLOBAL CANCER BURDEN GROWING, AMIDST MOUNTING NEED FOR SERVICES. **Saudi medical journal**, [s. l.], v. 45, n. 3, p. 326–327, 2024.

GOESLING, J.; LIN, L. A.; CLAUW, D. J. Psychiatry and Pain Management: at

the Intersection of Chronic Pain and Mental Health. **Current Psychiatry Reports**, [s. l.], v. 20, n. 2, 2018.

GOLCHIN, L. *et al.* Pistachio supplementation attenuates motor and cognition impairments induced by cisplatin or vincristine in rats. **Advanced Biomedical Research**, [s. l.], v. 4, n. 1, p. 92, 2015.

GOMBER, S.; DEWAN, P.; CHHONKER, D. Vincristine induced neurotoxicity in cancer patients. **Indian Journal of Pediatrics**, [s. l.], v. 77, n. 1, p. 97–100, 2010a.

GOMBER, S.; DEWAN, P.; CHHONKER, D. Vincristine induced neurotoxicity in cancer patients. **Indian Journal of Pediatrics**, [s. l.], v. 77, n. 1, p. 97–100, 2010b.

GÓMEZ, V. *et al.* Breast cancer-associated macrophages promote tumorigenesis by suppressing succinate dehydrogenase in tumor cells. **Science Signaling**, [s. l.], v. 13, n. 652, 2020.

GOUVEIA, D. N. *et al.* α -Terpineol reduces cancer pain via modulation of oxidative stress and inhibition of iNOS. **Biomedicine & Pharmacotherapy**, [s. l.], v. 105, p. 652–661, 2018.

GRANT, C. H. *et al.* Multimorbidity and analgesic-related harms: a systematic review. **British Journal of Anaesthesia**, [s. l.], v. 134, n. 6, p. 1717–1745, 2025.

GROTEN, C. J.; MACVICAR, B. A. Mitochondrial Ca^{2+} uptake by the MCU facilitates pyramidal neuron excitability and metabolism during action potential firing. **Communications Biology**, [s. l.], v. 5, n. 1, p. 900, 2022.

GU, C. *et al.* Cancer Cells Promote Immune Regulatory Function of Macrophages by Upregulating Scavenger Receptor MARCO Expression. **The Journal of Immunology**, [s. l.], v. 211, n. 1, p. 57–70, 2023.

GUHA, L.; SINGH, N.; KUMAR, H. Different Ways to Die: Cell Death Pathways and Their Association With Spinal Cord Injury. **Neurospine**, [s. l.], v. 20, n. 2, p. 430–448, 2023a.

GUHA, L.; SINGH, N.; KUMAR, H. Different Ways to Die: Cell Death Pathways and Their Association With Spinal Cord Injury. **Neurospine**, [s. l.], v. 20, n. 2, p. 430–448, 2023b.

HABIF, M. *et al.* Early Long-Term Memory Impairment and Changes in the Expression of Synaptic Plasticity-Associated Genes, in the McGill-R-Thy1-APP Rat Model of Alzheimer's-Like Brain Amyloidosis. **Frontiers in Aging Neuroscience**, [s. l.], v. 12, 2021. Disponível em: <https://www.frontiersin.org/articles/10.3389/fnagi.2020.585873/full>.

HABIG, W. H.; JAKOBY, M. J. P.; B., W. J. Glutathione S-Transferases: The first enzymatic step in mercapturic acid formation. **THE JOURNAL OF BIOLOGICAL**

CHEMISTRY, [s. l.], v. 249, n. 22, p. 7130–7139, 1974.

HARRIS, J. C. *et al.* Sustained delivery of vincristine inside an orthotopic mouse sarcoma model decreases tumor growth. **Journal of Pediatric Surgery**, [s. l.], v. 51, n. 12, p. 2058–2062, 2016.

HASHMI, J. A.; DAVIS, K. D. Women experience greater heat pain adaptation and habituation than men. **Pain**, [s. l.], v. 145, n. 3, p. 350–357, 2009a.

HASHMI, J. A.; DAVIS, K. D. Women experience greater heat pain adaptation and habituation than men. **Pain**, [s. l.], v. 145, n. 3, p. 350–357, 2009b. Disponível em: <http://dx.doi.org/10.1016/j.pain.2009.07.002>.

HATHWAY, G. J. *et al.* Cancer Chemotherapy in Early Life Significantly Alters the Maturation of Pain Processing. **Neuroscience**, [s. l.], v. 387, p. 214–229, 2018.

HE, X.; SUN, J.; HUANG, X. Expression of caspase-3, Bax and Bcl-2 in hippocampus of rats with diabetes and subarachnoid hemorrhage. **Experimental and Therapeutic Medicine**, [s. l.], 2017.

HODAPP, J. W.; ALI, S.; DRENDEL, A. L. Bringing It All Together: A Review of the Challenges in Measuring Children's Satisfaction as a Key Component of Acute Pain Management. **Children**, [s. l.], v. 7, n. 11, p. 243, 2020.

HOLLIDAY, L. S. Vacuolar H⁺-ATPases (V-ATPases) as therapeutic targets: a brief review and recent developments. **Biotarget**, [s. l.], v. 1, n. 7, p. 18–18, 2017.

HONE, A. J.; MCINTOSH, J. M. **Nicotinic Acetylcholine Receptors in Neuropathic and Inflammatory Pain**. [S. l.: s. n.], 2018-. ISSN 1751553X.v. 592

HOOGEN, N. J. van den *et al.* Neonatal Plasticity of the Nociceptive System: Mechanisms, Effects, and Treatment of Repetitive Painful Procedures During NICU Admittance. **Current Pharmaceutical Design**, [s. l.], v. 23, n. 38, p. 5902–5910, 2018.

HORIE, K.; MA, J.; UMEZAWA, K. Inhibition of Canonical NF- κ B Nuclear Localization by (-)-DHMEQ via Impairment of DNA Binding. **Oncology Research Featuring Preclinical and Clinical Cancer Therapeutics**, [s. l.], v. 22, n. 2, p. 105–115, 2015.

HOU, Y. *et al.* Ageing as a risk factor for neurodegenerative disease. **Nature Reviews Neurology**, [s. l.], v. 15, n. 10, p. 565–581, 2019.

HUANG, Y. L. *et al.* Chronic pain and use of analgesics in the elderly: A nationwide population-based study. **Archives of Medical Science**, [s. l.], v. 16, n. 2, p. 627–634, 2020.

ISAKSEN, T. J.; LYKKE-HARTMANN, K. Insights into the Pathology of the α 2-Na⁺/K⁺-ATPase in Neurological Disorders; Lessons from Animal Models.

Frontiers in Physiology, [s. l.], v. 7, 2016a.

ISAKSEN, T. J.; LYKKE-HARTMANN, K. Insights into the Pathology of the $\alpha 2$ -Na⁺/K⁺-ATPase in Neurological Disorders; Lessons from Animal Models. **Frontiers in Physiology**, [s. l.], v. 7, 2016b. Disponível em: <http://journal.frontiersin.org/Article/10.3389/fphys.2016.00161/abstract>.

JAGANJAC, M. *et al.* The relevance of pathophysiological alterations in redox signaling of 4-hydroxynonenal for pharmacological therapies of major stress-associated diseases. **Free Radical Biology and Medicine**, [s. l.], v. 157, p. 128–153, 2020.

JIANG, K.; SHI, Jinshan; SHI, Jing. Morin Alleviates Vincristine-Induced Neuropathic Pain via Nerve protective Effect and Inhibition of NF- κ B Pathway in Rats. **Cellular and Molecular Neurobiology**, [s. l.], v. 39, n. 6, p. 799–808, 2019a.

JIANG, K.; SHI, Jinshan; SHI, Jing. Morin Alleviates Vincristine-Induced Neuropathic Pain via Nerve protective Effect and Inhibition of NF- κ B Pathway in Rats. **Cellular and Molecular Neurobiology**, [s. l.], v. 39, n. 6, p. 799–808, 2019b. Disponível em: <https://doi.org/10.1007/s10571-019-00679-3>.

JIN, T.; LENG, B. Cynaropicrin Averts the Oxidative Stress and Neuroinflammation in Ischemic/Reperfusion Injury Through the Modulation of NF- κ B. **Applied Biochemistry and Biotechnology**, [s. l.], v. 195, n. 9, p. 5424–5438, 2023.

JOSEPH, E. K.; LEVINE, J. D. Mitochondrial electron transport in models of neuropathic and inflammatory pain. **Pain**, [s. l.], v. 121, n. 1–2, p. 105–114, 2006.

KAI, K. *et al.* Species and Sex Differences in Susceptibility to Olfactory Lesions Among the Mouse, Rat and Monkey Following an Intravenous Injection of Vincristine Sulphate. **Toxicologic Pathology**, [s. l.], v. 34, n. 3, p. 223–231, 2006.

KAKATKAR, S.; NARAYAN, A.; BALKRISHNAN, R. Prescription analgesic overuse in older adults: Can we mitigate this growing problem?. **AGING MEDICINE**, [s. l.], v. 5, n. 4, p. 294–296, 2022.

KALTSCHMIDT, B.; KALTSCHMIDT, C. NF-KappaB in Long-Term Memory and Structural Plasticity in the Adult Mammalian Brain. **Frontiers in Molecular Neuroscience**, [s. l.], v. 8, 2015.

KANG, L. *et al.* Oxaliplatin-induced peripheral neuropathy: clinical features, mechanisms, prevention and treatment. **Journal of Neurology**, [s. l.], n. 0123456789, 2020. Disponível em: <https://doi.org/10.1007/s00415-020-09942-w>.

KANZAKI, H. *et al.* Disabling the Nuclear Translocalization of RelA/NF- κ B by a Small Molecule Inhibits Triple-Negative Breast Cancer Growth. **Breast Cancer**:

Targets and Therapy, [s. l.], v. Volume 13, p. 419–430, 2021.

KASAI, S. *et al.* Regulation of Nrf2 by Mitochondrial Reactive Oxygen Species in Physiology and Pathology. **Biomolecules**, [s. l.], v. 10, n. 2, p. 320, 2020.

KATSUYAMA, S. *et al.* Antinociceptive Effects of the Serotonin and Noradrenaline Reuptake Inhibitors Milnacipran and Duloxetine on Vincristine-Induced Neuropathic Pain Model in Mice. **ISRN Pain**, [s. l.], v. 2014, p. 1–7, 2014.

KAZARYAN, S. *et al.* Oxidative stress and histopathological changes in several organs of mice injected with biogenic silver nanoparticles. **Artificial Cells, Nanomedicine, and Biotechnology**, [s. l.], v. 50, n. 1, p. 331–342, 2022.

KESZTYÜS, D. *et al.* Use of Infrared Thermography in Medical Diagnosis, Screening, and Disease Monitoring: A Scoping Review. **Medicina**, [s. l.], v. 59, n. 12, p. 2139, 2023.

KHALILZADEH, M. *et al.* Aripiprazole prevents from development of vincristine-induced neuropathic nociception by limiting neural NOS overexpression and NF- κ B hyperactivation. **Cancer Chemotherapy and Pharmacology**, [s. l.], v. 86, n. 3, p. 393–404, 2020a.

KHALILZADEH, M. *et al.* Aripiprazole prevents from development of vincristine-induced neuropathic nociception by limiting neural NOS overexpression and NF- κ B hyperactivation. **Cancer Chemotherapy and Pharmacology**, [s. l.], v. 86, n. 3, p. 393–404, 2020b. Disponível em: <https://doi.org/10.1007/s00280-020-04127-8>.

KHIDR, H. Y. *et al.* Formoterol attenuated mitochondrial dysfunction in rotenone-induced Parkinson's disease in a rat model: Role of PINK-1/PARKIN and PI3K/Akt/CREB/BDNF/TrKB axis. **International Immunopharmacology**, [s. l.], v. 125, p. 111207, 2023.

KIGUCHI, N. *et al.* The critical role of invading peripheral macrophage-derived interleukin-6 in vincristine-induced mechanical allodynia in mice. **European Journal of Pharmacology**, [s. l.], v. 592, n. 1–3, p. 87–92, 2008.

KIM, S. J. *et al.* Antitumor Effects of Selenium. **International Journal of Molecular Sciences**, [s. l.], v. 22, n. 21, p. 11844, 2021.

KIM, Y. S. *et al.* Assessment of pain in the elderly: A literature review. **National Medical Journal of India**, [s. l.], v. 30, n. 4, p. 203–207, 2017a.

KIM, Y. S. *et al.* Assessment of pain in the elderly: A literature review. **National Medical Journal of India**, [s. l.], v. 30, n. 4, p. 203–207, 2017b.

KIM, S. H. *et al.* Regulation of P21-Activated Kinase-4 by Progesterone and Tumor Necrosis Factor- α in Human Endometrium and Its Increased Expression in Advanced-Stage Endometriosis. **The Journal of Clinical Endocrinology & Metabolism**, [s. l.], v. 98, n. 2, p. E238–E248, 2013a.

KIM, S. H. *et al.* Regulation of P21-Activated Kinase-4 by Progesterone and Tumor Necrosis Factor- α in Human Endometrium and Its Increased Expression in Advanced-Stage Endometriosis. **The Journal of Clinical Endocrinology & Metabolism**, [s. l.], v. 98, n. 2, p. E238–E248, 2013b. Disponível em: <https://academic.oup.com/jcem/article-lookup/doi/10.1210/jc.2012-2969>.

KIM, J.; SHARMA, R. P. Calcium-mediated activation of c-Jun NH2-terminal kinase (JNK and apoptosis in response to cadmium in murine macrophages. **Toxicological Sciences**, [s. l.], v. 81, n. 2, p. 518–527, 2004.

KINOSHITA, P. F. *et al.* The influence of Na⁺, K⁺-ATPase on glutamate signaling in neurodegenerative diseases and senescence. **Frontiers in Physiology**, [s. l.], v. 7, n. JUN, p. 1–19, 2016.

KINTOSSOU, A. K. *et al.* Early Life Nutrition Factors and Risk of Acute Leukemia in Children: Systematic Review and Meta-Analysis. **Nutrients**, [s. l.], v. 15, n. 17, p. 3775, 2023.

KOHNO, T. *et al.* Peripheral nerve injury alters excitatory synaptic transmission in laminal II of the rat dorsal horn. **Journal of Physiology**, [s. l.], v. 548, n. 1, p. 131–138, 2003.

KOSTIĆ, M.; MARJANOVIĆ, J.; DIVAC, V. Organoselenium transition metal complexes as promising candidates in medicine area. **JBIC Journal of Biological Inorganic Chemistry**, [s. l.], v. 29, n. 6, p. 555–571, 2024.

KREMER, M. *et al.* How to study anxiety and depression in rodent models of chronic pain?. **European Journal of Neuroscience**, [s. l.], v. 53, n. 1, p. 236–270, 2021.

KUPPUSAMY, P. *et al.* Targeting metabolic pathways alleviates bortezomib-induced neuropathic pain without compromising anticancer efficacy in a sex-specific manner. **Frontiers in Pain Research**, [s. l.], v. 5, 2024.

LAFORGIA, M. *et al.* Peripheral Neuropathy under Oncologic Therapies: A Literature Review on Pathogenetic Mechanisms. **International Journal of Molecular Sciences**, [s. l.], v. 22, n. 4, p. 1980, 2021.

LAURITZEN, M. *et al.* Clinical Relevance of Cortical Spreading Depression in Neurological Disorders: Migraine, Malignant Stroke, Subarachnoid and Intracranial Hemorrhage, and Traumatic Brain Injury. **Journal of Cerebral Blood Flow & Metabolism**, [s. l.], v. 31, n. 1, p. 17–35, 2011a.

LAURITZEN, M. *et al.* Clinical Relevance of Cortical Spreading Depression in Neurological Disorders: Migraine, Malignant Stroke, Subarachnoid and Intracranial Hemorrhage, and Traumatic Brain Injury. **Journal of Cerebral Blood Flow & Metabolism**, [s. l.], v. 31, n. 1, p. 17–35, 2011b. Disponível em: <http://journals.sagepub.com/doi/10.1038/jcbfm.2010.191>.

LAW, A. Y. S. *et al.* Histone deacetylase inhibitor-induced cellular apoptosis involves stanniocalcin-1 activation. **Experimental Cell Research**, [s. l.], v. 314, n. 16, p. 2975–2984, 2008.

LEE, S. J. *et al.* Fetal Pain. **JAMA**, [s. l.], v. 294, n. 8, p. 947, 2005.

LEE, J. Y. *et al.* The Antiallodynic Effect of Nefopam on Vincristine-Induced Neuropathy in Mice. **Journal of Pain Research**, [s. l.], v. Volume 13, p. 323–329, 2020. Disponível em: <https://www.dovepress.com/the-antiallodynic-effect-of-nefopam-on-vincristine-induced-neuropathy--peer-reviewed-article-JPR>.

LEE, B. Y.; HUR, E. M. A role of microtubules in oligodendrocyte differentiation. **International Journal of Molecular Sciences**, [s. l.], v. 21, n. 3, 2020.

LEGAKIS, L. P.; BIGBEE, J. W.; NEGUS, S. S. Lack of paclitaxel effects on intracranial Self-Stimulation in male and female rats: Comparison to mechanical sensitivity. **Behavioural Pharmacology**, [s. l.], v. 29, p. 290–298, 2018.

LEMOIS, B. B. *et al.* ROLE OF 7-CHLORO-4- (PHENYLSELANYL) QUINOLINE IN THE TREATMENT. **Canadian physiology and pharmacology**, [s. l.], v. 99(4), n. 378–388, p. 1–50, 2021a.

LEMOIS, B. B. *et al.* ROLE OF 7-CHLORO-4- (PHENYLSELANYL) QUINOLINE IN THE TREATMENT. **Canadian physiology and pharmacology**, [s. l.], v. 99(4), n. 378–388, p. 1–50, 2021b.

LI, H. *et al.* Adipocyte Fatty Acid-Binding Protein Promotes Palmitate-Induced Mitochondrial Dysfunction and Apoptosis in Macrophages. **Frontiers in Immunology**, [s. l.], v. 9, 2018.

LI, G. zhou *et al.* CaMKII and CaV3.2 T-type calcium channel mediate Connexin-43-dependent inflammation by activating astrocytes in vincristine-induced neuropathic pain. **Cell Biology and Toxicology**, [s. l.], p. 679–702, 2021a.

LI, G. zhou *et al.* CaMKII and CaV3.2 T-type calcium channel mediate Connexin-43-dependent inflammation by activating astrocytes in vincristine-induced neuropathic pain. **Cell Biology and Toxicology**, [s. l.], p. 679–702, 2021b.

LI, T. *et al.* Characterising vincristine-induced peripheral neuropathy in adults: symptom development and long-term persistent outcomes. **Supportive Care in Cancer**, [s. l.], v. 32, n. 5, p. 278, 2024.

LI, Y. *et al.* Dorsal root ganglion neurons become hyperexcitable and increase expression of voltage-gated T-type calcium channels (Cav3.2) in paclitaxel-induced peripheral neuropathy. **Pain**, [s. l.], v. 158, n. 3, p. 417–429, 2017.

LI, W. *et al.* Ibrutinib alleviates LPS-induced neuroinflammation and synaptic defects in a mouse model of depression. **Brain, Behavior, and Immunity**, [s. l.], v. 92, p. 10–24, 2021.

LI, G. zhou *et al.* Vincristine-induced peripheral neuropathy: A mini-review. **NeuroToxicology**, [s. l.], v. 81, p. 161–171, 2020a.

LI, G. zhou *et al.* Vincristine-induced peripheral neuropathy: A mini-review. **NeuroToxicology**, [s. l.], v. 81, p. 161–171, 2020b.

LIU, J. *et al.* Glutamatergic Neurons in the Amygdala Are Involved in Paclitaxel-Induced Pain and Anxiety. **Frontiers in Psychiatry**, [s. l.], v. 13, n. April, p. 1–11, 2022.

LIU, J. *et al.* Na/K-ATPase signaling and salt sensitivity: The role of oxidative stress. **Antioxidants**, [s. l.], v. 6, n. 1, p. 12–14, 2017a.

LIU, J. *et al.* Na/K-ATPase signaling and salt sensitivity: The role of oxidative stress. **Antioxidants**, [s. l.], v. 6, n. 1, p. 12–14, 2017b.

LIU, J.; LILLY, M. N.; SHAPIRO, J. I. Targeting Na/K-ATPase Signaling: A New Approach to Control Oxidative Stress. **Current Pharmaceutical Design**, [s. l.], v. 24, n. 3, p. 359–364, 2018a.

LIU, J.; LILLY, M. N.; SHAPIRO, J. I. Targeting Na/K-ATPase Signaling: A New Approach to Control Oxidative Stress. **Current Pharmaceutical Design**, [s. l.], v. 24, n. 3, p. 359–364, 2018b. Disponível em: <https://www.eurekaselect.com/158913/article>.

LIVAK, K. J.; SCHMITTGEN, T. D. Analysis of Relative Gene Expression Data Using Real-Time Quantitative PCR and the 2- $\Delta\Delta$ CT Method. **Methods**, [s. l.], v. 25, n. 4, p. 402–408, 2001a.

LIVAK, K. J.; SCHMITTGEN, T. D. Analysis of relative gene expression data using real-time quantitative PCR and the 2- $\Delta\Delta$ CT method. **Methods**, [s. l.], v. 25, n. 4, p. 402–408, 2001b.

LOWRY, OliverH. *et al.* PROTEIN MEASUREMENT WITH THE FOLIN PHENOL REAGENT. **Journal of Biological Chemistry**, [s. l.], v. 193, n. 1, p. 265–275, 1951.

LUHMANN, H. J.; FUKUDA, A. Can we understand human brain development from experimental studies in rodents?. **Pediatrics International**, [s. l.], v. 62, n. 10, p. 1139–1144, 2020.

MACDONALD, A. D.; WOOLFE, G. Analgesic action of pethidine derivatives and related compounds. **British journal of pharmacology and chemotherapy**, [s. l.], v. 1, p. 4–14, 1946.

MADSEN, M. L. *et al.* Aspects of vincristine-induced neuropathy in hematologic malignancies: a systematic review. **Cancer Chemotherapy and Pharmacology**, [s. l.], v. 84, n. 3, p. 471–485, 2019. Disponível em: <https://doi.org/10.1007/s00280-019-03884-5>.

MAGEE, J. C.; GRIENBERGER, C. Synaptic Plasticity Forms and Functions. **Annual Review of Neuroscience**, [s. l.], v. 43, n. 1, p. 95–117, 2020a.

MAGEE, J. C.; GRIENBERGER, C. Synaptic Plasticity Forms and Functions. **Annual Review of Neuroscience**, [s. l.], v. 43, n. 1, p. 95–117, 2020b. Disponível em: <https://www.annualreviews.org/doi/10.1146/annurev-neuro-090919-022842>.

MALDONADO, L. A. G. *et al.* Influence of tumor cell-derived TGF- β on macrophage phenotype and macrophage-mediated tumor cell invasion. **The International Journal of Biochemistry & Cell Biology**, [s. l.], v. 153, p. 106330, 2022.

MALONEYHUSS, M. A. *et al.* Efficacy and toxicity of mustargen, vincristine, procarbazine and prednisone (MOPP) for the treatment of relapsed or resistant lymphoma in cats. **Journal of Feline Medicine and Surgery**, [s. l.], v. 22, n. 4, p. 299–304, 2020.

MARKOVIC, T. *et al.* Pain induces adaptations in ventral tegmental area dopamine neurons to drive anhedonia-like behavior. **Nature Neuroscience**, [s. l.], v. 24, n. 11, p. 1601–1613, 2021.

MASKO, M. *et al.* A novel approach to thermographic images analysis of equine thoracolumbar region: the effect of effort and rider's body weight on structural image complexity. **BMC Veterinary Research**, [s. l.], v. 17, n. 1, p. 99, 2021.

MCCALLUM, J. B. *et al.* Loss of T-type calcium current in sensory neurons of rats with neuropathic pain. **Anesthesiology**, [s. l.], v. 98, n. 1, p. 209–216, 2003.

MCILWAIN, K. L. *et al.* The use of behavioral test batteries: Effects of training history. **Physiology & Behavior**, [s. l.], v. 73, n. 5, p. 705–717, 2001.

MCKELVEY, R. *et al.* Neuropathic pain is constitutively suppressed in early life by anti-inflammatory neuroimmune regulation. **Journal of Neuroscience**, [s. l.], v. 35, n. 2, p. 457–466, 2015.

MEFFERT, M. K. *et al.* NF- κ B functions in synaptic signaling and behavior. **Nature Neuroscience**, [s. l.], v. 6, n. 10, p. 1072–1078, 2003.

MELÉNDEZ, D. M. *et al.* Spatial memory deficits after vincristine-induced lesions to the dorsal hippocampus. **PLoS ONE**, [s. l.], v. 15, n. 4, p. 1–16, 2020.

MESTDAGH, F.; STEYAERT, A.; LAVAND'HOMME, P. Cancer Pain Management: A Narrative Review of Current Concepts, Strategies, and Techniques. **Current Oncology**, [s. l.], v. 30, n. 7, p. 6838–6858, 2023.

MICLESCU, A. A. *et al.* Association between systemic inflammation and experimental pain sensitivity in subjects with pain and painless neuropathy after traumatic nerve injuries. **Scandinavian Journal of Pain**, [s. l.], v. 7, 2022.

MINJ, E.; UPADHAYAY, S.; MEHAN, S. Nrf2/HO-1 Signaling Activator Acetyl-11-keto-beta Boswellic Acid (AKBA)-Mediated Neuroprotection in Methyl Mercury-Induced Experimental Model of ALS. **Neurochemical Research**, [s. l.], v. 46, n. 11, p. 2867–2884, 2021.

MISRA, H. P.; FRIDOVICH, I. The role of superoxide anion in the autoxidation of epinephrine and a simple assay for superoxide dismutase. **Journal of Biological Chemistry**, [s. l.], v. 247, n. 10, p. 3170–3175, 1972.

MOJARAD-JABALI, S. *et al.* Comparison of three synthetic transferrin mimetic small peptides to promote the blood–brain barrier penetration of vincristine liposomes for improved glioma targeted therapy. **International Journal of Pharmaceutics**, [s. l.], v. 613, p. 121395, 2022.

MOK, C. C.; LOK, E. Y. C.; CHEUNG, E. F. C. Concurrent psychiatric disorders are associated with significantly poorer quality of life in patients with rheumatoid arthritis. **Scandinavian Journal of Rheumatology**, [s. l.], v. 41, n. 4, p. 253–259, 2012.

MONTAGUE, K. *et al.* A novel interaction between CX 3 CR 1 and CCR 2 signalling in monocytes constitutes an underlying mechanism for persistent vincristine-induced pain. **Journal of Neuroinflammation**, [s. l.], v. 15, n. 1, p. 1–15, 2018.

MONTAGUE-CARDOSO, K.; MALCANGIO, M. Changes in blood–spinal cord barrier permeability and neuroimmune interactions in the underlying mechanisms of chronic pain. **Pain Reports**, [s. l.], v. 6, n. 1, p. 1–7, 2021.

MORA, E. *et al.* Vincristine-induced peripheral neuropathy in pediatric cancer patients. **American Journal of Cancer Research**, [s. l.], v. 6, n. 11, p. 2416–2430, 2016.

MORTAZAVI, H. Balance training as a promising intervention for reducing the risk of fall in elderly patients with chemotherapy-induced peripheral neuropathy. **Journal of Cancer Research and Therapeutics**, [s. l.], v. 15, n. 5, p. 1192, 2019.

MOSCHETTI, G. *et al.* Prokineticin 2 promotes and sustains neuroinflammation in vincristine treated mice: Focus on pain and emotional like behavior. **Brain, Behavior, and Immunity**, [s. l.], v. 82, n. September, p. 422–431, 2019a.

MOSCHETTI, G. *et al.* Prokineticin 2 promotes and sustains neuroinflammation in vincristine treated mice: Focus on pain and emotional like behavior. **Brain, Behavior, and Immunity**, [s. l.], v. 82, n. September, p. 422–431, 2019b.

MOSELEY, A. E. *et al.* Deficiency in Na,K-ATPase α isoform genes alters spatial learning, motor activity, and anxiety in mice. **Journal of Neuroscience**, [s. l.], v. 27, n. 3, p. 616–626, 2007.

MOTTA, K. P. da *et al.* **7-Chloro-4- (phenylselanyl) quinoline reduces renal oxidative stress induced by oxaliplatin in mice.** [S. l.: s. n.], 2021a.

MOTTA, K. P. da *et al.* 7-Chloro-4- (phenylselanyl) quinoline reduces renal oxidative stress induced by oxaliplatin in mice. **Canadian physiology and pharmacology**, [s. l.], p. 1–37, 2021b.

MOTTA, K. P. da *et al.* 7-Chloro-4- (phenylselanyl) quinoline reduces renal oxidative stress induced by oxaliplatin in mice. **Canadian physiology and pharmacology**, [s. l.], p. 1–37, 2021c.

MOTTA, K. P. da *et al.* Target enzymes in oxaliplatin-induced peripheral neuropathy in Swiss mice: A new acetylcholinesterase inhibitor as therapeutic strategy. **Chemico-Biological Interactions**, [s. l.], v. 352, n. November 2021, p. 109772, 2022. Disponível em: <https://doi.org/10.1016/j.cbi.2021.109772>.

MOWLAVI, A. *et al.* Increased cutaneous nerve fibers in female specimens. **Plastic and Reconstructive Surgery**, [s. l.], v. 116, n. 5, p. 1407–1410, 2005.

MUSSBACHER, M. *et al.* NF- κ B in monocytes and macrophages – an inflammatory master regulator in multitasked immune cells. **Frontiers in Immunology**, [s. l.], v. 14, 2023a.

MUSSBACHER, M. *et al.* NF- κ B in monocytes and macrophages – an inflammatory master regulator in multitasked immune cells. **Frontiers in Immunology**, [s. l.], v. 14, 2023b. Disponível em: <https://www.frontiersin.org/articles/10.3389/fimmu.2023.1134661/full>.

NAGAI, J.; GOSHIMA, Y.; OHSHIMA, T. CRMP4 mediates MAG-induced inhibition of axonal outgrowth and protection against Vincristine-induced axonal degeneration. **Neuroscience Letters**, [s. l.], v. 519, n. 1, p. 56–61, 2012a. Disponível em: <http://dx.doi.org/10.1016/j.neulet.2012.05.020>.

NAGAI, J.; GOSHIMA, Y.; OHSHIMA, T. CRMP4 mediates MAG-induced inhibition of axonal outgrowth and protection against Vincristine-induced axonal degeneration. **Neuroscience Letters**, [s. l.], v. 519, n. 1, p. 56–61, 2012b.

NGO, V.; DUENNWALD, M. L. Nrf2 and Oxidative Stress: A General Overview of Mechanisms and Implications in Human Disease. **Antioxidants**, [s. l.], v. 11, n. 12, p. 2345, 2022.

NOGUEIRA, C. W.; ROCHA, J. B. T. Toxicology and pharmacology of selenium: Emphasis on synthetic organoselenium compounds. **Archives of Toxicology**, [s. l.], v. 85, n. 11, p. 1313–1359, 2011.

NOGUEIRA, C. W.; ZENI, G.; ROCHA, J. B. T. Organoselenium and organotellurium compounds: Toxicology and pharmacology. **Chemical Reviews**, [s. l.], v. 104, n. 12, p. 6255–6285, 2004.

NOVELLE, M. G.; CAMACHO-MORALES, A.; MARTÍNEZ DE MORENTIN, P. B. Editorial: Role of estrogens as key regulators of energy homeostasis. **Frontiers in Endocrinology**, [s. l.], v. 14, 2023.

OHKAWA, H.; OHISHI, N.; YAGI, K. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. **Analytical Biochemistry**, [s. l.], v. 95, n. 2, p. 351–358, 1979.

OLD, E. A. *et al.* Monocytes expressing CX3CR1 orchestrate the development of vincristine-induced pain. **Journal of Clinical Investigation**, [s. l.], v. 124, n. 5, p. 2023–2036, 2014a.

OLD, E. A. *et al.* Monocytes expressing CX3CR1 orchestrate the development of vincristine-induced pain. **Journal of Clinical Investigation**, [s. l.], v. 124, n. 5, p. 2023–2036, 2014b.

O'ROURKE, S. A.; SHANLEY, L. C.; DUNNE, A. The Nrf2-HO-1 system and inflammaging. **Frontiers in Immunology**, [s. l.], v. 15, 2024.

PAICE, J. A. *et al.* Management of Chronic Pain in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. **Journal of Clinical Oncology**, [s. l.], v. 34, n. 27, p. 3325–3345, 2016.

PALTIAN, J. J. *et al.* 7-chloro-4-(phenylselanyl) quinoline incorporation into polymeric nanocapsules improves its pharmacological action: Physicochemical, toxicological, and behavioral studies. **International Journal of Pharmaceutics**, [s. l.], v. 673, p. 125370, 2025.

PALTIAN, J. J. *et al.* 7-Chloro-4-(Phenylselanyl) Quinoline Is a Novel Multitarget Therapy to Combat Peripheral Neuropathy and Comorbidities Induced by Paclitaxel in Mice. **Molecular Neurobiology**, [s. l.], n. 0123456789, 2022a. Disponível em: <https://doi.org/10.1007/s12035-022-02991-4>.

PALTIAN, J. J. *et al.* 7-Chloro-4-(Phenylselanyl) Quinoline Is a Novel Multitarget Therapy to Combat Peripheral Neuropathy and Comorbidities Induced by Paclitaxel in Mice. **Molecular Neurobiology**, [s. l.], n. 0123456789, 2022b.

PALTIAN, J. J. *et al.* The anxiolytic effect of a promising quinoline containing selenium with the contribution of the serotonergic and GABAergic pathways: Modulation of parameters associated with anxiety in mice. **Behavioural Brain Research**, [s. l.], v. 393, n. June, p. 112797, 2020a. Disponível em: <https://doi.org/10.1016/j.bbr.2020.112797>.

PALTIAN, J. J. *et al.* The anxiolytic effect of a promising quinoline containing selenium with the contribution of the serotonergic and GABAergic pathways: Modulation of parameters associated with anxiety in mice. **Behavioural Brain Research**, [s. l.], v. 393, n. June, p. 112797, 2020b.

PATIL, M. J. *et al.* Ginger Constituent 6-Shogaol Attenuates Vincristine-Induced Activation of Mouse Gastroesophageal Vagal Afferent C-Fibers. **Molecules**, [s. l.], v. 27, n. 21, 2022.

PAUWELS, B. *et al.* Comparison of the sulforhodamine B assay and the

clonogenic assay for in vitro chemoradiation studies. **Cancer Chemotherapy and Pharmacology**, [s. l.], v. 51, n. 3, p. 221–226, 2003.

PEDRA, N. S. *et al.* Impact of gallic acid on tumor suppression: Modulation of redox homeostasis and purinergic response in in vitro and a preclinical glioblastoma model. **The Journal of Nutritional Biochemistry**, [s. l.], v. 110, p. 109156, 2022.

PELLOW, S. *et al.* Validation of open : closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. **Journal of Neuroscience Methods**, [s. l.], v. 14, n. 3, p. 149–167, 1985.

PÉREZ-GONZÁLEZ, M. Z. *et al.* Anti-inflammatory, antioxidant, and acute toxicity of Brugmansia arborea extracts from wild plants and shoots obtained by indirect organogenesis. A thermographic assay to anti-inflammatory evaluation. **Biomedicine & Pharmacotherapy**, [s. l.], v. 186, p. 117972, 2025.

PIETROBON, D.; MOSKOWITZ, M. A. Pathophysiology of Migraine. **Annual Review of Physiology**, [s. l.], v. 75, n. 1, p. 365–391, 2013a.

PIETROBON, D.; MOSKOWITZ, M. A. Pathophysiology of Migraine. **Annual Review of Physiology**, [s. l.], v. 75, n. 1, p. 365–391, 2013b. Disponível em: <https://www.annualreviews.org/doi/10.1146/annurev-physiol-030212-183717>.

PINZ, M. *et al.* 4-Phenylselenyl-7-chloroquinoline, a new quinoline derivative containing selenium, has potential antinociceptive and anti-inflammatory actions. **European Journal of Pharmacology**, [s. l.], v. 780, p. 122–128, 2016a. Disponível em: <http://dx.doi.org/10.1016/j.ejphar.2016.03.039>.

PINZ, M. *et al.* 4-Phenylselenyl-7-chloroquinoline, a new quinoline derivative containing selenium, has potential antinociceptive and anti-inflammatory actions. **European Journal of Pharmacology**, [s. l.], v. 780, p. 122–128, 2016b.

PINZ, M. P. *et al.* Current advances of pharmacological properties of 7-chloro-4-(phenylselenyl) quinoline: Prevention of cognitive deficit and anxiety in Alzheimer's disease model. **Biomedicine and Pharmacotherapy**, [s. l.], v. 105, n. June, p. 1006–1014, 2018a. Disponível em: <https://doi.org/10.1016/j.biopha.2018.06.049>.

PINZ, M. P. *et al.* Current advances of pharmacological properties of 7-chloro-4-(phenylselenyl) quinoline: Prevention of cognitive deficit and anxiety in Alzheimer's disease model. **Biomedicine and Pharmacotherapy**, [s. l.], v. 105, n. June, p. 1006–1014, 2018b.

PURSER, M. J.; JOHNSTON, D. L.; MCMILLAN, H. J. Chemotherapy-induced Peripheral Neuropathy Among Paediatric Oncology Patients. **Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques**, [s. l.], v. 41, n. 4, p. 442–447, 2014.

QUEIROZ, M. P. *et al.* Effect of Conjugated Linoleic Acid on Memory and Reflex

Maturation in Rats Treated During Early Life. **Frontiers in Neuroscience**, [s. l.], v. 13, 2019.

QUEIROZ, K. F. F. da C.; DE CÁSSIA FERNANDES DE LIMA, R. Smart screening system for breast cancer: the use of thermographic images, evolutionary algorithms, and oversampling. **Biomedical Physics & Engineering Express**, [s. l.], v. 9, n. 5, p. 055027, 2023.

QUINES, C. B. *et al.* Involvement of the serotonergic system in the anxiolytic-like effect of 2-phenylethynyl butyltellurium in mice. **Behavioural Brain Research**, [s. l.], v. 277, p. 221–227, 2015.

QUINN, R. Comparing rat's to human's age: How old is my rat in people years? **Nutrition**, [s. l.], v. 21, n. 6, p. 775–777, 2005.

QUITON, R. L.; GREENSPAN, J. D. Sex differences in endogenous pain modulation by distracting and painful conditioning stimulation. **Pain**, [s. l.], p. 132–149, 2007.

RAASING, L. R. M. *et al.* Current View of Diagnosing Small Fiber Neuropathy. **Journal of Neuromuscular Diseases**, [s. l.], v. 8, n. 2, p. 185–207, 2021.

REIS, A. S. *et al.* 4-phenylselenyl-7-chloroquinoline, a novel multitarget compound with anxiolytic activity: Contribution of the glutamatergic system. **Journal of Psychiatric Research**, [s. l.], v. 84, p. 191–199, 2017a.

REIS, A. S. *et al.* 4-phenylselenyl-7-chloroquinoline, a novel multitarget compound with anxiolytic activity: Contribution of the glutamatergic system. **Journal of Psychiatric Research**, [s. l.], v. 84, p. 191–199, 2017b.

REIS, A. S. *et al.* 4-phenylselenyl-7-chloroquinoline, a novel multitarget compound with anxiolytic activity: Contribution of the glutamatergic system. **Journal of Psychiatric Research**, [s. l.], v. 84, p. 191–199, 2017c. Disponível em: <https://linkinghub.elsevier.com/retrieve/pii/S0022395616304976>.

REIS, A. S. *et al.* Advances in the Understanding of Oxaliplatin-Induced Peripheral Neuropathy in Mice: 7-Chloro-4-(Phenylselenyl) Quinoline as a Promising Therapeutic Agent. **Molecular Neurobiology**, [s. l.], v. 57, n. 12, p. 5219–5234, 2020a.

REIS, A. S. *et al.* Advances in the Understanding of Oxaliplatin-Induced Peripheral Neuropathy in Mice: 7-Chloro-4-(Phenylselenyl) Quinoline as a Promising Therapeutic Agent. **Molecular Neurobiology**, [s. l.], v. 57, n. 12, p. 5219–5234, 2020b.

REIS, A. S. *et al.* Interface of Aging and Acute Peripheral Neuropathy Induced by Oxaliplatin in Mice: Target-Directed Approaches for Na⁺, K⁺—ATPase, Oxidative Stress, and 7-Chloro-4-(phenylselenyl) quinoline Therapy. **Molecular Neurobiology**, [s. l.], v. 59, n. 3, p. 1766–1780, 2022. Disponível em: <https://doi.org/10.1007/s12035-021-02659-5>.

REIS, A. S. *et al.* Pharmacological modulation of Na⁺, K⁺-ATPase as a potential target for OXA-induced neurotoxicity: Correlation between anxiety and cognitive decline and beneficial effects of 7-chloro-4-(phenylselanyl) quinoline. **Brain Research Bulletin**, [s. l.], v. 162, n. June, p. 282–290, 2020c.

REIS, A. S. *et al.* Pharmacological modulation of Na⁺, K⁺-ATPase as a potential target for OXA-induced neurotoxicity: Correlation between anxiety and cognitive decline and beneficial effects of 7-chloro-4-(phenylselanyl) quinoline. **Brain Research Bulletin**, [s. l.], v. 162, n. June, p. 282–290, 2020d.

REIS, A. S. *et al.* Platinum Deposition in the Central Nervous System: A Novel Insight into Oxaliplatin-induced Peripheral Neuropathy in Young and Old Mice. **Molecular Neurobiology**, [s. l.], v. 62, n. 3, p. 3712–3729, 2025.

REZENDE, A. A. *et al.* Anti-Tumor Efficiency of Perillylalcohol/ β -Cyclodextrin Inclusion Complexes in a Sarcoma S180-Induced Mice Model. **Pharmaceutics**, [s. l.], v. 13, n. 2, p. 245, 2021.

RODRIGUES, K. C. *et al.* The neurotherapeutic role of a selenium-functionalized quinoline in hypothalamic obese rats. **Psychopharmacology**, [s. l.], v. 238, n. 7, p. 1937–1951, 2021a.

RODRIGUES, K. C. *et al.* The neurotherapeutic role of a selenium-functionalized quinoline in hypothalamic obese rats. **Psychopharmacology**, [s. l.], v. 238, n. 7, p. 1937–1951, 2021b.

ROHN, T. T.; HINDS, T. R.; VINCENZI, F. F. Ion transport ATPases as targets for free radical damage. **Biochemical Pharmacology**, [s. l.], v. 46, n. 3, p. 525–534, 1993.

RUAN, Y. *et al.* An effective and concise device for detecting cold allodynia in mice. **Scientific Reports**, [s. l.], v. 8, n. 1, 2018.

RUBIO, M. *et al.* The immunosuppressive effect of vincristine on allostimulatory potential of human dendritic cells interferes with their function and survival. **International Journal of Oncology**, [s. l.], 2004.

RUDNITSKAYA, E. A. *et al.* Features of Postnatal Hippocampal Development in a Rat Model of Sporadic Alzheimer's Disease. **Frontiers in Neuroscience**, [s. l.], v. 14, 2020.

RUHEE, R. T. *et al.* Organosulfur Compounds: A Review of Their Anti-inflammatory Effects in Human Health. **Frontiers in Nutrition**, [s. l.], v. 7, 2020.

SAGALAJEV, B. *et al.* Bidirectional amygdaloid control of neuropathic hypersensitivity mediated by descending serotonergic pathways acting on spinal 5-HT₃ and 5-HT_{1A} receptors. **Behavioural Brain Research**, [s. l.], v. 282, p. 14–24, 2015.

SAHRANAVARD, S. *et al.* Hydroethanolic extract of *Lavandula angustifolia* ameliorates vincristine-induced peripheral neuropathy in rats. **Research in Pharmaceutical Sciences**, [s. l.], v. 17, n. 3, p. 265, 2022. Disponível em: <https://journals.lww.com/10.4103/1735-5362.343080>.

SALAŁAT, K.; FILIPEK, B. Antinociceptive activity of transient receptor potential channel TRPV1, TRPA1, and TRPM8 antagonists in neurogenic and neuropathic pain models in mice. **Journal of Zhejiang University-SCIENCE B**, [s. l.], v. 16, n. 3, p. 167–178, 2015.

SAMPATHKUMAR, V. *et al.* Integration of signals from different cortical areas in higher order thalamic neurons. **Proceedings of the National Academy of Sciences**, [s. l.], v. 118, n. 30, 2021.

SANTOS, G. J. L. *et al.* *Himatanthus drasticus* (Apocynaceae) latex reduces oxidative stress and modulates CD4+, CD8+, FoxP3+ and HSP-60+ expressions in Sarcoma 180-bearing mice. **Journal of Ethnopharmacology**, [s. l.], v. 220, p. 159–168, 2018.

SAVEGNAGO, L. *et al.* Synthesis and antioxidant properties of novel quinoline-chalcogenium compounds. **Tetrahedron Letters**, [s. l.], v. 54, n. 1, p. 40–44, 2013a.

SAVEGNAGO, L. *et al.* Synthesis and antioxidant properties of novel quinoline-chalcogenium compounds. **Tetrahedron Letters**, [s. l.], v. 54, n. 1, p. 40–44, 2013b. Disponível em: <http://dx.doi.org/10.1016/j.tetlet.2012.10.067>.

SCHAPPACHER, K. A. *et al.* Neonatal vincristine administration modulates intrinsic neuronal excitability in the rat dorsal root ganglion and spinal dorsal horn during adolescence. **Pain**, [s. l.], v. 160, n. 3, p. 645–657, 2019a.

SCHAPPACHER, K. A. *et al.* Neonatal vincristine administration modulates intrinsic neuronal excitability in the rat dorsal root ganglion and spinal dorsal horn during adolescence. **Pain**, [s. l.], v. 160, n. 3, p. 645–657, 2019b.

SCHAPPACHER, K. A. *et al.* Neonatal vincristine administration modulates intrinsic neuronal excitability in the rat dorsal root ganglion and spinal dorsal horn during adolescence. **Pain**, [s. l.], v. 160, n. 3, p. 645–657, 2019c.

SCHAPPACHER, K. A.; STYCZYNSKI, L.; BACCEI, M. L. **Early life vincristine exposure evokes mechanical pain hypersensitivity in the developing rat.** [S. l.: s. n.], 2017-. ISSN 18726623.v. 158

SEKERES, M. J.; WINOCUR, G.; MOSCOVITCH, M. The hippocampus and related neocortical structures in memory transformation. **Neuroscience Letters**, [s. l.], v. 680, p. 39–53, 2018.

SEMPLE, B. D. *et al.* Brain development in rodents and humans: Identifying benchmarks of maturation and vulnerability to injury across species. **Progress in Neurobiology**, [s. l.], v. 106–107, p. 1–16, 2013.

SENGUPTA, S. *et al.* Adverse Neonatal Outcomes Associated With Early-Term Birth. **JAMA Pediatrics**, [s. l.], v. 167, n. 11, p. 1053, 2013.

SHABANI, M. *et al.* Profound destructive effects of adolescent exposure to Vincristine accompanied with some sex differences in motor and memory performance. **Canadian Journal of Physiology and Pharmacology**, [s. l.], v. 90, n. 4, p. 379–386, 2012a.

SHABANI, M. *et al.* Profound destructive effects of adolescent exposure to Vincristine accompanied with some sex differences in motor and memory performance. **Canadian Journal of Physiology and Pharmacology**, [s. l.], v. 90, n. 4, p. 379–386, 2012b.

SHAO, Y. *et al.* Morin Regulates M1/M2 Microglial Polarization via NF- κ B p65 to Alleviate Vincristine-Induced Neuropathic Pain. **Drug Design, Development and Therapy**, [s. l.], v. Volume 18, p. 3143–3156, 2024.

SHAYESTEH, S. *et al.* Dapsone improves the vincristine-induced neuropathic nociception by modulating neuroinflammation and oxidative stress. **DARU, Journal of Pharmaceutical Sciences**, [s. l.], v. 30, n. 2, p. 303–310, 2022a.

SHAYESTEH, S. *et al.* Dapsone improves the vincristine-induced neuropathic nociception by modulating neuroinflammation and oxidative stress. **DARU, Journal of Pharmaceutical Sciences**, [s. l.], v. 30, n. 2, p. 303–310, 2022b. Disponível em: <https://doi.org/10.1007/s40199-022-00448-6>.

SHEN, Y. *et al.* Exogenous induction of HO-1 alleviates vincristine-induced neuropathic pain by reducing spinal glial activation in mice. **Neurobiology of Disease**, [s. l.], v. 79, p. 100–110, 2015a.

SHEN, Y. *et al.* Exogenous induction of HO-1 alleviates vincristine-induced neuropathic pain by reducing spinal glial activation in mice. **Neurobiology of Disease**, [s. l.], v. 79, p. 100–110, 2015b. Disponível em: <http://dx.doi.org/10.1016/j.nbd.2015.04.012>.

SHINWARI, Z. *et al.* Vincristine and lomustine induce apoptosis and p21WAF1 up-regulation in medulloblastoma and normal human epithelial and fibroblast cells. **Journal of Neuro-Oncology**, [s. l.], v. 87, n. 2, p. 123–132, 2008.

SILVA, A. V. Associations between clinical signs and pathological findings in toxicity testing. **ALTEX**, [s. l.], 2020.

SILVA, V. D. G. *et al.* Further analysis of acute antinociceptive and anti-inflammatory actions of 4-phenylselenyl-7-chloroquinoline in mice. **Fundamental and Clinical Pharmacology**, [s. l.], v. 31, n. 5, p. 513–525, 2017a.

SILVA, V. D. G. *et al.* Further analysis of acute antinociceptive and anti-inflammatory actions of 4-phenylselenyl-7-chloroquinoline in mice. **Fundamental and Clinical Pharmacology**, [s. l.], v. 31, n. 5, p. 513–525, 2017b.

SIMÃO, D. A. da S. *et al.* Chemotherapy-induced peripheral neuropathy: review for clinical practice. **Revista Dor**, [s. l.], v. 16, n. 3, p. 215–220, 2015.

ŞİMŞEK, Ş.; OYMAK SOYSAL, A. N.; KAŞ ÖZDEMİR, A. Association between Pain Intensity, Pain Belief, and Coping Strategies in Older Adults. **Experimental Aging Research**, [s. l.], v. 49, n. 3, p. 244–251, 2023a. Disponível em: <https://doi.org/10.1080/0361073X.2022.2101304>.

ŞİMŞEK, Ş.; OYMAK SOYSAL, A. N.; KAŞ ÖZDEMİR, A. Association between Pain Intensity, Pain Belief, and Coping Strategies in Older Adults. **Experimental Aging Research**, [s. l.], v. 49, n. 3, p. 244–251, 2023b.

SINGH, G. *et al.* Bergapten Ameliorates Vincristine-Induced Peripheral Neuropathy by Inhibition of Inflammatory Cytokines and NFκB Signaling. research-article. **ACS Chemical Neuroscience**, [s. l.], v. 10, n. 6, p. 3008–3017, 2019a.

SINGH, G. *et al.* Bergapten Ameliorates Vincristine-Induced Peripheral Neuropathy by Inhibition of Inflammatory Cytokines and NFκB Signaling. research-article. **ACS Chemical Neuroscience**, [s. l.], v. 10, n. 6, p. 3008–3017, 2019b.

SMART, J. L.; DOBBING, J. Vulnerability of developing brain. II. Effects of early nutritional deprivation on reflex ontogeny and development of behaviour in the rat. **Brain Research**, [s. l.], v. 28, n. 1, p. 85–95, 1971.

SMITH, E. M. L. *et al.* Predictors of duloxetine response in patients with oxaliplatin-induced painful chemotherapy-induced peripheral neuropathy (CIPN): a secondary analysis of randomised controlled trial – CALGB/alliance 170601. **European Journal of Cancer Care**, [s. l.], v. 26, n. 2, 2017.

SNIJDERS, R. *et al.* Update on Prevalence of Pain in Patients with Cancer 2022: A Systematic Literature Review and Meta-Analysis. **Cancers**, [s. l.], v. 15, n. 3, p. 591, 2023.

SONG, B. *et al.* Inhibitory phosphorylation of GSK-3 by CaMKII couples depolarization to neuronal survival. **Journal of Biological Chemistry**, [s. l.], v. 285, n. 52, p. 41122–41134, 2010.

SORIANO, D. *et al.* Chemotherapy-induced neuropathy and pain in pediatric oncology patients: impact of combination therapies. **European Journal of Pediatrics**, [s. l.], v. 183, n. 9, p. 3749–3756, 2024.

SOYOCAK, A. *et al.* Tannic acid exhibits anti-inflammatory effects on formalin-induced paw edema model of inflammation in rats. **Human & Experimental Toxicology**, [s. l.], v. 38, n. 11, p. 1296–1301, 2019.

STANGHERLIN, E. C.; ROCHA, J. B. T.; NOGUEIRA, C. W. Diphenyl ditelluride impairs short-term memory and alters neurochemical parameters in young rats.

Pharmacology Biochemistry and Behavior, [s. l.], v. 91, n. 3, p. 430–435, 2009.

STAROBOVA, H. *et al.* Minocycline prevents the development of mechanical allodynia in mouse models of vincristine-induced peripheral neuropathy. **Frontiers in Neuroscience**, [s. l.], v. 13, n. JUN, p. 1–10, 2019.

STAROBOVA, H.; VETTER, I. Pathophysiology of chemotherapy-induced peripheral neuropathy. **Frontiers in Molecular Neuroscience**, [s. l.], v. 10, n. May, p. 1–21, 2017a.

STAROBOVA, H.; VETTER, I. Pathophysiology of chemotherapy-induced peripheral neuropathy. **Frontiers in Molecular Neuroscience**, [s. l.], v. 10, n. May, p. 1–21, 2017b.

STEEL, A. *et al.* A network linking scene perception and spatial memory systems in posterior cerebral cortex. **Nature Communications**, [s. l.], v. 12, n. 1, p. 2632, 2021.

STERU, L. *et al.* The tail suspension test: A new method for screening antidepressants in mice. **Psychopharmacology**, [s. l.], v. 85, n. 3, p. 367–370, 1985.

STYCZYNSKI, L. M.; SCHAPPACHER, K. A.; BACCEI, M. L. Early life vincristine fails to prime developing pain pathways. **Neuroscience Letters**, [s. l.], v. 720, n. January, p. 134764, 2020. Disponível em: <https://doi.org/10.1016/j.neulet.2020.134764>.

SU, H. *et al.* Regulation of the Nrf2/HO-1 axis by mesenchymal stem cells-derived extracellular vesicles: implications for disease treatment. **Frontiers in Cell and Developmental Biology**, [s. l.], v. 12, 2024.

SU, Y.-C. *et al.* Survivors of Non-Hodgkin's Lymphoma: A Comparative Study on Patients With Vincristine-Induced Neuropathy and Their Quality of Life. **Journal of Nursing Research**, [s. l.], v. 33, n. 3, p. e393, 2025.

SUN, J. *et al.* Hemoprotein Bach1 regulates enhancer availability of heme oxygenase-1 gene. **The EMBO Journal**, [s. l.], v. 21, n. 19, p. 5216–5224, 2002.

SUN, G. *et al.* Temporal pain processing in the primary somatosensory cortex and anterior cingulate cortex. **Molecular Brain**, [s. l.], v. 16, n. 1, p. 3, 2023.

SUNG, J. Y. *et al.* Sensory axonal dysfunction in cervical radiculopathy. **Journal of Neurology, Neurosurgery and Psychiatry**, [s. l.], v. 86, n. 6, p. 640–645, 2015a.

SUNG, J. Y. *et al.* Sensory axonal dysfunction in cervical radiculopathy. **Journal of Neurology, Neurosurgery and Psychiatry**, [s. l.], v. 86, n. 6, p. 640–645, 2015b.

SWARM, R. A. *et al.* Adult Cancer Pain. **Journal of the National Comprehensive Cancer Network**, [s. l.], v. 11, n. 8, p. 992–1022, 2013.

SY, A. *et al.* Heterozygosity for CMT Type 4 Predicts a Severe Vincristine-induced Polyneuropathy Phenotype: A Case Report and Review of Literature. **Journal of Pediatric Hematology/Oncology**, [s. l.], v. 41, n. 1, p. E41–E43, 2019a.

SY, A. *et al.* Heterozygosity for CMT Type 4 Predicts a Severe Vincristine-induced Polyneuropathy Phenotype: A Case Report and Review of Literature. **Journal of Pediatric Hematology/Oncology**, [s. l.], v. 41, n. 1, p. E41–E43, 2019b.

TAKEDA, M.; TAKAHASHI, M.; MATSUMOTO, S. Suppression of neurokinin-1 receptor in trigeminal ganglia attenuates central sensitization following inflammation. **Journal of the Peripheral Nervous System**, [s. l.], v. 17, n. 2, p. 169–181, 2012.

TANTAWY, S. I. *et al.* Targeting MCL-1 protein to treat cancer: opportunities and challenges. **Frontiers in Oncology**, [s. l.], v. 13, 2023.

TAVES, S. *et al.* Microglia and Spinal Cord Synaptic Plasticity in Persistent Pain. **Neural Plasticity**, [s. l.], v. 2013, p. 1–10, 2013. Disponível em: <http://www.hindawi.com/journals/np/2013/753656/>.

TAY, N. *et al.* Chemotherapy-induced peripheral neuropathy in children and adolescent cancer patients. **Frontiers in Molecular Biosciences**, [s. l.], v. 9, 2022.

TAY, S. Y. *et al.* Pediatric Oncology Patients With Vincristine-Induced Recurrent Laryngeal Nerve Palsy: Two Case Reports and a Brief Review of Literature. **Ear, Nose and Throat Journal**, [s. l.], v. 100, n. 10, p. NP459–NP463, 2021a.

TAY, S. Y. *et al.* Pediatric Oncology Patients With Vincristine-Induced Recurrent Laryngeal Nerve Palsy: Two Case Reports and a Brief Review of Literature. **Ear, Nose and Throat Journal**, [s. l.], v. 100, n. 10, p. NP459–NP463, 2021b.

TIMMINS, H. C. *et al.* The impact of obesity on neuropathy outcomes for paclitaxel- and oxaliplatin-treated cancer survivors. **Journal of Cancer Survivorship**, [s. l.], v. 16, n. 2, p. 223–232, 2022.

TINNIRELLO, A.; MAZZOLENI, S.; SANTI, C. Chronic Pain in the Elderly: Mechanisms and Perspectives. **Biomolecules**, [s. l.], v. 11, n. March, p. 1256, 2021.

TOWER, J.; POMATTO, L. C. D.; DAVIES, K. J. A. Sex differences in the response to oxidative and proteolytic stress. **Redox Biology**, [s. l.], v. 31, p. 101488, 2020.

TREEDE, R. D. The International Association for the Study of Pain definition of

pain: As valid in 2018 as in 1979, but in need of regularly updated footnotes. **Pain Reports**, [s. l.], v. 3, n. 2, p. 1–3, 2018.

TREVISAN, G. *et al.* Antinociceptive Effects of 14-Membered Cyclopeptide Alkaloids. **Journal of natural products**, [s. l.], v. 72, p. 608–612, 2009.

TRIARICO, S. *et al.* Vincristine-induced peripheral neuropathy (Vipn) in pediatric tumors: Mechanisms, risk factors, strategies of prevention and treatment. **International Journal of Molecular Sciences**, [s. l.], v. 22, n. 8, 2021a.

TRIARICO, S. *et al.* Vincristine-induced peripheral neuropathy (Vipn) in pediatric tumors: Mechanisms, risk factors, strategies of prevention and treatment. **International Journal of Molecular Sciences**, [s. l.], v. 22, n. 8, 2021b.

TRIARICO, S. *et al.* Vincristine-Induced Peripheral Neuropathy (VIPN) in Pediatric Tumors: Mechanisms, Risk Factors, Strategies of Prevention and Treatment. **International Journal of Molecular Sciences**, [s. l.], v. 22, n. 8, p. 4112, 2021c.

TUCKER, M. H.; TIWARI, P.; CARTER, B. S. The physiology, assessment, and treatment of neonatal pain. **Seminars in Fetal and Neonatal Medicine**, [s. l.], v. 28, n. 4, p. 101465, 2023.

TUMMALA, R. *et al.* Expression of Na,K-ATPase- β 1 subunit increases uptake and sensitizes carcinoma cells to oxaliplatin. **Cancer Chemotherapy and Pharmacology**, [s. l.], v. 64, n. 6, p. 1187–1194, 2009.

TUNJUNGSARI, D. A.; GUNAWAN, P. I.; UGRASENA, I. D. G. RISK FACTORS OF VINCRISTINE-INDUCED PERIPHERAL NEUROPATHY IN ACUTE LYMPHOBLASTIC LEUKAEMIA CHILDREN. **The Journal of Medical Investigation**, [s. l.], v. 68, n. 3.4, p. 232–237, 2021.

TURCU-STIOLICA, A. *et al.* Diagnostic Accuracy of Machine-Learning Models on Predicting Chemo-Brain in Breast Cancer Survivors Previously Treated with Chemotherapy: A Meta-Analysis. **International Journal of Environmental Research and Public Health**, [s. l.], v. 19, n. 24, p. 16832, 2022.

UITTENBOOGAARD, A. *et al.* Pharmacogenomics of Vincristine-Induced Peripheral Neuropathy in Children with Cancer: A Systematic Review and Meta-Analysis. **Cancers**, [s. l.], v. 14, n. 3, p. 612, 2022.

UMANA, I. C. *et al.* **Nicotinic modulation of descending pain control circuitry.** [S. l.: s. n.], 2017-. ISSN 18726623.v. 158

VAN DE VELDE, M. E. *et al.* The association between vincristine-induced peripheral neuropathy and health-related quality of life in children with cancer. **Cancer Medicine**, [s. l.], v. 10, n. 22, p. 8172–8181, 2021.

VAN DE VELDE, M. E. *et al.* Vincristine-induced peripheral neuropathy in children with cancer: A systematic review. **Critical Reviews in Oncology/Hematology**,

[s. l.], v. 114, p. 114–130, 2017a. Disponível em: <https://doi.org/10.1016/j.critrevonc.2017.04.004>.

VAN DE VELDE, M. E. *et al.* Vincristine-induced peripheral neuropathy in children with cancer: A systematic review. **Critical Reviews in Oncology/Hematology**, [s. l.], v. 114, p. 114–130, 2017b.

VAN DEN BEUKEN-VAN EVERDINGEN, M. H. J. *et al.* Prevalence of pain in patients with cancer: a systematic review of the past 40 years. **Annals of Oncology**, [s. l.], v. 18, n. 9, p. 1437–1449, 2007.

VEGA-AVELAIRA, D.; MOSS, A.; FITZGERALD, M. Age-related changes in the spinal cord microglial and astrocytic response profile to nerve injury. **Brain, Behavior, and Immunity**, [s. l.], v. 21, n. 5, p. 617–623, 2007.

VOGT, A. G. *et al.* Organoselenium group is critical for antioxidant activity of 7-chloro-4-phenylselenyl-quinoline. **Chemico-Biological Interactions**, [s. l.], v. 282, p. 7–12, 2018a. Disponível em: <https://doi.org/10.1016/j.cbi.2018.01.003>.

VOGT, A. G. *et al.* Organoselenium group is critical for antioxidant activity of 7-chloro-4-phenylselenyl-quinoline. **Chemico-Biological Interactions**, [s. l.], v. 282, p. 7–12, 2018b.

VOSS, G. T. *et al.* Therapeutic and technological potential of 7-chloro-4-phenylselenyl quinoline for the treatment of atopic dermatitis-like skin lesions in mice. **Materials Science and Engineering C**, [s. l.], v. 84, n. August 2017, p. 90–98, 2017a. Disponível em: <https://doi.org/10.1016/j.msec.2017.11.026>.

VOSS, G. T. *et al.* Therapeutic and technological potential of 7-chloro-4-phenylselenyl quinoline for the treatment of atopic dermatitis-like skin lesions in mice. **Materials Science and Engineering C**, [s. l.], v. 84, n. August 2017, p. 90–98, 2017b.

WALKER, J. L. *et al.* Gait-stance duration as a measure of injury and recovery in the rat sciatic nerve model. **Journal of Neuroscience Methods**, [s. l.], v. 52, n. 1, p. 47–52, 1994.

WALSH, R. N.; CUMMINS, R. A. The open-field test: A critical review. **Psychological Bulletin**, [s. l.], v. 83, n. 3, p. 482–504, 1976.

WANG, F. *et al.* Influence of blood-brain barrier efflux pumps on the distribution of vincristine in brain and brain tumors. **Neuro-Oncology**, [s. l.], v. 12, n. 10, p. 1043–1049, 2010.

WANG, X. *et al.* Observation of Acetylcholinesterase in Stress-Induced Depression Phenotypes by Two-Photon Fluorescence Imaging in the Mouse Brain. **Journal of the American Chemical Society**, [s. l.], v. 141, n. 5, p. 2061–2068, 2019.

WANG, M. S. *et al.* Pathogenesis of axonal degeneration: Parallels between

Wallerian degeneration and vincristine neuropathy. **Journal of Neuropathology and Experimental Neurology**, [s. l.], v. 59, n. 7, p. 599–606, 2000a.

WANG, M. S. *et al.* Pathogenesis of axonal degeneration: Parallels between Wallerian degeneration and vincristine neuropathy. **Journal of Neuropathology and Experimental Neurology**, [s. l.], v. 59, n. 7, p. 599–606, 2000b.

WANG, J. H. *et al.* Relationship between prescribed opioids, pain management satisfaction, and pain intensity in oncology outpatients. **Supportive Care in Cancer**, [s. l.], v. 30, n. 4, p. 3233–3240, 2022. Disponível em: <https://doi.org/10.1007/s00520-021-06722-8>.

WANG, L.; AHN, Y. J.; ASMIS, R. Sexual dimorphism in glutathione metabolism and glutathione-dependent responses. **Redox Biology**, [s. l.], v. 31, p. 101410, 2020.

WEEKS, J. C.; LEVINE, R. B. Steroid hormone effects on neurons subserving behavior. **Current Opinion in Neurobiology**, [s. l.], v. 5, n. 6, p. 809–815, 1995.

WHITE, D. *et al.* Targeting translation: A review of preclinical animal models in the development of treatments for chemotherapy-induced peripheral neuropathy. **Journal of the Peripheral Nervous System**, [s. l.], v. 28, n. 2, p. 179–190, 2023.

WIESKOPF, J. S. *et al.* The nicotinic $\alpha 6$ subunit gene determines variability in chronic pain sensitivity via cross-inhibition of P2X2/3 receptors. **Science Translational Medicine**, [s. l.], v. 7, n. 287, 2015.

WILHELM, E. A. *et al.* Antioxidant effect of quinoline derivatives containing or not selenium: Relationship with antinociceptive action quinolines are antioxidant and antinociceptive. **Anais da Academia Brasileira de Ciencias**, [s. l.], v. 89, n. 1, p. 457–467, 2017.

WILLIAMS, M. D.; LASCELLES, B. D. X. Early Neonatal Pain—A Review of Clinical and Experimental Implications on Painful Conditions Later in Life. **Frontiers in Pediatrics**, [s. l.], v. 8, 2020a.

WILLIAMS, M. D.; LASCELLES, B. D. X. Early Neonatal Pain—A Review of Clinical and Experimental Implications on Painful Conditions Later in Life. **Frontiers in Pediatrics**, [s. l.], v. 8, 2020b.

WOLF, E. *et al.* Innate Conformational Dynamics Drive Binding Specificity in Anti-Apoptotic Proteins Mcl-1 and Bcl-2. **Biochemistry**, [s. l.], v. 62, n. 11, p. 1619–1630, 2023.

WOOLF, C. J. Pain modulation in the spinal cord. **Frontiers in Pain Research**, [s. l.], v. 3, 2022.

WOOLFE, G.; MACDONALD, A. D. The Evaluation of the analgesic action of pethidine hydrochloride (demerol). **Journal of Pharmacology and Experimental Therapeutics**, [s. l.], v. 80, n. 3, p. 300–307, 1944.

WORLD HEALTH ORGANIZATION (WHO). **Global cancer burden growing, amidst mounting need for services**. [S. l.: s. n.], 2024. Disponível em: : <https://www.who.int/news/item/01-02-2024-global-cancer-burden-growing--amidstmounting-need-for-services>. Acesso em: 14 jul. 2025.

XIAOHONG, G. *et al.* [Effects of glucocorticoid receptor agonists on hyperalgesia of rats with neuropathic pain and its mechanisms]. **Chinese Journal of Applied Physiology**, [s. l.], v. 38, n. 5, p. 470–474, 2022.

XU, T. *et al.* Epigenetic upregulation of CXCL12 expression mediates antitubulin chemotherapeutics-induced neuropathic pain. **Pain**, [s. l.], v. 158, n. 4, p. 637–648, 2017a.

XU, T. *et al.* Epigenetic upregulation of CXCL12 expression mediates antitubulin chemotherapeutics-induced neuropathic pain. **Pain**, [s. l.], v. 158, n. 4, p. 637–648, 2017b.

XU, J. *et al.* Longer versus Shorter Schedules of Vincristine, Irinotecan, and Temozolomide (VIT) for Relapsed or Refractory Ewing Sarcoma: A Randomized Controlled Phase 2 Trial. **Clinical Cancer Research**, [s. l.], v. 29, n. 6, p. 1040–1046, 2023.

XUE, V. W. *et al.* Transforming Growth Factor- β : A Multifunctional Regulator of Cancer Immunity. **Cancers**, [s. l.], v. 12, n. 11, p. 3099, 2020.

YOHN, C. N.; GERGUES, M. M.; SAMUELS, B. A. The role of 5-HT receptors in depression Tim Bliss. **Molecular Brain**, [s. l.], v. 10, n. 1, p. 1–12, 2017.

YOON, S. Y.; OH, J. Neuropathic cancer pain: Prevalence, pathophysiology, and management. **Korean Journal of Internal Medicine**, [s. l.], v. 33, n. 6, p. 1058–1069, 2018.

ZAJĄCZKOWSKA, R. *et al.* Mechanisms of Chemotherapy-Induced Peripheral Neuropathy. **International Journal of Molecular Sciences**, [s. l.], v. 20, n. 6, p. 1451, 2019.

ŽARKOVIĆ, N. *et al.* Spontaneous Regression of Cancer: Revealing Granulocytes and Oxidative Stress as the Crucial Double-edge Sword. **Frontiers in Bioscience-Landmark**, [s. l.], v. 27, n. 4, 2022.

ZHAN, X.; LI, J.; ZHOU, T. Targeting Nrf2-Mediated Oxidative Stress Response Signaling Pathways as New Therapeutic Strategy for Pituitary Adenomas. **Frontiers in Pharmacology**, [s. l.], v. 12, 2021.

ZHANG, H. Cancer Pain Management—New Therapies. **Current Oncology Reports**, [s. l.], v. 24, n. 2, p. 223–226, 2022.

ZHANG, S. Chemotherapy-induced peripheral neuropathy and rehabilitation: A review. **Seminars in Oncology**, [s. l.], v. 48, n. 3, p. 193–207, 2021.

ZHAO, J. Y. *et al.* DNA methyltransferase DNMT3a contributes to neuropathic pain by repressing Kcna2 in primary afferent neurons. **Nature Communications**, [s. l.], v. 8, n. May 2016, p. 1–15, 2017.

ZHAO, B. *et al.* Supplementation of lycopene attenuates oxidative stress induced neuroinflammation and cognitive impairment via Nrf2/NF- κ B transcriptional pathway. **Food and Chemical Toxicology**, [s. l.], v. 109, p. 505–516, 2017a.

ZHAO, B. *et al.* Supplementation of lycopene attenuates oxidative stress induced neuroinflammation and cognitive impairment via Nrf2/NF- κ B transcriptional pathway. **Food and Chemical Toxicology**, [s. l.], v. 109, p. 505–516, 2017b. Disponível em: <https://doi.org/10.1016/j.fct.2017.09.050>.

ZHENG, S. *et al.* TNF- α Impairs Pericyte-Mediated Cerebral Microcirculation via the NF- κ B/iNOS Axis after Experimental Traumatic Brain Injury. **Journal of Neurotrauma**, [s. l.], v. 40, n. 3–4, p. 349–364, 2023a.

ZHENG, S. *et al.* TNF- α Impairs Pericyte-Mediated Cerebral Microcirculation via the NF- κ B/iNOS Axis after Experimental Traumatic Brain Injury. **Journal of Neurotrauma**, [s. l.], v. 40, n. 3–4, p. 349–364, 2023b. Disponível em: <https://www.liebertpub.com/doi/10.1089/neu.2022.0016>.

ZHU, Y. *et al.* Inhibition of PINK1 senses ROS signaling to facilitate neuroblastoma cell pyroptosis. **Autophagy**, [s. l.], p. 1–20, 2025.

ZHU, M. *et al.* Na⁺/K⁺-ATPase-dependent autophagy protects brain against ischemic injury. **Signal Transduction and Targeted Therapy**, [s. l.], v. 5, n. 1, p. 55, 2020.

ZHU, S. *et al.* Roles of tumor-associated macrophages in tumor progression: implications on therapeutic strategies. **Experimental Hematology & Oncology**, [s. l.], v. 10, n. 1, p. 60, 2021.

ZHU, J. *et al.* The neuroprotective effect of oxytocin on vincristine-induced neurotoxicity in mice. **Toxicology Letters**, [s. l.], v. 340, p. 67–76, 2021. Disponível em: <https://linkinghub.elsevier.com/retrieve/pii/S0378427421000096>.

Figure Captions

Fig. 1 - Chemical structure of 7-chloro-4-(phenylselanyl) quinoline (4-PSQ).

Fig. 2 - Experimental design scheme. Evaluation of the therapeutic potential of 7-chloro-4-(phenylselanyl)quinoline (4-PSQ) against vincristine (VCR)-induced peripheral neuropathy. Male and female mice were divided into four groups: I)

Control; II) VCR; III) 4-PSQ; IV) VCR + 4-PSQ. On days 1 to 5, two groups of males and females received VCR (0.1 mg/kg, intraperitoneally), while the other two groups received 0.9% saline solution (10 mg/ml, intraperitoneally). From day 7 to 16, animals received daily treatment with 4-PSQ (1 mg/kg, orally). Responses to mechanical hyperalgesia were assessed on days 0, 6, 11, and 16 using a digital aesthesiometer. Thermal sensitivity was evaluated on days 0, 6, and 16 using the hot plate test. On day 17, all animals were euthanized, and nervous system structures were dissected for biochemical and gene expression analysis.

Fig. 3 - Effect of 7-chloro-4-(phenylselanyl) quinoline (4-PSQ) (1 mg/kg, p.o.) and vincristine (VCR) (0.1 mg/kg, i.p.) exposure on the paw withdrawal threshold to mechanical stimulus in the digital aesthesiometer on days 0, 6, 11 and 16 in males mice (a), in females mice (b) and both sexes (c). Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 7 animals per group. (****) $P < 0.0001$ denotes significance levels when compared with the control group; (#####) $P < 0.0001$ denotes significance levels when compared with the VCR group. Two-way ANOVA followed by Tukey's test was used.

Fig. 4 - Effect of 7-chloro-4-(phenylselanyl) quinoline (4-PSQ) (1 mg/kg, p.o.) and vincristine (VCR) (0.1 mg/kg, i.p.) on thermal stimulation in the hot plate test on days 0, 6, 11, and 16 in males mice (a), females mice (b) and both sexes. Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 7 animals per group. (*) $P < 0.05$; (***) $P < 0.001$ and (****) $P < 0.0001$ denote significance levels when compared with the control group; (#) $P < 0.05$; (###) $P < 0.001$ and (#####) $P < 0.0001$ denote significance levels compared with VCR groups. Two-way ANOVA followed by Tukey's test was used.

Fig. 5 - Effect of 7-chloro-4-(phenylselanyl) quinoline (4-PSQ) (1 mg/kg, p.o.) and vincristine (VCR) (0.1 mg/kg, i.p.) on lipid peroxidation levels measured by the thiobarbituric acid reactive species test (TBARS) in mice. TBARS levels in the cerebral cortex of males (a) and females (d), in the spinal cord of males (b) and females (e), and in the cerebellum of males (c) and females (f). Each column shows the mean $\pm$ standard error of the mean (S.E.M) for 7 animals per group. (*) $P < 0.05$ and (***) $P < 0.001$ indicate significance versus the control group; (#) $P < 0.05$ and (####) $P < 0.0001$ indicate significance versus VCR groups. Two-way ANOVA followed by Tukey's test was used.

Fig. 6 - Effect of 7-chloro-4-(phenylselanyl) quinoline (4-PSQ) (1 mg/kg, p.o.) and vincristine (VCR) (0.1 mg/kg, i.p.) on the assessment of thiol levels non-protein (NPSH) in mice. NPSH levels in the cerebral cortex of males (a) and females (d), in the spinal cord of males (b) and females (e), and in the cerebellum of males (c) and females (f). Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 7 animals per group. Two-way ANOVA followed by Tukey's test was used.

Fig. 7 - Effect of 7-chloro-4-(phenylselanyl) quinoline (4-PSQ) (1 mg/kg, p.o.) and vincristine (VCR) (0.1 mg/kg, i.p.) on catalase (CAT) activity in mice. The CAT activity in the cerebral cortex of males (a) and females (d), in the spinal cord of males (b) and females (e), and in the cerebellum of males (c) and females (f). Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 7 animals per group. (*) $P < 0.05$; (**) $P < 0.01$ and (***) $P < 0.001$ denote significance levels when compared with the control group; (##) $P < 0.01$ and (###) $P < 0.001$ denote significance levels compared with VCR groups. Two-way ANOVA followed by Tukey's test was used.

Fig. 8 - Effect of 7-chloro-4-(phenylselanyl) quinoline (4-PSQ) (1 mg/kg, p.o.) and vincristine (VCR) (0.1 mg/kg, i.p.) on the enzymatic activity of Total ATPases in mice. Total ATPase activity in the cerebral cortex of males (a) and females (e), in the spinal cord of males (b) and females (f), in the cerebellum of males (c) and females (g), and in the hippocampus of males (d) and females (h). Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 7 animals per group. (*) $P < 0.05$ and (***) $P < 0.001$ denote significance levels when compared with the control group. Two-way ANOVA followed by Tukey's test was used.

Fig. 9 - Effect of 7-chloro-4-(phenylselanyl) quinoline (4-PSQ) (1 mg/kg, p.o.) and vincristine (VCR) (0.1 mg/kg, i.p.) on Ca^{2+} - ATPase activity. The Ca^{2+} - ATPase activity in the cerebral cortex of males (a) and females (e), in the spinal cord of males (b) and females (f), in the cerebellum of males (c) and females (g), and in the hippocampus of males (d) and females (h). Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 7 animals per group. (*) $P < 0.05$, (**) $P < 0.01$, (***) $P < 0.001$, and (****) $P < 0.0001$ denote significance levels when compared with the control group. (#) $P < 0.05$, (##) $P < 0.01$, (###) $P < 0.001$, and (####) $P < 0.0001$ denotes significance levels compared with VCR groups. Two-way ANOVA followed by Tukey's test was used.

Fig. 10 - Effect of 7-chloro-4-(phenylselanyl)quinoline (4-PSQ) (1 mg/kg, p.o.) and vincristine (VCR) (0.1 mg/kg, i.p.) on nuclear factor erythroid 2-related factor 2 (Nrf2) mRNA expression in the cerebral cortex of males (a) and females (b), and in the spinal cord of males (c) and females (d). Each column shows the mean $\pm$ standard error of the mean (S.E.M.) based on 6 animals per group. (*) $P < 0.05$ indicates significance compared to the control group. (#) $P < 0.05$, (##) $P < 0.01$, and (###) $P < 0.001$ indicate significance compared with the VCR groups. Two-

way ANOVA followed by Tukey's test was used.

Fig. 11 - Effect of 7-chloro-4-(phenylselanyl)quinoline (4-PSQ) (1 mg/kg, p.o.) and vincristine (VCR) (0.1 mg/kg, i.p.) on Heme oxygenase-1 (HO-1) mRNA expression in the cerebral cortex of males (a) and females (b) and in the spinal cord of males (c) and females (d). Each column represents the mean $\pm$ standard error of the mean (S.E.M.) of 6 animals per group. (*) $P < 0.05$ denotes significance levels when compared with the control group. (##) $P < 0.01$ and (####) $P < 0.0001$ denote the significance levels when compared with the VCR groups. Two-way ANOVA followed by Tukey's test was used.

Fig. 12 - Effect of 7-chloro-4-(phenylselanyl)quinoline (4-PSQ) (1 mg/kg, p.o.) and vincristine (VCR) (0.1 mg/kg, i.p.) on lipid peroxidation levels measured by the thiobarbituric acid reactive species test (TBARS) (a) and on the assessment of thiol levels non-protein (NPSH) (b) in the spinal cord of male and female mice. Each column represents the mean $\pm$ standard error of the mean (S.E.M.) of 7 animals per group. (*) $P < 0.05$, (**) $P < 0.01$ and (****) $P < 0.0001$ denotes significance levels between the groups. Statistical analysis was performed using Student's t-test.

Fig. 13 - Effect of 7-chloro-4-(phenylselanyl)quinoline (4-PSQ) (1 mg/kg, p.o.) and vincristine (VCR) (0.1 mg/kg, i.p.) on Ca^{2+} -ATPase activity in the spinal cord (a) and cerebellum (b) and total ATPases activity in the cerebellum (c) of male and female mice. Each column represents the mean $\pm$ standard error of the mean (S.E.M.) of 7 animals per group. (*) $P < 0.05$, (**) $P < 0.01$, (***) $P < 0.001$ and (****) $P < 0.0001$ denotes significance levels between the groups. Statistical analysis was performed using Student's t-test.

Fig. 14 - Cytotoxic effect of 4-PSQ and Vincristine in HL-60 cells determined by

the MTT assay. Cells were treated for 48 h with increasing concentrations of **(A)** 4-PSQ (2, 5, 20, 60, 100, and 120 μ M), **(B)** Vincristine (0.5, 1, 5, 25, 50, and 100 nM), and **(C)** combination of 4-PSQ and Vincristine. Data are expressed as mean of growth inhibition $\pm$ S.E.M. from three independent experiments, each performed in three technical replicates. Different letters indicate statistically significant differences between concentrations, $p < 0.05$.

Fig. 15 - Cytotoxic effect of 4-PSQ and Vincristine on CHO cells measured by the MTT assay. Cells were treated for 48 hours with increasing concentrations of **(A)** 4-PSQ (2, 5, 20, 60, 100, and 120 μ M) and **(B)** Vincristine (0.5, 1, 5, 25, 50, and 100 nM). Data are shown as the mean growth inhibition $\pm$ S.E.M. from three independent experiments, each with three technical replicates.

Figures

Fig. 1

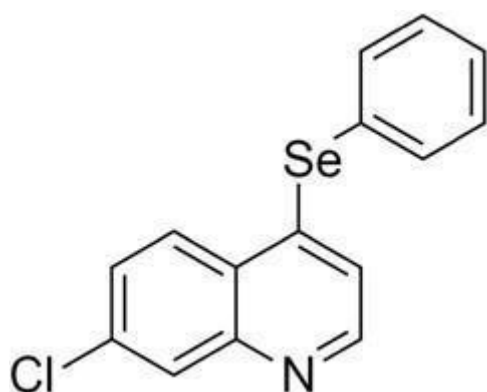


Fig.2

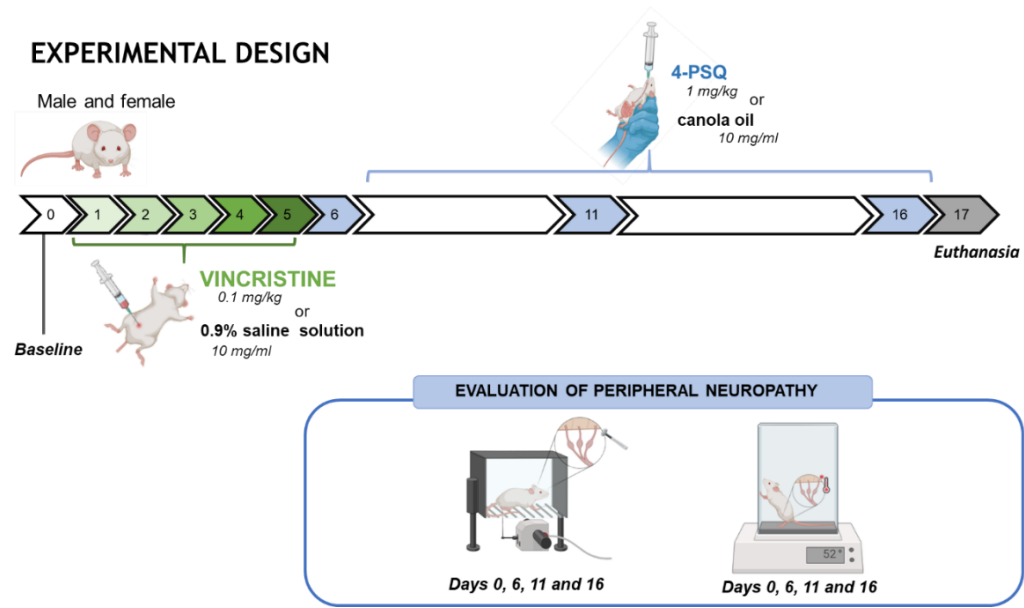


Fig.3

EVALUATION OF MECHANICAL SENSITIVITY

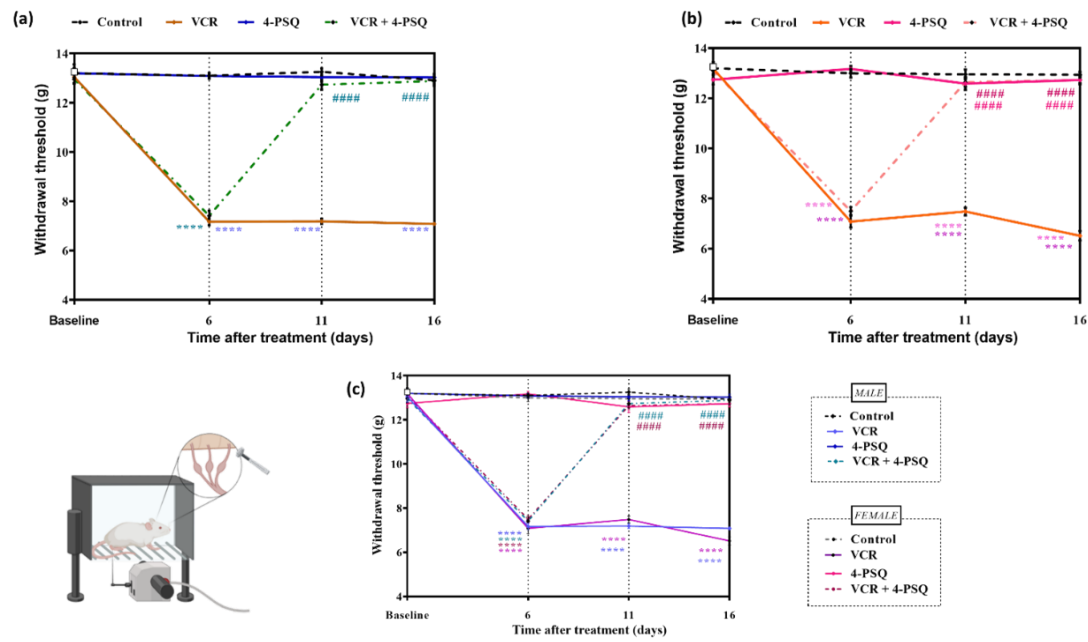


Fig.4

EVALUATION OF THERMAL SENSITIVITY

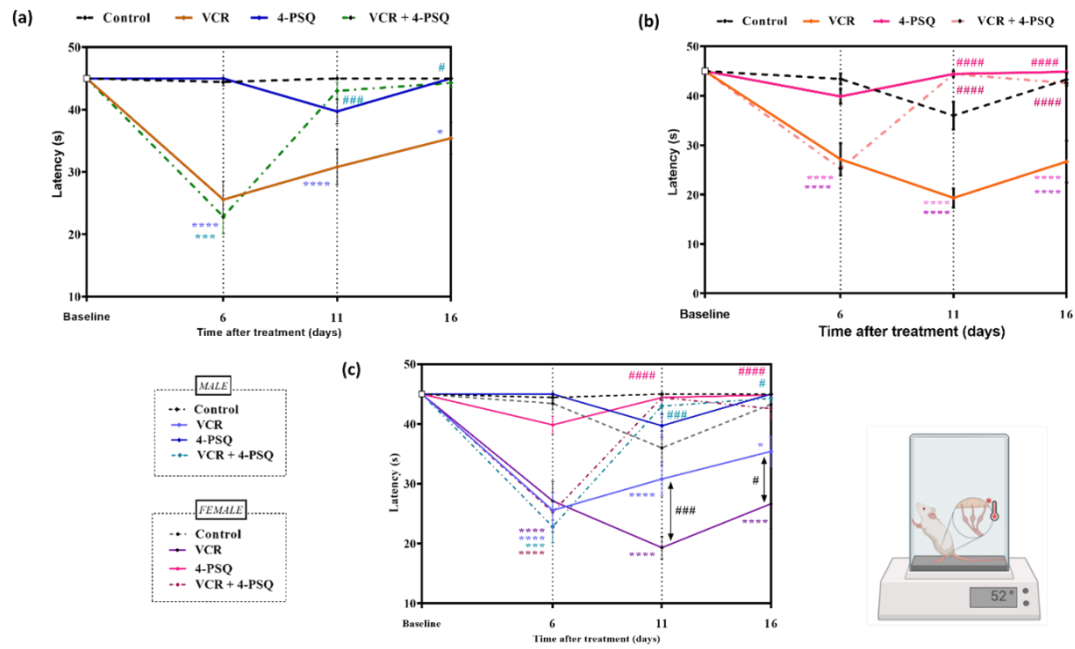


Fig.5

LIPID PEROXIDATION

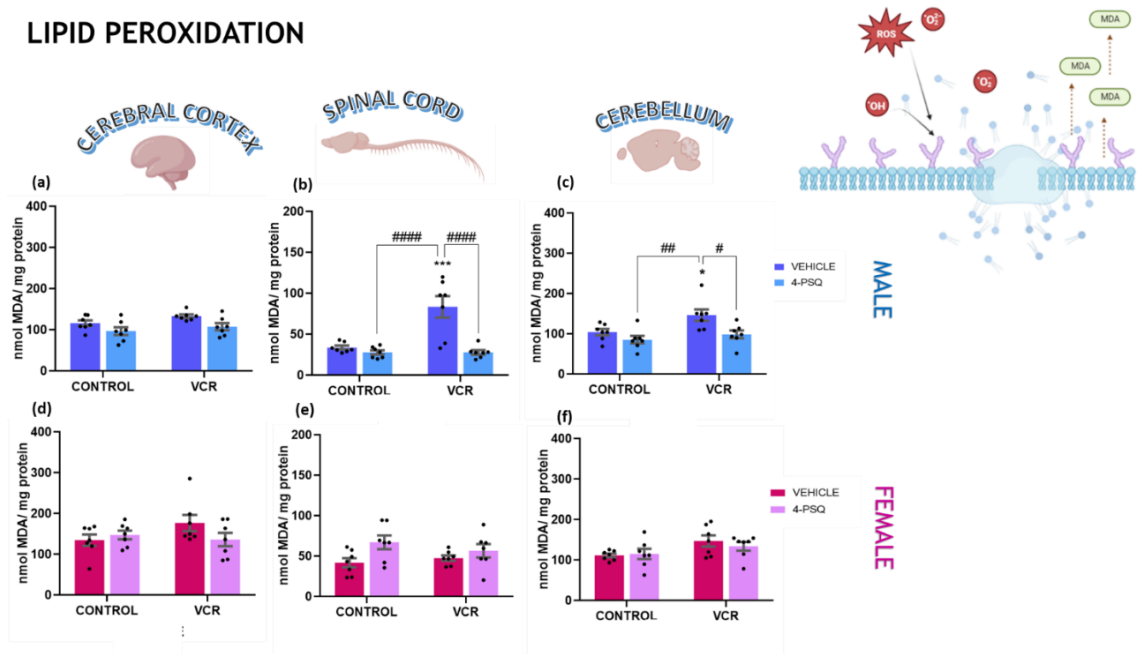


Fig.6

LEVELS OF NON-PROTEIN THIOLS

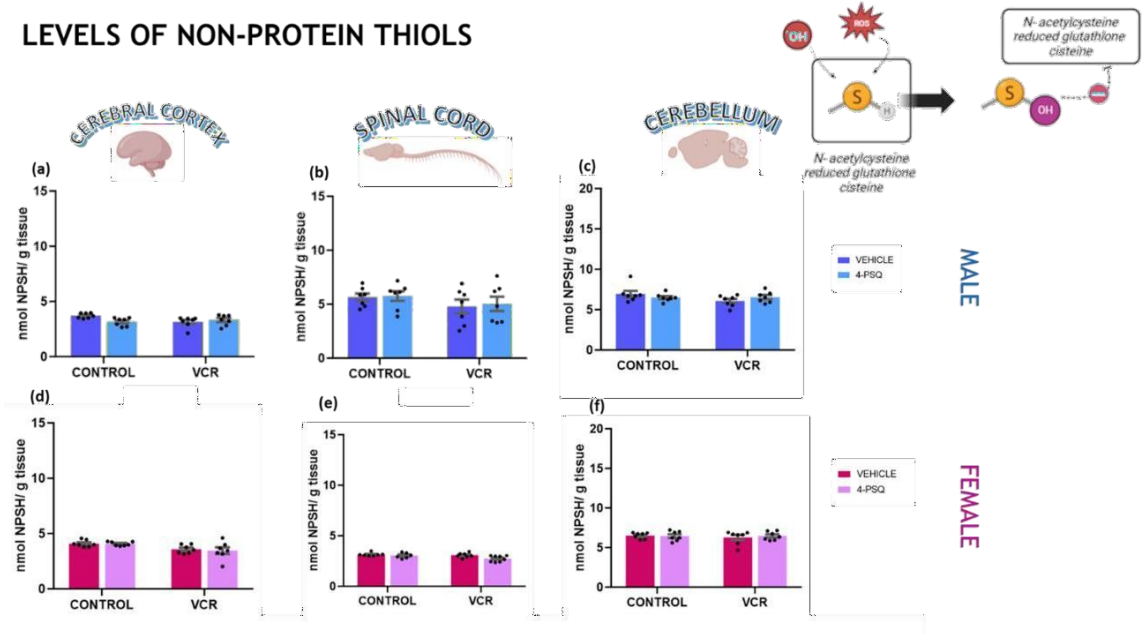


Fig.7

CATALASE ACTIVITY

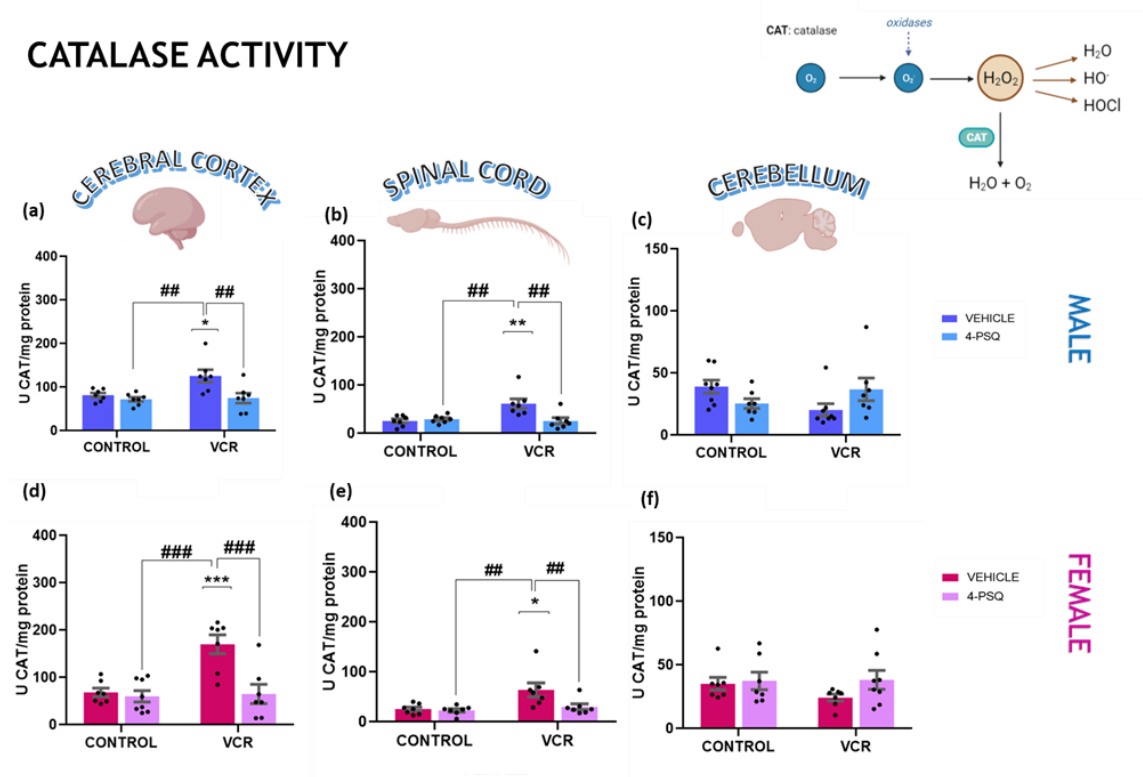


Fig.8

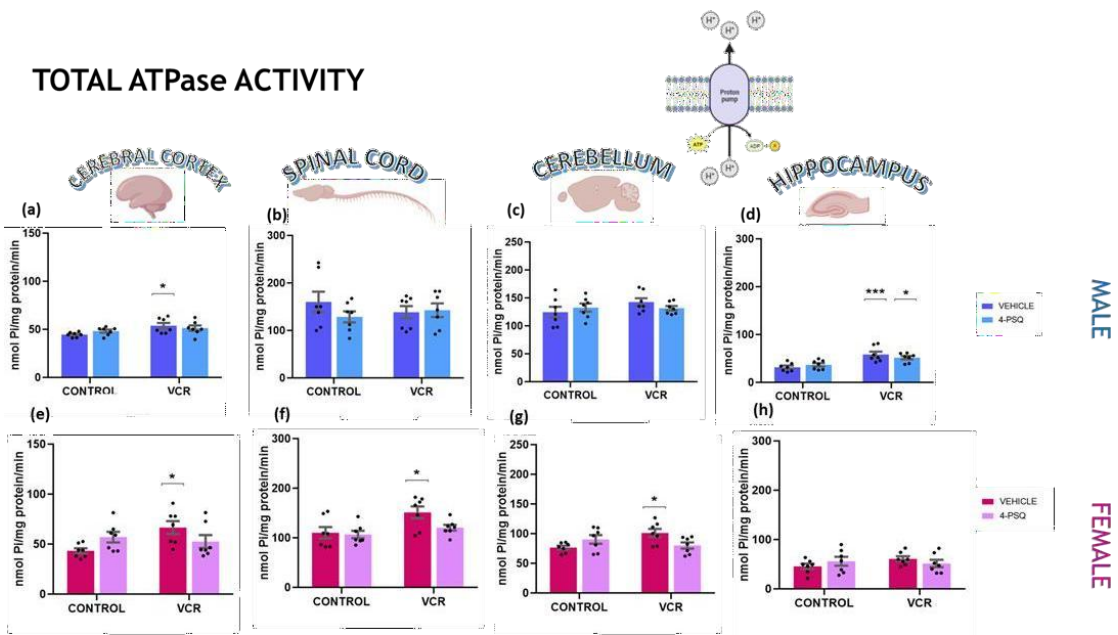


Fig.9

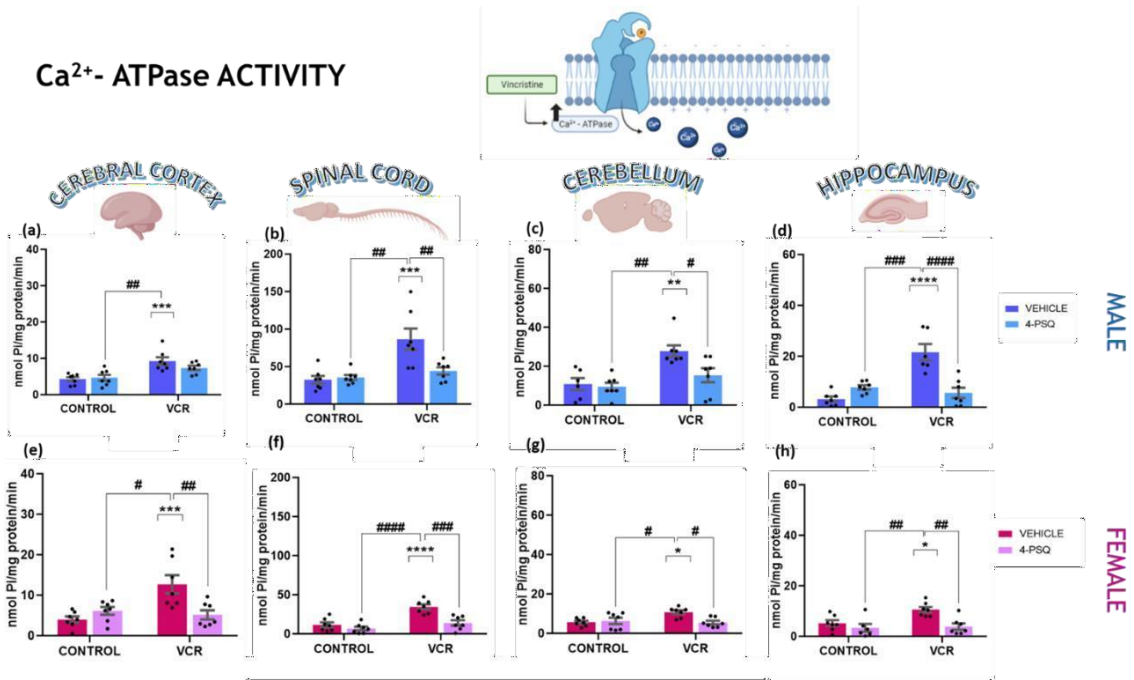


Fig.10

GENE EXPRESSION OF Nrf2

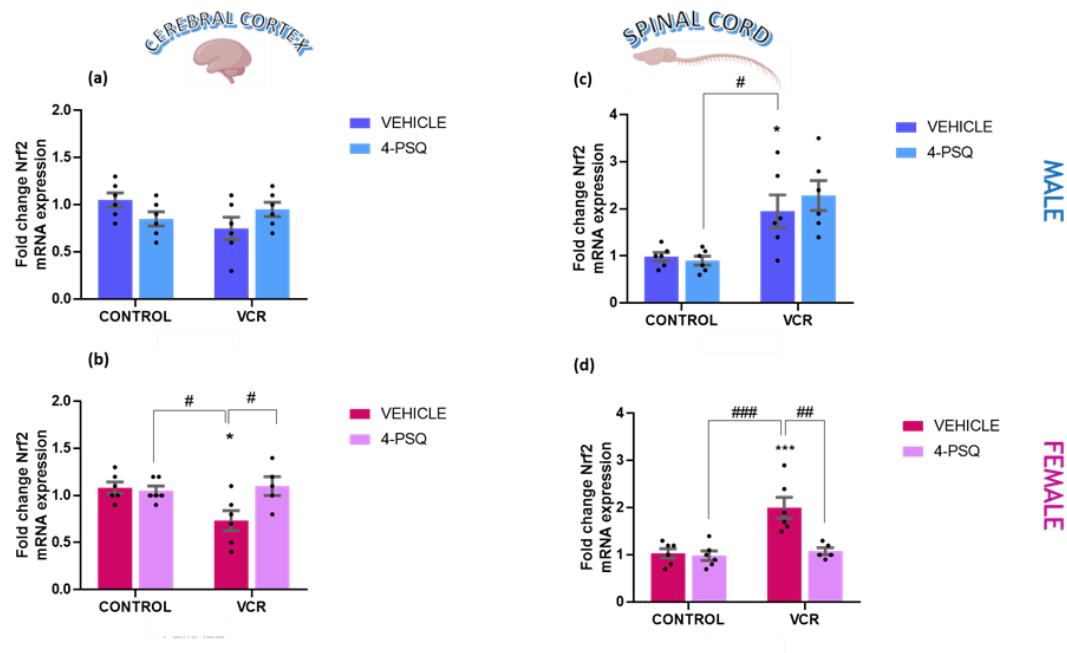


Fig.11

GENE EXPRESSION OF HO-1

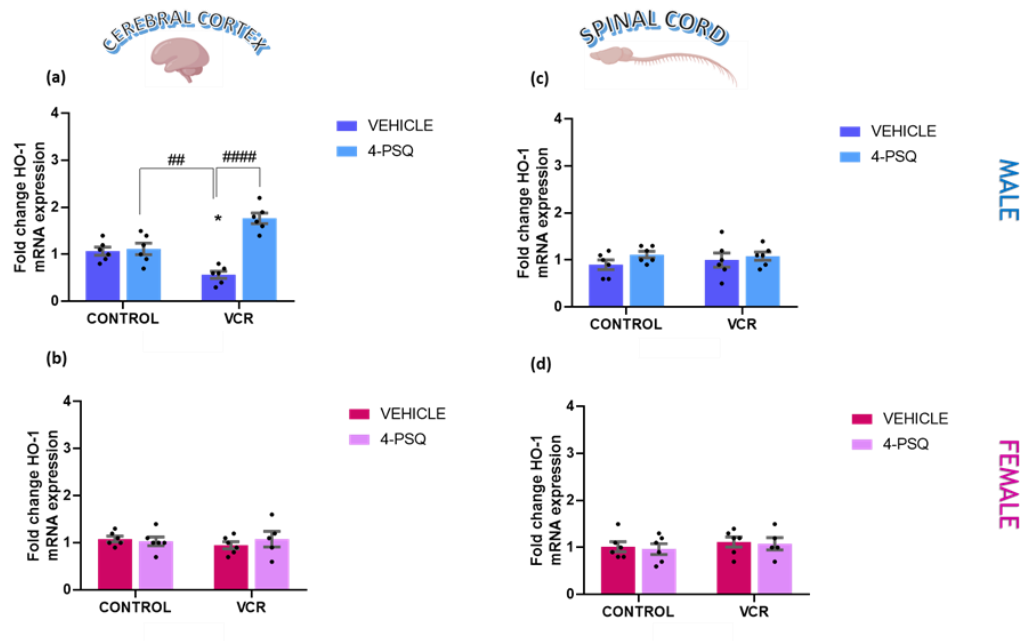


Fig.12

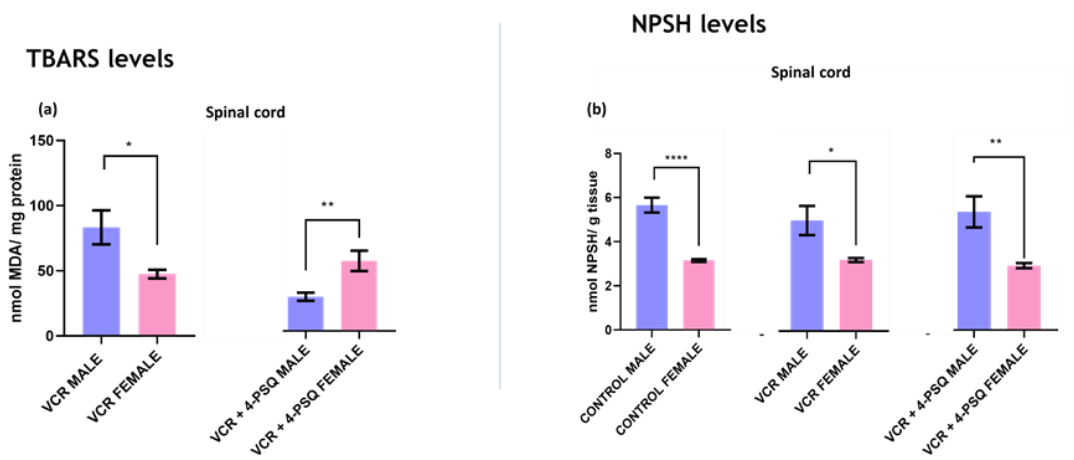
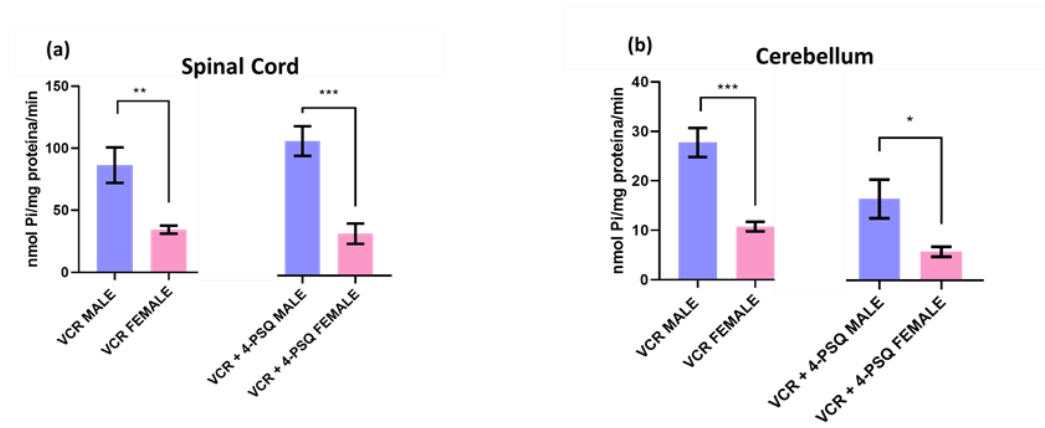


Fig.13

Ca²⁺- ATPase ACTIVITY



Total ATPases ACTIVITY

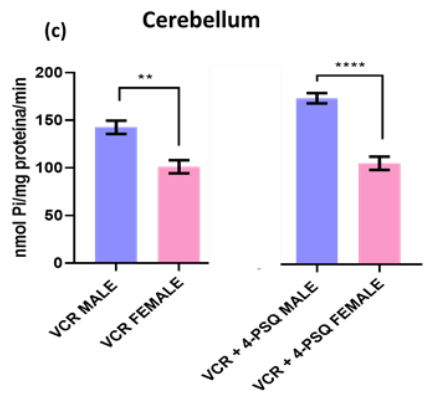


Fig.14

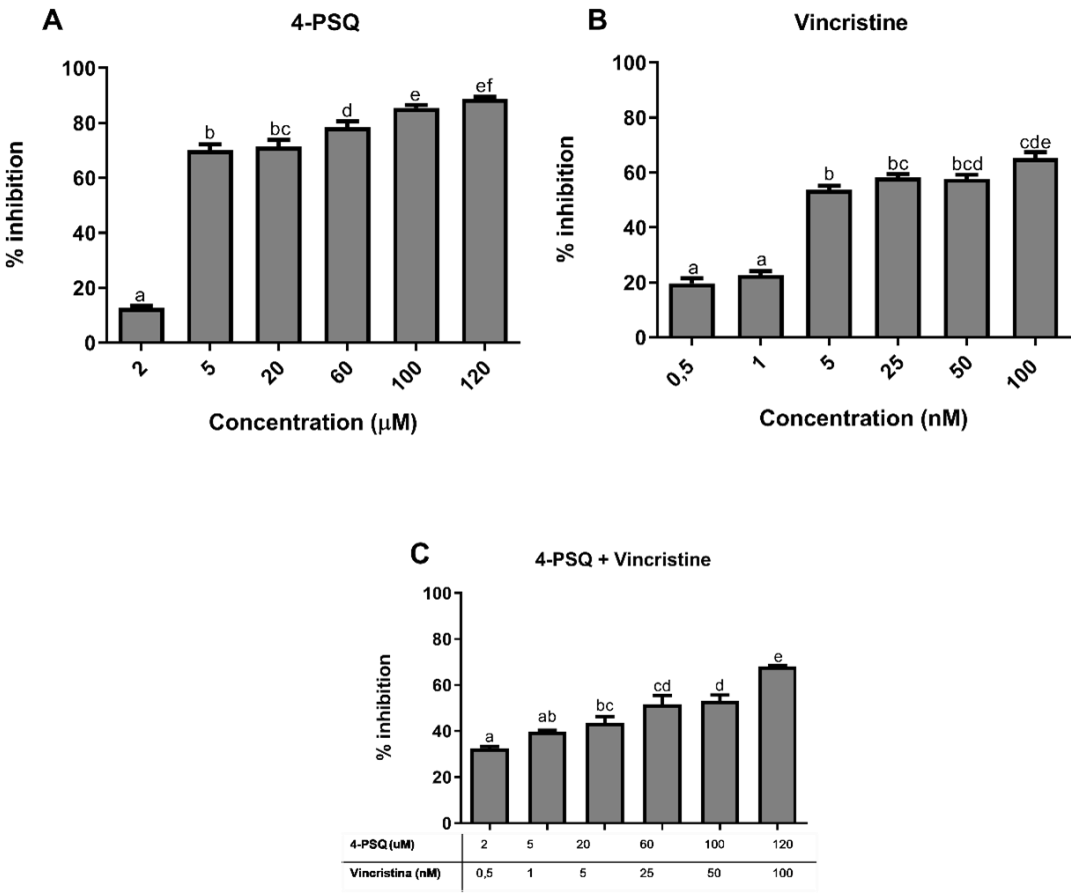
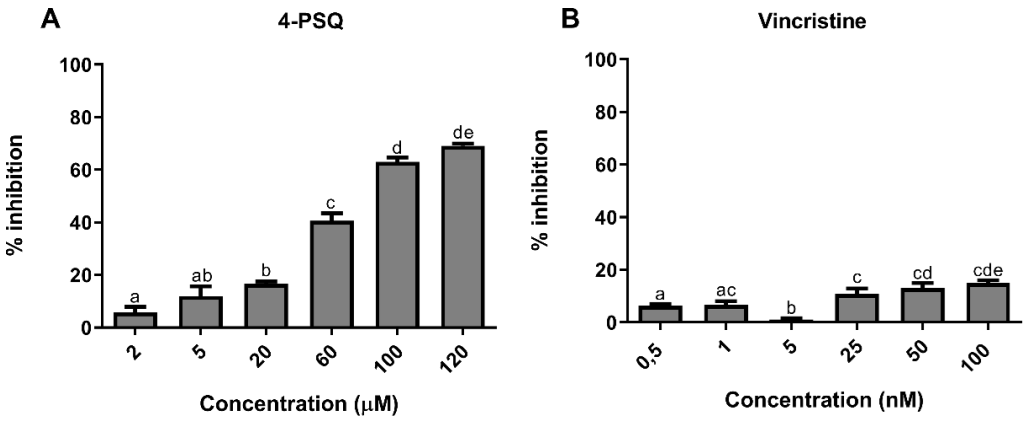
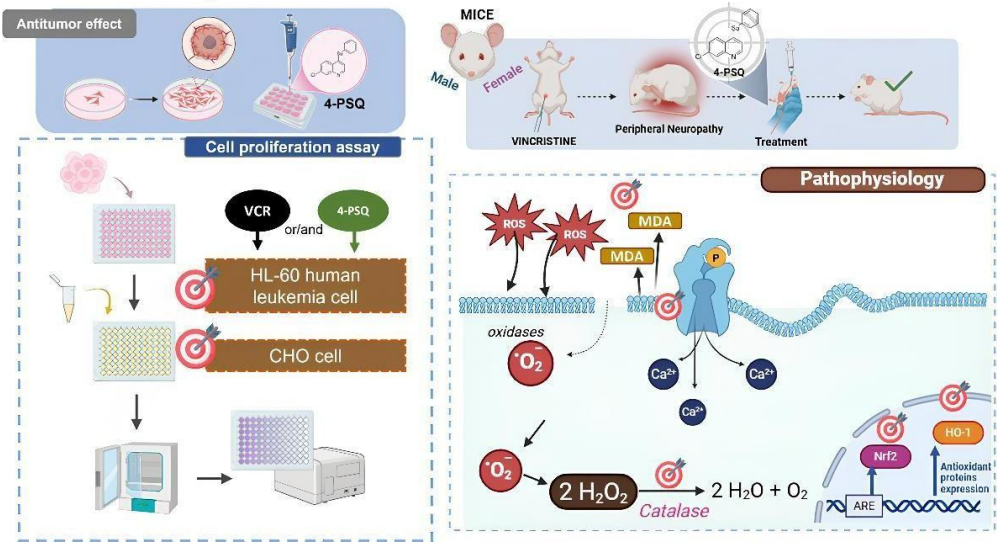


Fig.15



Graphical Abstract

Dual Action of 4-PSQ: Antinociceptive Effects in Vincristine-Induced Neuropathy and Antitumor Activity in HL-60 Cells



4.4. Capítulo 4 – Manuscrito Científico 3

Interrupção da ontogenia sensório-motora e da integridade neural induzida por vincristina em ratos neonatais: percepções comportamentais, histopatológicas e moleculares

Na etapa 4, buscamos avaliar a NPIV no contexto pediátrico, identificando uma lacuna notável nas pesquisas científicas robustas relacionadas à VCR: de que forma esse fármaco poderia afetar o sistema nervoso em fases de desenvolvimento, considerando sua relevância no eixo da oncopediatria. Assim, o manuscrito a seguir visou investigar a susceptibilidade à NPIV em ratos neonatos expostos a VCR – observou-se comportamentos de ontogenese de reflexos, coordenação motora, nocicepção, histopatologia, estresse oxidativo e marcadores moleculares de neurotoxicidade. O manuscrito é inédito em diferentes frentes, associando a NPIV com a neuropatia motora, neurodesenvolvimento e fisiopatologia com diferentes marcadores avaliados.

Observou-se que ratos neonatos machos e fêmeas expostos uma única vez à VCR apresentaram prejuízo no desenvolvimento de reflexos-chave (geotaxia negativa, posicionamento de vibrissas e endireitamento), além de déficits na resposta à aversão a penhascos e ao sobressalto. A disfunção motora foi confirmada por alterações na marcha e por desempenho reduzido no teste de rotarod. Como esperado, a VCR induziu NPIV, evidenciada por hiperalgesia mecânica e térmica. A análise histológica revelou degeneração da medula espinhal e infiltração inflamatória.

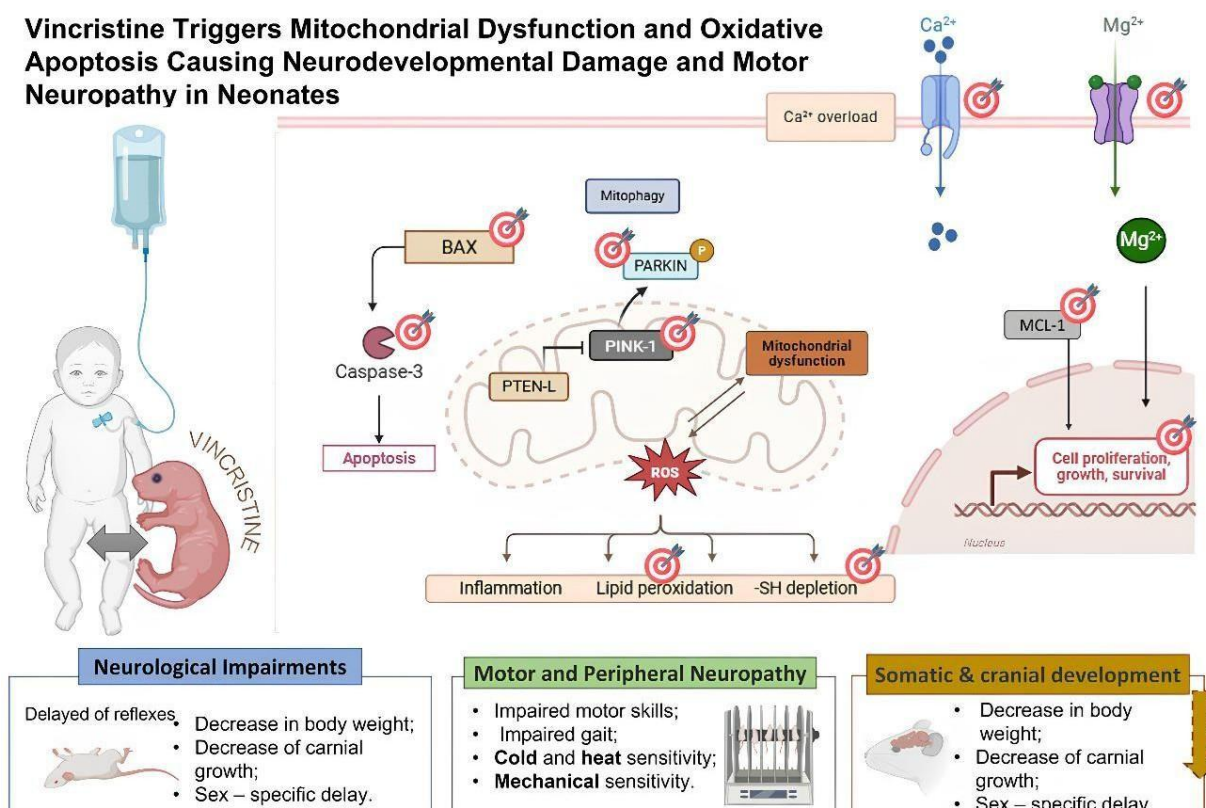
No nível molecular, verificou-se aumento da expressão de caspase-3 e BAX, redução de MCL-1, além de desregulação sexo-dependente de PINK-1 e PARKIN. Atividades elevadas de Ca^{2+} - e Mg^{2+} -ATPases indicaram que a VCR promoveu hiperexcitabilidade neuronal. Do ponto de vista bioquímico, observou-se aumento de TBARS e redução de NPSH em múltiplas regiões cerebrais.

Em conjunto, esses achados demonstram que a VCR compromete o neurodesenvolvimento por meio de estresse oxidativo, apoptose e disfunção mitocondrial, reforçando a necessidade de monitoramento rigoroso do neurodesenvolvimento em crianças submetidas à quimioterapia baseada em VCR.

MANUSCRITO 3

Os resultados do Capítulo 4 da tese estão apresentados sob a forma de manuscrito científico, o qual se encontra assim organizado. Os itens Materiais e Métodos, Resultados, Discussão dos Resultados e Referências Bibliográficas encontram-se no próprio artigo. O manuscrito científico encontra-se submetido na revista *Molecular Neurobiology*.

Vincristine Triggers Mitochondrial Dysfunction and Oxidative Apoptosis Causing Neurodevelopmental Damage and Motor Neuropathy in Neonates



Vincristine-Induced Disruption of Sensorimotor Ontogeny and Neural Integrity in Neonatal Rats: Behavioral, Histopathological, and Molecular Insights

Ketlyn P. da Motta^a, Vanessa M. E. da Rocha^a, Eduardo B. Blödorn^a, Ana Paula B. Wille^a, Caren Aline R. da Fonseca^a, Joanna V. Z. Echenique^b, Mauro P. Soares^b, and Ethel A. Wilhelm^{a*}

^a *Graduate Program in Biochemistry and Bioprospecting, Preclinical and Translational Research Group on Pain and Chronic Diseases, Center for Chemical, Pharmaceutical and Food Sciences, Center for Chemical, Pharmaceutical and Food Sciences, Federal University of Pelotas, Box 354, CEP 96010-900, Pelotas, RS, Brazil*

^b *Regional Diagnostic Laboratory Faculty of Veterinary Medicine, Federal University of Pelotas (UFPEL), Pelotas, CEP 96010-900, RS, Brazil.*

*Address for Correspondence:

Ethel Antunes Wilhelm; e-mail: ethelwilhelm@yahoo.com.br / Phone: +55-53-32757360

Postgraduate Program in Biochemistry and Bioprospecting (PPGBBio), Center for Chemical, Pharmaceutical and Food Sciences, Federal University of Pelotas (UFPEL), Capão do Leão Campus, Pelotas, Zip Code 96010-900, RS, Brazil.

Abstract

Vincristine (VCR) is a widely used chemotherapeutic agent in pediatric oncology, but its neurotoxic effects on the developing nervous system remain insufficiently understood. This study investigated the impact of early-life VCR exposure (6 µg/kg, intraperitoneally, on postnatal day (PND) 11) on reflex ontogeny, motor coordination, nociception, oxidative stress, and molecular markers of neurotoxicity in neonatal rats. Reflex development was assessed from PND 1 to 25, followed by evaluations of motor performance (PNDs 21–22), nociceptive thresholds (PNDs 23–24), and late reflexes (PND 25). On PND 25, animals were euthanized for histological, biochemical, and gene expression analyses. VCR exposure delayed the development of key reflexes (negative geotaxis, vibrissae placement, righting), and impaired cliff aversion and startle responses. Motor dysfunction was confirmed by altered gait and reduced performance in the rotarod test. Signs of mechanical and thermal hyperalgesia were indicative of peripheral neuropathy. Histological analysis revealed spinal cord degeneration and inflammatory infiltration. At the molecular level, increased expression of caspase-3 (Caspase-3) and BCL-2-associated X protein (BAX), reduced myeloid cell leukemia-1 (MCL-1), and sex-dependent dysregulation of PTEN-induced putative kinase 1 (PINK-1) and Parkin RBR E3 ubiquitin protein ligase (PARKIN) were observed. Elevated activities of Ca²⁺- and Mg²⁺-ATPases suggested neuronal hyperexcitability. Biochemically, increased thiobarbituric acid reactive substances (TBARS) and decreased non-protein sulfhydryl groups (NPSH) in multiple regions confirmed oxidative imbalance. Collectively, these findings demonstrate that VCR disrupts neurodevelopment through oxidative stress, apoptosis, and mitochondrial dysfunction, underscoring the need for neurodevelopmental monitoring in children receiving VCR-based chemotherapy.

Keywords: Neuropathy, chemotherapy, neurodevelopment, apoptosis, pediatric oncology.

Introduction

Vincristine (VCR) is a key chemotherapeutic agent widely used in combination protocols for treating acute lymphoblastic leukemia (ALL), the most common pediatric cancer, accounting for approximately 18.8% of cases worldwide (CureAll Framework: WHO Global Initiative for Childhood Cancer Increasing access, advancing quality, saving lives, [s. d.]; Tay *et al.*, 2021b; Triarico *et al.*, 2021a). Although pediatric oncology currently has an overall survival rate of nearly 80%(CureAll Framework: WHO Global Initiative for Childhood Cancer Increasing access, advancing quality, saving lives, [s. d.]) , early childhood remains a crucial period for physical and neurological development. Disruptions during this stage can result in long-lasting or irreversible consequences (Gilchrist; Tanner, 2016; Styczynski; Schappacher; Baccei, 2020; Triarico *et al.*, 2021a; van de Velde *et al.*, 2017a).

During this developmental window, intense neurogenesis and synaptogenesis create the neural networks that underlie future cognitive, motor, sensory, and emotional functions (Coluzzi *et al.*, 2020; Dupuis *et al.*, 2016; Zhu, J. *et al.*, 2021). Chemotherapeutic agents like VCR may disrupt these processes, impairing proper neural connectivity and maturation (Li *et al.*, 2020a; Zhu, J. *et al.*, 2021). Reflex ontogeny and physical growth milestones serve as useful indicators of neurodevelopmental progression and are particularly sensitive to neurotoxic insults (Brown; Ross; Belsky, 2025; Queiroz *et al.*, 2019)

In addition to its effects on the central nervous system, VCR is also known to induce peripheral neuropathy, which is a common and dose-limiting side effect

(Li *et al.*, 2020a; Sahranavard *et al.*, 2022; Tunjungsari; Gunawan; Ugrasena, 2021). Neuropathic symptoms may include mechanical and thermal hyperalgesia, muscle weakness, and gait disturbances, even among the pediatric population (Geisler, 2021b; Li *et al.*, 2020a; Shayesteh *et al.*, 2022b).

Despite the widespread clinical use of VCR, particularly in pediatric oncology, the comprehensive evaluation of its neurological impact remains underexplored. Considering VCR's well-established neurotoxic profile, the extent to which it may interfere with the maturation of the developing nervous system represents a critical and largely unaddressed gap in current neuropharmacological research (Schappacher *et al.*, 2019b; Schappacher; Styczynski; Baccei, 2017-).

Emerging evidence indicates that VCR-induced neurotoxicity involves a complex interplay of cellular stress responses, including the activation of apoptotic pathways, mitochondrial dysfunction, and oxidative imbalance (Chen; Wang; Song, 2020; Filippi-Chiela *et al.*, 2022; Shayesteh *et al.*, 2022b; Triarico *et al.*, 2021a). Key regulators of apoptosis and neuronal survival are often dysregulated in this context, contributing to progressive neuronal damage (Cheon *et al.*, 2017b; Khalilzadeh *et al.*, 2020b). In parallel, impairment of mitochondrial dynamics and quality control mechanisms, such as mitophagy, may compromise energy homeostasis and neuronal resilience (Burt *et al.*, 2019; Eltokhy; Toema; El-Deeb, 2022). Additionally, the accumulation of reactive oxygen species (ROS) and failure of antioxidant defenses have been proposed as critical factors exacerbating neural vulnerability (Cobb; Cole, 2015; Ngo; Duennwald, 2022). Given these interrelated processes, molecular markers associated with apoptosis, mitochondrial stability, and redox regulation may provide valuable

insights into the mechanisms underlying neurodevelopmental disturbances caused by VCR exposure.

Considering this context, our study hypothesizes that VCR exposure during early postnatal development leads to impairments in neurodevelopment and physical growth. We aim to assess peripheral and motor neuropathy in neonatal rats and identify potential pathways underlying VCR-induced neurotoxicity through behavioral, histopathological, biochemical, and molecular markers related to apoptosis, oxidative stress, neuronal survival, and maintenance.

Materials and Methods

Animals and Drug Administration

The experiments utilized newborn male and female Wistar rats up to postnatal day 25 (PND 25). The animals were housed with free access to food and water; humidity (20 - 80%) and temperature ($22\pm 2^{\circ}\text{C}$) were controlled, maintaining the light/dark cycle (12h/12h) of the rodents. All experiments were conducted in accordance with the guidelines of the Animal Use Ethics Committee from Federal University of Pelotas (CEUA-UFPe) (038650/2021-19). The animals were randomly assigned to one of two groups: neonatal control or neonatal VCR.

VCR chemotherapeutic was purchased as sulfate by INTAS pharmaceuticals® (Batch: M2103904) and allocated at 4°C . During neonatal treatment, animals received one intraperitoneal (i.p.) injection of VCR ($6\text{ }\mu\text{g.kg}^{-1}$) or saline (vehicle control). The experimental protocol was based on previous studies evaluating the action of VCR in neonatal rats, with modifications (Styczynski; Schappacher; Baccei, 2020). Rats aged PND 1-PND 21 are called

neonates (pre-weaning), PND 22-PND 25 as adolescents (encompassing puberty), and > PND 56 as adults (Sengupta *et al.*, 2013).

Experimental design

This study evaluated the potential of VCR chemotherapy to cause delays in physical or neurological development in rats exposed to VCR during the neonatal period. The animals were observed from the first postnatal day (PND) until PND 25, with the first day of the experimental protocol labeled as PND 1. Physical responses related to neurodevelopment (recovery from decubitus, vibrissae placement, cliff aversion) and physical development (cranial width, cranial length, and body weight) were assessed every 5 days. On PND 11, the animals received either VCR ($6 \mu\text{g.kg}^{-1}$) or its control vehicle (0.9% saline solution) in a volume of 10 ml.kg^{-1} , both via the i.p. route. Motor function and locomotion were evaluated on PND 21 and 22 using the Rotarod (RR) and gait analysis (GA) tests, respectively. Nociceptive responses were evaluated on PND 23 with mechanical sensitivity using a digital anesthesiometer (DA) and thermal sensitivity using a hot plate (HP), and on PND 24 with the cold plate test (CP). Behavioral responses associated with neurodevelopment that were considered more aversive, such as negative geotaxis, startle response, acceleration, and palmar grip, were assessed specifically on PND 25.

Following the behavioral assessments, the animals were euthanized, and the cerebral cortex, hippocampus, cerebellum, spinal cord and hypothalamus were partially dissociated for gene expression analysis via polymerase chain reaction (PCR), as well as for enzymatic activity and oxidative stress evaluation by spectrophotometry. Additionally, the spinal column was dissociated for histopathological analysis. The experimental design was summarized graphically in Fig. 1.

Experimental Design for Neonatal Exposure to Vincristine: A Comprehensive Approach to Neurodevelopment, Peripheral Neuropathy, and Motor Function in Rats

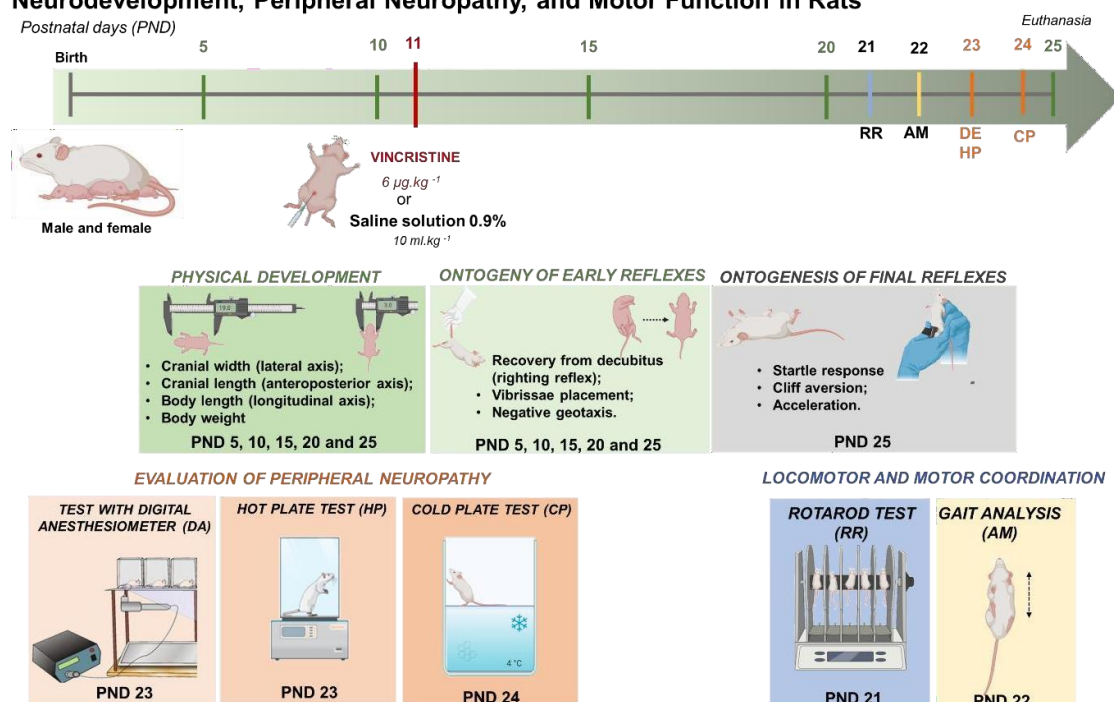


Fig. 1 – Experimental protocol to evaluate the neurodevelopmental, physical, nociceptive, and motor effects of vincristine (VCR) in neonatal rats. Newborn animals were obtained at birth and monitored every five days for physical and neurodevelopmental parameters. On postnatal day (PND) 11, animals received a single intraperitoneal injection of VCR ($6 \mu\text{g} \cdot \text{kg}^{-1}$). From PND 5 to 25, physical development was assessed by measuring the cranial (lateral and anteroposterior) and body (longitudinal) axes, as well as body weight. Simultaneously, neurodevelopmental reflexes were evaluated, including the righting reflex (recovery from recumbency), negative geotaxis, and vibrissae positioning. At PND 21 and 22, motor function and locomotion were assessed using the Rotarod test (RR) and gait analysis (GA), respectively. Nociception was assessed at PND 23 using the digital anesthesiometer (DA) and hot plate (HP) tests, and at PND 24 using the cold plate (CP) test. At PND 25, the animals were assessed for the ontogeny of their final reflexes, namely, cliff aversion, startle response, and acceleration. Then, still at PND 25, they were euthanized for

subsequent biochemical analysis of the brain tissues involved in neurotoxicity.

Physical development

Somatic growth was observed as a measure associated with physical development bias. Measurements and weight were taken every five days during the experimental protocol.

- *Cranial width (lateral axis)* - The distance between the animal's two ears was measured with a caliper. The results were expressed in centimeters.
- *Cranial length (anteroposterior axis)* - The distance between the animal's snout and the atlanto-occipital joint was measured in the animal under restraint. The measurement was made with a caliper. The results were expressed in centimeters.
- *Body length (longitudinal axis)* - To obtain this measurement, the animal was restrained against a flat surface with a piece of paper underneath the animal. Once the animal was restrained, two marks were made on the paper, one coinciding with the snout (P1) and the other at the base of the tail (P2). The longitudinal axis of the animal's body was measured by the distance between P1 and P2 with the aid of a caliper. The results were expressed in centimeters.
- *Body weight* - It was measured using a digital scale to establish the weight gain between the groups during the protocol period. The results were expressed in grams.

Neurodevelopment analysis

Neurodevelopmental reflex tests were performed every five days between 11 and 12 a.m. since rats are nocturnal. The rats were removed from the box with

the mother rat only for analysis, and as soon as the evaluation was completed, they were returned directly to the box. A maximum separation period of 10 minutes was established so as not to affect the animals' breastfeeding.

Negative geotaxis

Negative geotaxis is a test that aims to assess neurological maturation, muscle tone, balance, and motor coordination (Queiroz *et al.*, 2019; Smart; Dobbing, 1971). The animal is placed in the center of a ramp with a 45° incline, with its head pointing downwards. The reflex response was considered positive when the animal could rotate its body to the upward position within a maximum period of 10 seconds. The animal that did not reach the positive response within 10 seconds was considered to have responded at the maximum time (10 seconds). The test was repeated 3 times, and an average was calculated for statistical comparison purposes.

Recovery from decubitus

Recovery from decubitus is a behavioral test commonly used to assess neuromuscular function, balance, strength, and motor coordination in animals, particularly in studies involving animal models of neurological and muscular diseases, as well as in anesthetic and postoperative evaluations^{8,28}. For the evaluation, the rat was placed on a flat surface in dorsal decubitus. The average time it took for the animal to return to the ventral decubitus position supported on all four paws was measured. A maximum duration of 10 seconds was set for the animal to return to the ventral position. If the animal did not return to the ventral position, the test round was concluded, and the maximum time spent was recorded (10 seconds). Three rounds of the same behavior were conducted to determine the average response time of each animal. The premise of the test

indicates that prolonged times to stand up suggest signs of muscle weakness, neurological deficits, and lethargy.

Vibrissae placement

The vibrissae placement test is a behavioral and neurological test used in rodents to assess sensory and motor integrity, especially in pathways involving the brainstem, thalamus, and contralateral somatosensory cortex (Queiroz *et al.*, 2019; Smart; Dobbing, 1971). To perform the test, the animal is suspended by the tail so that the vibrissae lightly touch the edge of a table. The test was completed when the animal placed its front paws on the table to walk. The maximum test time was also set at 10 seconds. If the animal did not reach the time limit, it was removed from the test, and the maximum time was recorded. Three repetitions were performed, and the average response time of the animal was used for statistical comparison purposes.

Startle Response

The startle response is an innate and rapid motor reflex that responds to a sudden and intense stimulus, usually a loud sound (Queiroz *et al.*, 2019; Smart; Dobbing, 1971). Here, the animal was subjected to a sharp bang produced by two metals objects at a distance of approximately 10 cm. The response was considered positive given the simultaneous retraction behavior with rapid and involuntary immobilization of the animal's body, which is characteristic of startle. A startle response score was observed, classified as 0 = no apparent response to sound; 1 = head raised without response to startle (body retraction); 2 = body retraction without body immobilization; and 3 = body retraction and immobilization. The test was repeated 3 times, and an average was calculated for statistical comparison purposes.

Acceleration

The acceleration test evaluates muscle strength, motor coordination, endurance, and rapid neuromuscular response^{8,28}. The researcher suspends the rat by all four paws in a supine position, 12 cm above a table containing a sponge (30 cm x 12 cm thick). The animal is released, and its behavior during free fall is observed. A positive response is noted when the animal completely rotates its body during the fall and supports itself with all four paws on the foam. A score is assigned to better assess the animal's response, as follows: 0 = the animal does not rotate during free fall; 1 = the animal falls with its body on its side; 2 = the animal falls in a ventral position without being able to support all four paws; 3 = the animal falls in a ventral position with all four paws supported. The test was repeated 3 times, and an average was calculated for statistical comparison purposes.

Cliff aversion

The cliff aversion test assesses innate protective responses, sensorimotor integration, and neurological maturation (Queiroz *et al.*, 2019; Smart; Dobbing, 1971). The animal was placed with its front paws on the edge of a high, flat surface to detect the cliff. A positive response was considered when the animal, within a maximum time of 10 seconds, moved 90° in the opposite direction from the cliff. The animal that did not reach the positive response within 10 seconds was considered to have responded at the maximum time (10 seconds). The test was repeated 3 times, and an average was calculated for statistical comparison.

Nociception Investigation

Investigation of mechanical hyperalgesia

Test with digital anesthesiometer (DA)

Mechanical sensitivity in rats was assessed following the method described by Alamri et al. (Alamri *et al.*, 2018b) on PND 23 (with some modifications). For this procedure, rats were individually housed inside an acrylic box with a wire grid floor, which was conducted in a quiet room. The test involved obtaining a hind paw flexion reflex using a portable force transducer (digital aesthesiometer, Insight, São Paulo, Brazil) equipped with a polypropylene tip. Paw withdrawal threshold was measured by applying progressive pressure perpendicularly to the middle of the plantar surface of the hind paw until withdrawal occurred, with the pressure value recorded automatically. Data were expressed as withdrawal threshold (g).

Investigation of thermal hyperalgesia

Hot plate test

Thermal sensitivity to heat was assessed in rats following the protocol described by Woolfe and MacDonald (WOOLFE; MACDONALD, 1944), with some modifications. The hot plate test, a behavioral model for nociception, was used to investigate responses such as jumping and licking of the hind paw in response to a noxious thermal stimulus. Thermal sensitivity to heat was assessed on PND 23 of the experiment. Rats were placed in a Plexiglas box on a heated metal plate at 52 ± 1 °C. The latency of nociceptive responses was measured. Significant decreases in paw withdrawal latency were interpreted as indicative of heat hyperalgesia. Time spent on the plate was limited to 45 s to avoid damage to the animals' paws. Data were expressed as latency(s).

Cold plate test

Cold thermal nociception was assessed using a cold plate test as described by Ruan et. al (Ruan *et al.*, 2018) with modifications. The apparatus

consisted of a flat acrylic plate (0.5 to 1 cm thick) placed directly on a uniform layer of crushed ice in a shallow metal or insulated tray, ensuring a stable surface temperature of 4 ± 1 °C. The acrylic plate prevented direct contact between the animals and the ice, allowing efficient conduction of the cold stimulus.

Before the test, the surface temperature of the acrylic plate was checked with a calibrated digital thermometer to ensure consistency between tests. The animals were placed individually on the cold surface and observed for nociceptive behaviors, such as paw lifting, shaking, licking, or jumping. A maximum cutting time of 60 seconds was stipulated to avoid tissue damage or stress. The number of times the animal displayed nociceptive behaviors was counted within the test time limit and statistically analyzed. Data were presented as nociceptive behavior concerning the number of rear paw elevations (hind leg raises).

Locomotor and motor coordination

Rotarod test

The rotarod test assessed motor coordination in rats. The rotarod test was performed according to the procedure described by McIlwain et al. (McIlwain *et al.*, 2001) on the PND 21, with some modifications. Each rat was initially trained to remain on the rotating bar for 300 seconds while it rotated at a gradually increasing speed of 5 to 30 revolutions per minute (rpm). This training phase was repeated three times. Twenty-four hours later, the animals were again subjected to the test. The latency (in seconds) to fall from the rotarod was recorded up to a limit of 300 seconds.

Gait analysis

Gait assessment was performed using the footprint test, a well-established method for assessing rodent locomotor abnormalities (Walker *et al.*, 1994). The

gait analysis was performed on PND 22. The hind feet of each animal were carefully painted with non-toxic water-based paints in contrasting colors, using fine-tipped brushes to ensure even coverage. The animal was then placed at the entrance of a straight walking corridor (50–100 cm long, 8–10 cm wide, and 15–20 cm high), with the floor covered with a sheet of white paper. The animal was allowed to walk voluntarily towards a dark goal box at the end of the corridor containing standard rodent chow, promoting natural and uninterrupted locomotion. Data were displayed as stride distance (mm).

RNA extraction and one-step RT-qPCR

Total RNA was extracted from approximately 100 mg of cortex and spinal cord tissue. Total RNA extraction was conducted using TRIzol reagent (Invitrogen™, Carlsbad, USA) followed by DNase treatment with DNase I Amplification Grade (Invitrogen™, Carlsbad, USA) in order to ensure minimum DNA contamination of the samples. The total RNA isolated was quantified and its purity (260/280 and 260/230 ratios) was examined by spectrophotometer NanoVue (GE, Fairfield, CT, USA).

The one-step RT-qPCR was performed with GoTaq® 1-Step RT-qPCR Master Mix (Promega, Madison, WI) using the QuantStudio™ 1 Real-Time PCR System (Thermo Fisher Scientific Inc., MA, USA). The sequence of primers used are indicated in Table 1 (Supplementary material). The qPCR conditions were the following: 15 min at 37 °C for cDNA synthesis, 10 min at 95 °C for reverse transcription inactivation and Taq DNA polymerase activation, followed by 35 cycles of denaturation for 10 s at 95 °C, primer annealing for 30 s at 60 °C, and extension for 30 s at 72 °C (fluorescence signals were detected at the end of every cycle). Samples were analyzed in duplicates, and each qPCR reaction was

followed by the manufacturer's recommended conditions for melting curve analysis. Baseline values were automatically set by the thermocycler Software.

The number of PCR cycles required to reach the fluorescence threshold in each sample was defined as the Ct value. The $2^{-\Delta\Delta C_T}$ method was used to normalize the fold change in gene expressions (Livak; Schmittgen, 2001a), using B-actin as the housekeeping gene.

Preparation of samples for biochemical analysis

For biochemical analyses, samples were homogenized in 50 mM Tris-HCl buffer (pH 7.4) and subsequently centrifuged at $900 \times g$ for 10 minutes to obtain a supernatant (S1). The protein concentration was measured by the method of Bradford (Bradford, 1976b), using bovine serum albumin as the standard. At the same time, the spinal column was dissected to analyze the histological profile of the spinal cord.

Oxidative Parameters

Thiobarbituric Acid Reactive Substances (TBARS) levels

TBARS levels were used as an indirect measure to assess the amount of malondialdehyde (MDA), one of the products released by lipoperoxidation. TBARS levels were measured as described by Ohkawa et al (1979). An aliquot of S1 was added to the reaction mixture containing: thiobarbituric acid (0.8%), sodium dodecyl sulfate (8.1%), and acetic acid (pH 3.4), and incubated at 95°C for 2h. Absorbance was measured at 532 nm in a spectrophotometer. Results were reported as nmol MDA/mg protein.

Non-Protein Sulfhydryl Groups (NPSH) levels

NPSH levels were assessed to directly measure oxidative damage to thiols and indirectly assess reduced glutathione (GSH) levels. The determination of

NPSH levels was carried out using Ellman's method (Ellman, 1959). The supernatant was mixed with 10% TCA in a 1:1 volume ratio. The tubes were then centrifuged at 900 x g for 10 minutes, and the protein pellet was discarded. The clear supernatant was used to determine the levels of free-thiol (SH) groups. An aliquot of the supernatant was added to a solution containing 1 M potassium phosphate buffer (pH 7.4) and 10 mM 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB). The color reaction was measured at 412 nm using a spectrophotometer. NPSH levels were expressed as nmol NPSH/g of tissue.

ATPase Activities (Ca²⁺- and Mg²⁺-Dependent)

ATPase activities were determined according to the method described by Rohn (Rohn; Hinds; Vincenzi, 1993) and adapted by Trevisan (Trevisan *et al.*, 2009). Tissue homogenates (50 µL) were incubated at 37 °C for 30 minutes in a reaction medium containing 30 mM Tris-HCl (pH 7.4), 6 mM MgCl₂, 4 mM CaCl₂, and 3 mM ATP, in a final volume of 500 µL. The reaction was stopped by adding 10% trichloroacetic acid (TCA) and 10 mM HgCl₂ to stabilize inorganic phosphate (Pi).

Ca²⁺-ATPase activity was determined by subtracting the Pi released in the absence of Ca²⁺ (reaction medium without CaCl₂) from that measured in its presence. Mg²⁺-ATPase activity was assessed in a reaction mixture containing only 3 mM MgCl₂ and 3 mM ATP, under otherwise identical conditions. The released Pi was quantified using the Fiske and Subbarow (Fiske; Subbarow, 1925b) colorimetric method, and absorbance was measured at 650 nm. Results were expressed as nmol Pi/mg protein/min.

Histopathological analysis

The spinal column was collected and fixed by immersion in a 10% buffered

formalin solution for 24 hours. The spinal cord was not removed and remained in place, and the bones were decalcified in 8% hydrochloric acid and formic acid in a 1:1 ratio for approximately 5 days. The specimens were then sectioned transversely and processed routinely, embedded in paraffin, cut into 3-4 μm sections, stained with hematoxylin-eosin (HE), and examined under a light microscope.

Statistical analysis

The normality of the data was assessed using the Shapiro-Wilk normality test. Statistical analysis was conducted using GraphPad Prism 7.0 software (San Diego, CA, USA). No outliers were identified. Two-way ANOVA followed by Tukey's multiple comparisons test was used for statistical analysis in the somatic growth assessment tests and neurodevelopment assessment (negative geotaxis, decubitus recovery, and vibrissae placement). The unpaired and parametric T-test was used as a statistical test for the other analyses performed. Data were presented as mean $\pm$ standard error of the mean (S.E.M.). Statistical significance was defined as $P < 0.05$.

Results

Physical development

Impaired Cranial Morphogenesis Induced by Early-Life VCR Administration

The development of the lateral axis (cranial width) was observed every 5 days to verify the natural growth of the head of neonatal rats until adolescence (Fig. 2a). A two-way ANOVA followed by Tukey's post hoc test revealed statistically significant differences at multiple time points, indicating that VCR interrupts normal cranial expansion during this critical developmental window

between PND 15 and 20. On PND 15, we observed that VCR caused a delay in the development of the lateral axis in males (25%) and females (15%) compared to control animals. On PND 20, male (13%) and female (11%) rats that received VCR continued to show a delay in the growth of the lateral axis of the skull. On PNDs 5 and 25, there were no significant changes between the groups analyzed.

Anteroposterior axis growth was also impacted by VCR exposure (Fig. 2b). Statistical analysis showed that VCR delayed anteroposterior cranial growth in neonatal rats starting from PND 15 in males (12%) and females (13%), and from PND 20 in males (18%) and females (16%). By PND 25, VCR continued to influence cranial neurodevelopment along the anteroposterior axis only in females (12%).

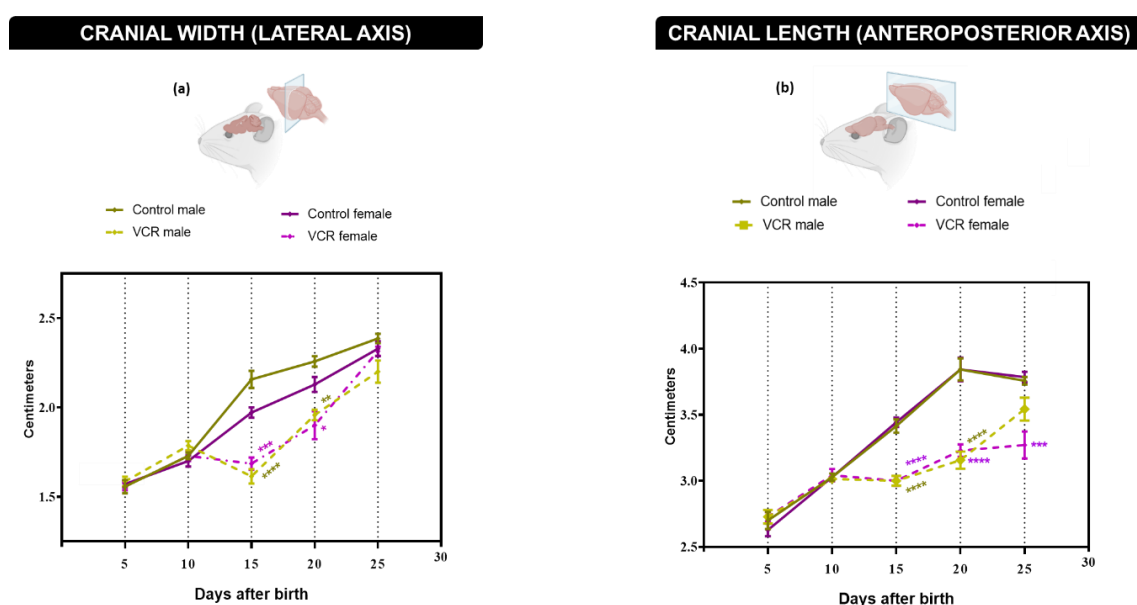


Fig. 2 - Effects of vincristine sulfate (VCR) ($6 \mu\text{g} \cdot \text{kg}^{-1}$, i.p.) on neurodevelopment in male and female rats. Lateral axis of skull (a) and anteroposterior axis of the skull (b). Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 7 animals per group. (*) $P < 0.05$, (**) $P < 0.01$, (***) $P < 0.001$, and (****) $P < 0.0001$ denote significance levels when comparing the VCR group to the control group. Two-way ANOVA followed by the Tukey's test was used.

Early-Life VCR Treatment Causes Persistent Growth Deficits

The development of body weight and length was monitored every 5 days to assess the natural growth of the heads of neonatal rats until adolescence (Fig. 3). A two-way ANOVA followed by Tukey's post hoc test showed significant differences at several time points, suggesting that VCR may influence body length and weight gain during the breastfeeding period. Regarding body length, it was found that VCR induction delayed physical development in female (7%) neonatal rats at PND 15. Additionally, VCR caused delays in body length development at PND 20 in males (8%) and females (7%); by PND 25, only females (8%) still showed a delay in growth. Similarly, in the assessment of body weight, VCR resulted in decreased weight gain at PND 20 in both male (20%) and female (18%) neonatal rats.

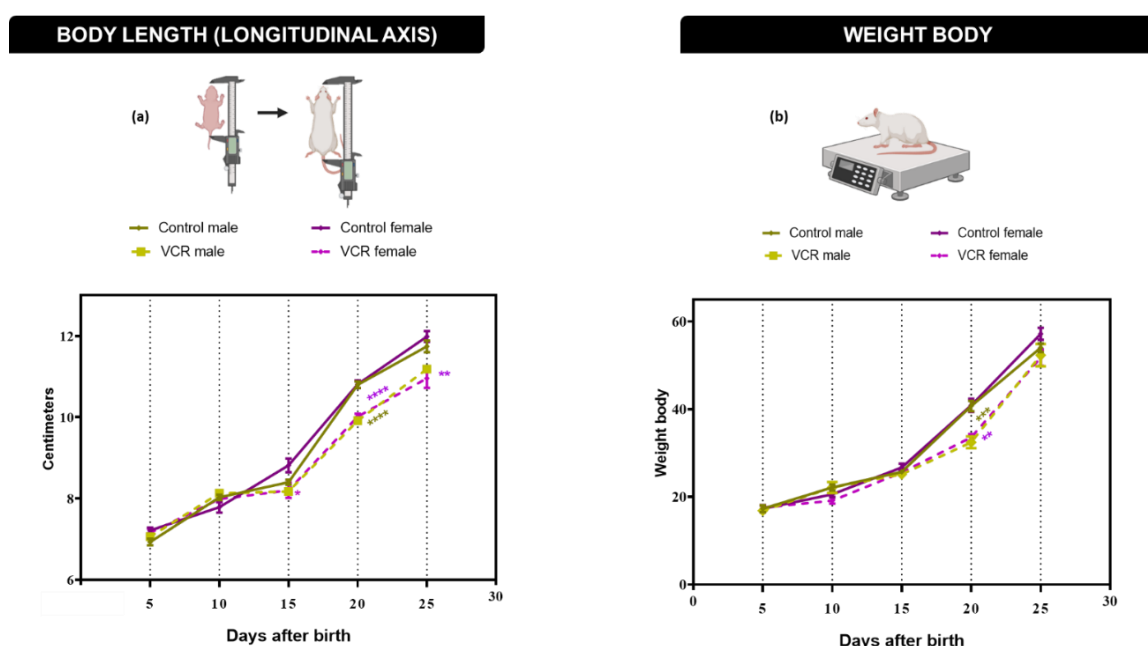


Fig. 3 - Effects of vincristine sulfate (VCR) ($6 \mu\text{g} \cdot \text{kg}^{-1}$, i.p.) on the body development in male and female rats. Longitudinal axis of body (a) and weight (b). Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 7 animals per group. (**)

$P < 0.01$, (***) $P < 0.001$, and (****) $P < 0.0001$ denote significance levels when comparing the VCR group to the control group. Two-way ANOVA followed by the Tukey's test was used.

Neurodevelopment

Disruption of Negative Geotaxis, Recovery of decubitus, and Placement of Vibrissae Following Neonatal VCR Exposure

To evaluate the effect of VCR on early postural reflexes, we conducted the negative geotaxis test at key developmental stages (Fig. 4a). A two-way analysis showed that VCR induction caused a delay in the negative geotaxis reflex response only at PND 20 in males (71%) and females (58%). We observed that the impaired postural reflexes, as measured by the negative geotaxis test, returned to normal by PND 25. On the days before VCR exposure (PNDs 5 and 10), no significant differences were found between the groups.

The righting reflex (recovery from decubitus) was assessed to examine the maturation of basic motor responses and neuromuscular coordination in neonatal rats induced with VCR (Fig. 4b). The statistical analysis revealed that male (285%) and female (257%) neonatal rats exposed to VCR had difficulty recovering from the recumbency position from day 20 onward. Similarly, on day 25, male (6500%) and female (6900%) rats exposed to VCR continued to show a retrograde response to the ventral position after recumbency. On the other days analyzed, days 5, 10, and 15, no significant differences were observed between the groups that received VCR and those that did not in the decubitus recovery test.

To determine whether VCR impairs early sensorimotor reflexes, we assessed the vibrissae positioning response in neonatal rats at different postnatal

stages (Fig. 4c). On PND 15, VCR induction triggered sensorimotor alterations in the vibrissae placement test in male (116%) and female (100%) rats. In parallel, on PND 20, male (100%) and female (128%) rats exposed to VCR continued to exhibit impaired stance reflexes in the vibrissae placement test. We found that impaired sensorimotor reflexes, as measured by the vibrissae placement test, recovered to normal by PND 25. On the test days preceding VCR exposure (PNDs 5 and 10), no statistical differences were observed between the groups.

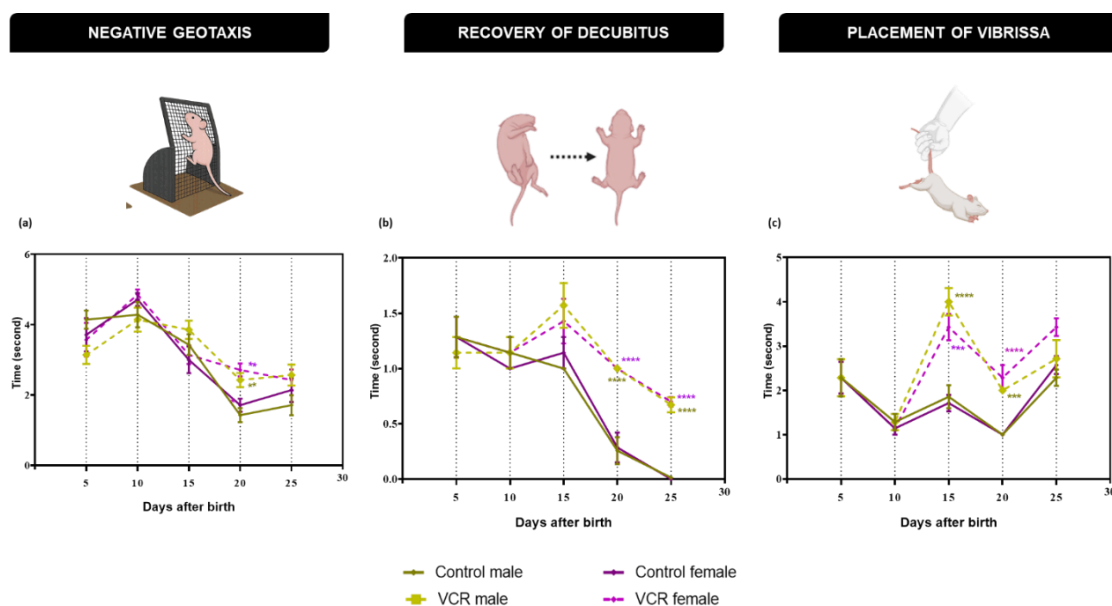


Fig. 4 - Effects of vincristine sulfate (VCR) ($6 \mu\text{g.kg}^{-1}$, i.p.) on neurodevelopmental assessment at each five days of the experimental protocol. Assessment of the negative geotaxis (a), recovery decubitus (b), and placement of vibrissae (c) in rats. Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 7 animals per group. (**) $P < 0.01$, (***) $P < 0.001$, and (****) $P < 0.0001$ denote significance levels when comparing the VCR group to the control group. Two-way ANOVA followed by the Tukey's test was used.

Disruption of Early Behavioral Reactivity and Risk Assessment Following Neonatal VCR Treatment

To investigate whether neonatal VCR exposure alters basic defensive behaviors, we assessed startle responses at key developmental stages in male (Fig. 5a) and female (Fig. 5b) rats. Statistical analysis showed that at PND 25 of the experimental protocol, male (48%) and female (48%) neonatal rats showed a decrease in the startle reflex response.

Since VCR is known to impair neuromuscular function, we examined whether early exposure affected the time to start movement in neonatal rats during the free fall acceleration test in male (Fig. 5c) and female (Fig. 5d) rats. In fact, early VCR exposure in male (43%) and female (57%) neonatal rats led to impaired movement latency in the test.

From another perspective, to determine whether VCR affects these innate responses, we assessed the latency and success of withdrawal from the edge across developmental stages in male (Fig. 5e) and female (Fig. 5f) rats. We found that VCR led to an impairment in the latency of the cliff response, as an innate response, in males (123%) and females (157%) at PND 25.

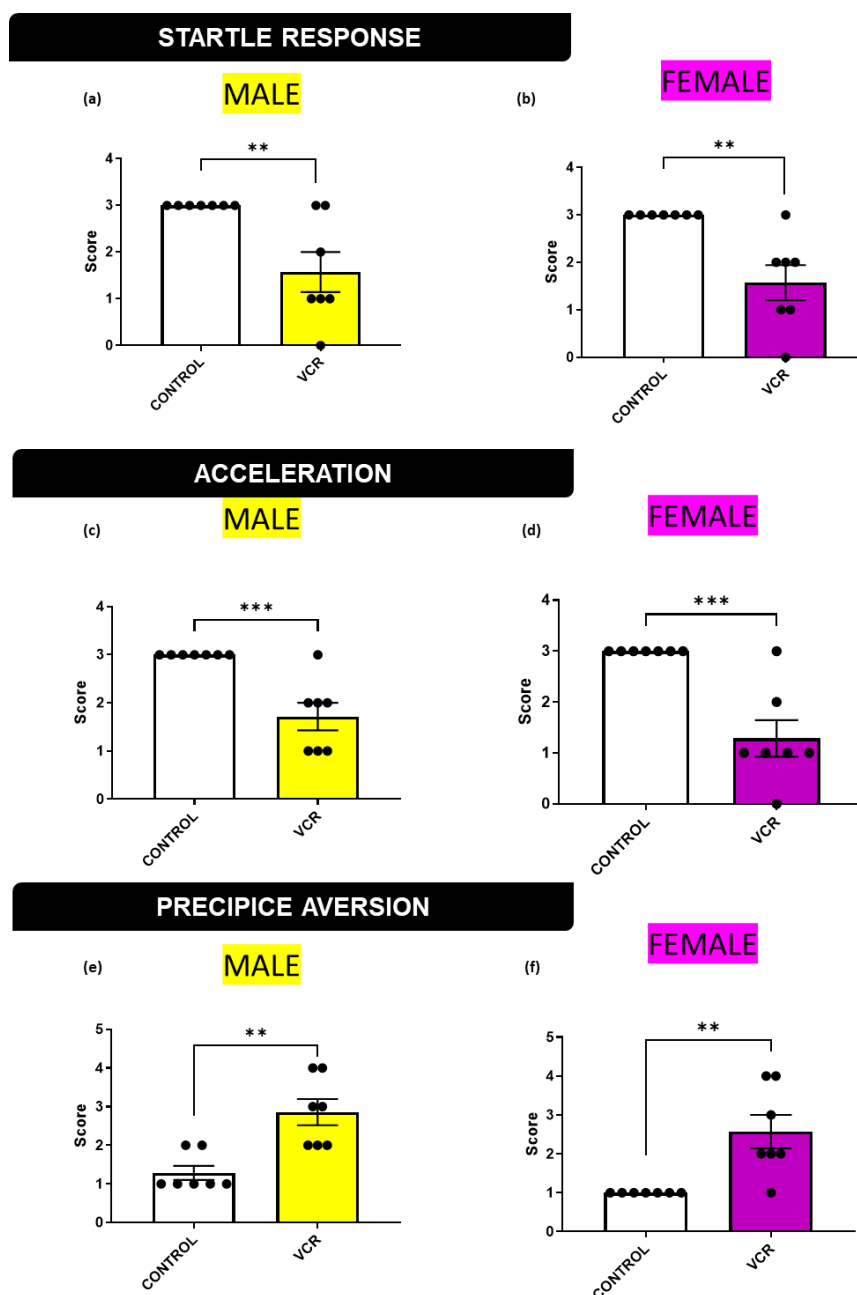


Fig. 5 - Effects of vincristine sulfate (VCR) ($6 \mu\text{g.kg}^{-1}$, i.p.) on final neurodevelopmental assessment. Assessment of the startle response in males (a) and females (b); free fall assessment in males (c) and females (d); cliff aversion in males (e) and females (f) rats. Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 7 animals per group. (**) $P < 0.01$ and (***) $P < 0.001$ denote significance levels when comparing the VCR group to the control group. The data were analyzed statistically using an unpaired, parametric t-test.

Nociception Investigation

Investigation of mechanical hyperalgesia

Test with digital anesthesiometer (DA)

To assess potential changes in mechanical nociceptive thresholds after neonatal exposure to VCR, animals were tested with a digital esthesiometer (Fig. 6). Statistical analysis of the data revealed that VCR induction led to a reduction in the paw withdrawal threshold characterizing mechanical hypernociception in male (Fig. 6a; 34%) and female (Fig. 6b; 40%) rats through the mechanical hyperalgesia test (digital anesthesiometer test).

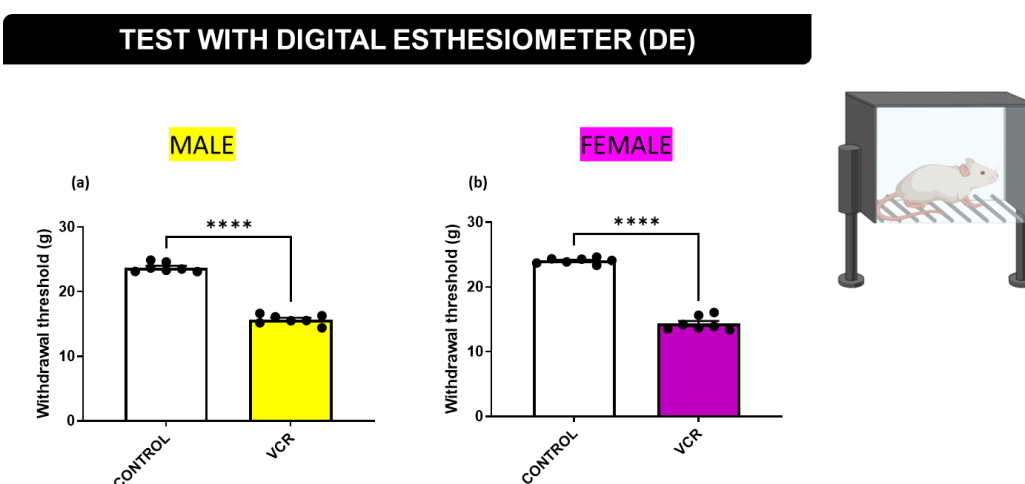


Fig. 6 - Effects of vincristine sulfate (VCR) ($6 \mu\text{g} \cdot \text{kg}^{-1}$, i.p.) on the mechanical hyperalgesia evaluation in male (a) and female (b) rats. Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 7 animals per group. (****) $P < 0.0001$ denotes significance levels when comparing the VCR group to the control group. The data were analyzed statistically using an unpaired, parametric t-test.

Investigation of thermal hyperalgesia

Hot and Cold plate test

To assess thermal nociceptive sensitivity after neonatal exposure to VCR, the animals were evaluated using the hot plate test (Fig. 7 a, b). The hot plate

test showed that early exposure to VCR in male (Fig. 7a, 62%) and female (Fig. 7b, 63%) neonatal rats caused increased heat sensitivity.

Regarding cold sensitivity, we employed the cold plate test to characterize better the sensory alterations associated with neonatal exposure to VCR. Indeed, induction with VCR triggered increased cold sensitivity, demonstrated by increased behavior associated with nociception in the cold plate test. This behavior was observed in male (Fig. 7c; 175%) and female (Fig. 7d; 175%) rats that received VCR.

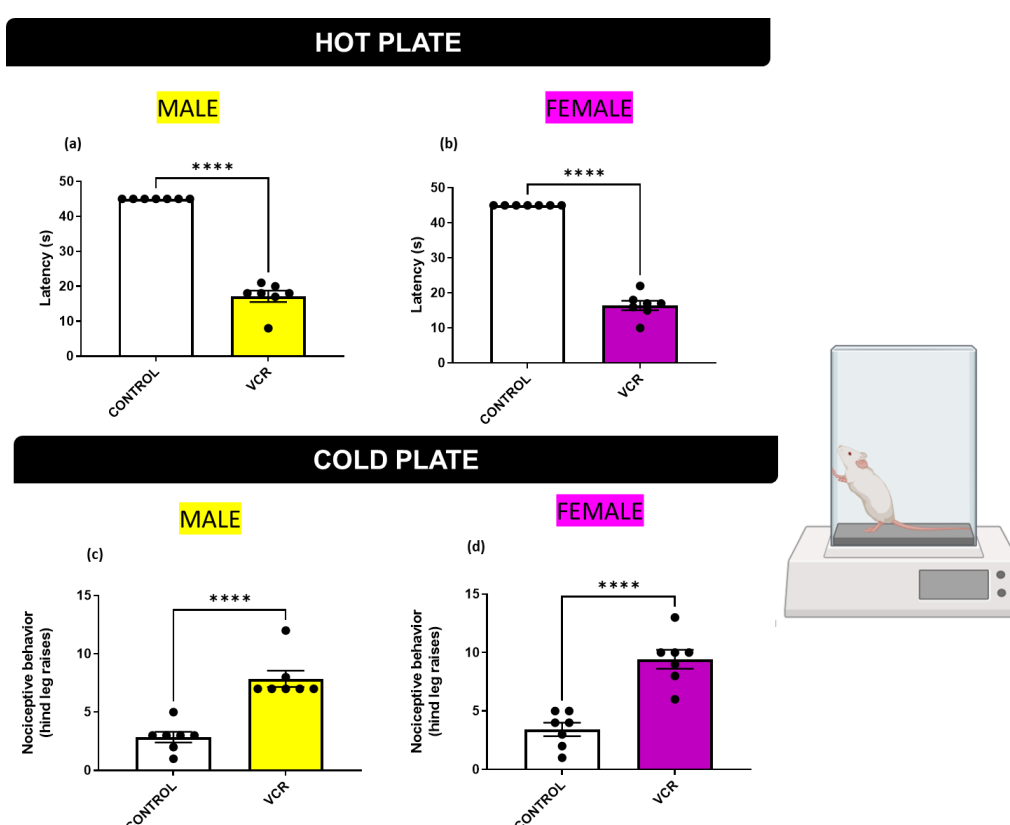


Fig. 7 - Effects of vincristine sulfate (VCR) ($6 \mu\text{g} \cdot \text{kg}^{-1}$, i.p.) on the thermal nociception evaluation in male and female rats. The hot nociception in male (a) and female (b) rats, and cold nociception in male (c) and female (d) rats. Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 7 animals per group. (****) $P < 0.0001$ denotes significance levels when comparing the VCR group to the control group. The data were analyzed statistically using an unpaired, parametric t-test.

Locomotor and motor coordination

Rotarod test

To determine whether neonatal exposure to VCR leads to long-term motor impairments, animals were evaluated on the rotarod apparatus (Fig. 8). Statistical analysis revealed that neonatal male (Fig. 8a; 36%) and female (Fig. 8b; 42%) rats exposed to VCR developed impaired motor coordination by the Rotarod test.

Gait analysis

To further investigate the effects of neonatal VCR exposure on locomotor function and peripheral motor control, gait analysis was performed by measuring the stride length of the animals (Fig. 7). Statistical analysis revealed that neonatal male (Fig. 8c; 28%) and female (Fig. 8d; 27%) rats exposed to VCR develop locomotor impairments by gait analysis test.

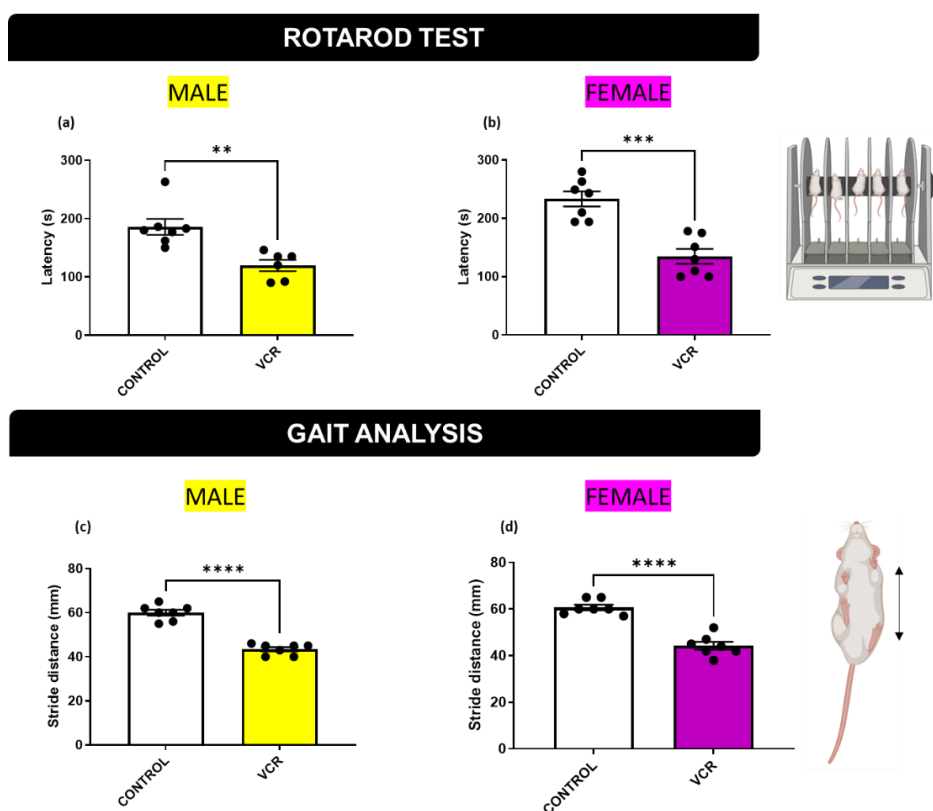


Fig. 8 - Effects of vincristine sulfate (VCR) ($6 \mu\text{g.kg}^{-1}$, i.p.) on the evaluation of motor and locomotor coordination using the Rotarod test and gait analysis. Rotarod test for evaluation of coordination in male (a) and female (b) rats. Gait analysis for evaluation of motor skills and locomotion in male (c) and female (d) rats. Each column represents the mean $\pm$ standard error of the mean (S.E.M.) of 7 animals per group. (**) $P < 0.01$, (***) $P < 0.001$, and (****) $P < 0.0001$ denote significance levels when comparing the VCR group to the control group. The data were statistically analyzed using the unpaired, parametric t-test.

VCR Modulates Mitochondrial Quality Control Pathways: Altered Expression of PTEN-induced kinase 1 (PINK-1) and Parkin RBR E3 ubiquitin protein ligase (PARKIN) in the Spinal Cord and Cerebral Cortex of Neonatal Rats

To investigate whether VCR disrupts mitochondrial homeostasis in the developing brain, we assessed the expression of two key genes involved in mitophagy, *PINK-1* (Fig. 9a - 9d) and *PARKIN* (Fig. 9e - 9h).

Statistical analyses of *PINK-1* expression demonstrated that VCR induction did not cause significant changes in the cerebral cortex of male (Fig. 9a) and female (Fig. 9b) rats. In the spinal cord, we found that early VCR induction in neonatal rats caused a decrease in *PINK-1* expression in males (Fig. 9c; 50%) and an increase in expression in females (Fig. 9d; 15%).

Statistical analysis of *PARKIN* revealed an increase in gene expression, especially in the cerebral cortex (Fig. 9f; 135%) and in the spinal cord (Fig. 9h; 21%) of female rats that received VCR. In male rats, *PARKIN* expression was not affected by VCR exposure in either the cerebral cortex (Fig. 9e) or spinal cord (Fig. 9g).

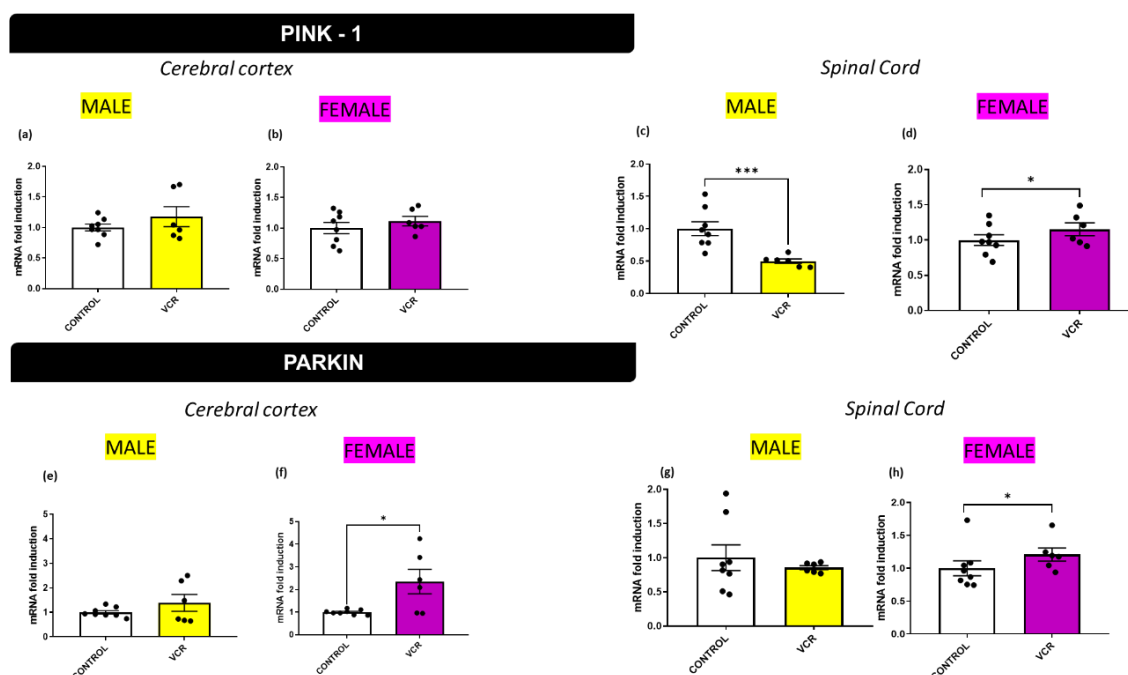


Fig. 9 - Effects of vincristine sulfate (VCR) ($6 \mu\text{g} \cdot \text{kg}^{-1}$, i.p.) on the neurotoxicity in protein expression in male and female rats. Expression of phosphatase and tensin homolog deleted on PTEN-induced putative kinase 1 (*PINK-1*) in the cerebral cortex of males (a) and females (b) and in the spinal cord of males (c) and females (d) rats. Expression of *PARKIN* RBR E3 Ubiquitin Protein Ligase (*PARKIN*) in the cerebral cortex of males (e) and females (f) rats and the spinal cord of males (g) and females (h) rats. Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 6-8 animals per group. (*) $P < 0.05$ and (***) $P < 0.001$ denote significance levels when comparing the VCR group to the control group. The data were analyzed statistically using an unpaired, parametric t-test.

VCR Influences Apoptotic Pathways: Altered Expression of CASPASE-3 and Myeloid Cell Leukemia-1 (MCL-1) in Neonatal Spinal Cord and Cerebral Cortex of Rats

To further investigate the molecular mechanisms underlying VCR-induced neurotoxicity, we examined the expression of CASPASE-3 (Fig. 10a–10d) and *MCL-1* (Fig. 10e–10h). CASPASE-3 is a key effector of the apoptotic cascade.

Here, we found that early induction of VCR in neonatal rats caused an increase in CASPASE-3 gene expression in the cerebral cortex of female rats (Fig. 10b; 32%) and a decrease in gene expression in the spinal cord of male rats (Fig. 10c; 42%). There were no significant changes in CASPASE-3 gene expression in the cerebral cortex of male rats (Fig. 10a) and spinal cord of female rats (Fig. 10d).

MCL-1 acts as an anti-apoptotic protein critical for cell survival. We found here that VCR induction caused inhibition of *MCL-1* gene expression in the cerebral cortex of male (Fig. 10e; 56%) and female (Fig. 10f; 27%) rats and the spinal cord of male (Fig. 10g; 38%) and female (Fig. 10h; 24%) rats.

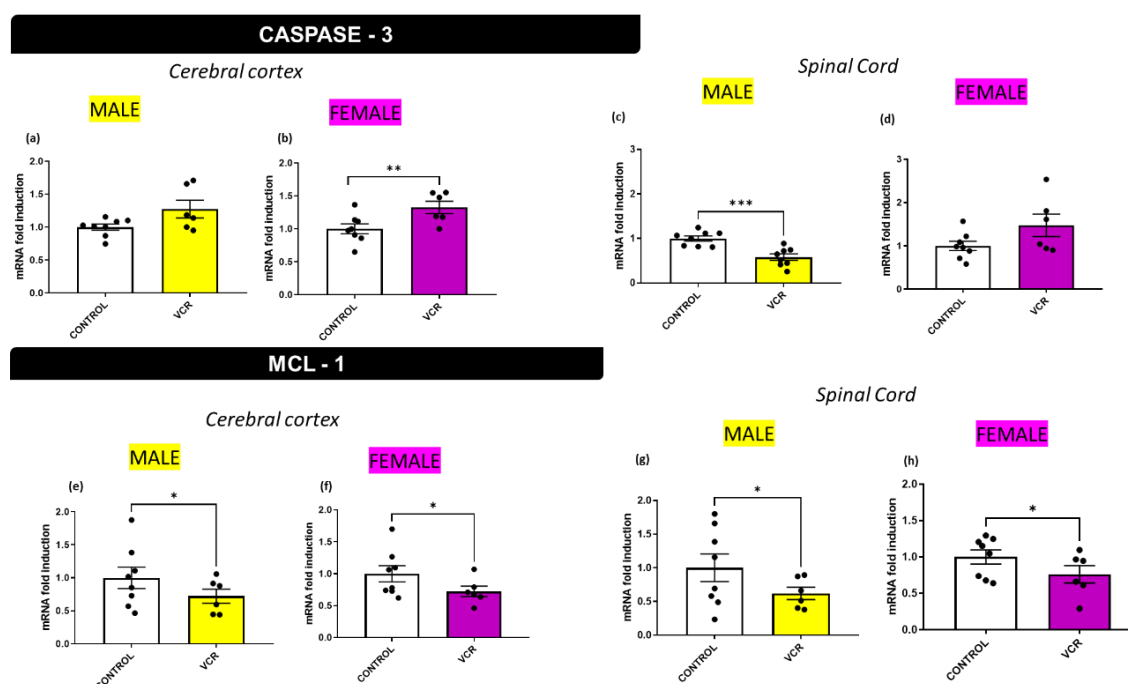


Fig. 10 - Effects of vincristine sulfate (VCR) ($6 \mu\text{g.kg}^{-1}$, i.p.) on the neurotoxicity in protein expression in male and female rats. Expression of CysteinyI aspartate-specific protease 3 (CASPASE-3) in the cerebral cortex of males (a) and females (b) and the spinal cord of males (c) and females (d) rats. Expression of Myeloid Cell Leukemia-1 (*MCL-1*) in the cerebral cortex of males (e) and females (f) rats and the spinal cord of males (g) and females (h) rats. Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 6-8 animals per group. (*) $P < 0.05$, (**) $P < 0.01$ and (***) $P < 0.001$.

0.001 denote significance levels when comparing the VCR group to the young control group. The data were analyzed statistically using an unpaired, parametric t-test.

VCR-Induced Neurotoxicity Involves Upregulation of the Pro-Apoptotic Marker BCL-2-associated X protein (BAX) in the Cerebral Cortex

To better assess the activation of apoptotic signaling pathways, we evaluated the expression of *BAX* (Fig. 11), a pro-apoptotic member of the BCL-2 family, in the cerebral cortex (Fig. 11a, b) and spinal cord (Fig. 11c, d) of neonatal rats exposed to VCR. In this sense, we verified that VCR led to an increase in *BAX* gene expression in the cerebral cortex of male (20%) and female (25%) rats. In the spinal cord, no changes in *BAX* gene expression were observed in either male or female rats.

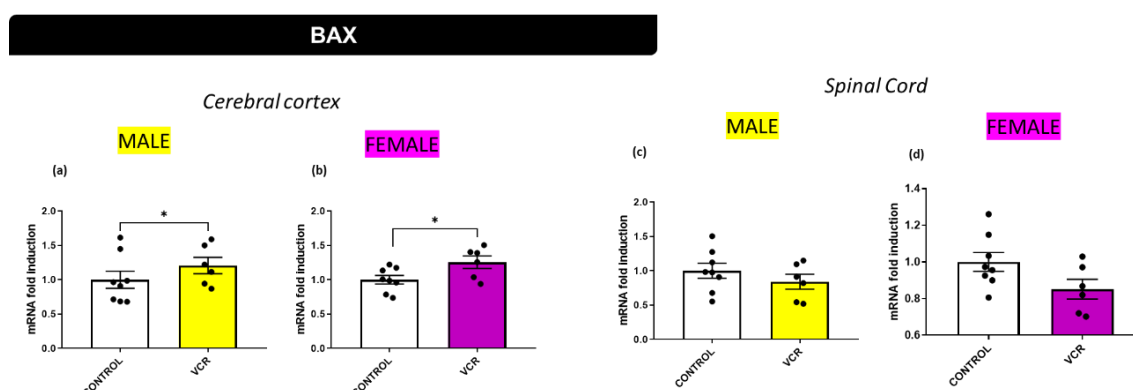


Fig. 11 - Effects of vincristine sulfate (VCR) ($6 \mu\text{g} \cdot \text{kg}^{-1}$, i.p.) on the neurotoxicity in protein expression in male and female rats. Expression of BCL-2-associated X protein (*BAX*) in the cerebral cortex of males (a) and females (b), and the spinal cord of males (c) and females (d) rats. Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 6-8 animals per group. (*) $P < 0.05$ and (***) $P < 0.001$ denote significance levels when comparing the VCR group to the control group. The data were analyzed statistically using an unpaired, parametric t-test.

Biochemical analysis

Oxidative Parameters

TBARS levels

To assess whether neonatal exposure to VCR induces oxidative stress in the central nervous system, lipid peroxidation levels were quantified (Table 6 - Supplementary material). We found that neonatal female rats exposed to VCR early in life exhibited a higher susceptibility to increased lipid peroxidation, as determined by TBARS analysis. Elevated TBARS levels were observed in the cerebral cortex of females (152%), the spinal cord of males (51%), the hippocampus of females (50%), and the hypothalamus of females (51%) rats exposed to VCR. In contrast, the cerebral cortex of males, the cerebellum of both males and females, the spinal cord of females, the hippocampus of males, and the hypothalamus of male rats treated with VCR did not exhibit significant changes in TBARS levels.

NPSH levels

To further investigate the redox state and antioxidant capacity of the brain after neonatal exposure to VCR, we quantified the levels of NPSH (Table 6, Supplementary material), primarily represented by reduced glutathione (GSH). NPSH levels were depleted in the cerebral cortex of males (18%) and females (11%), cerebellum of males (14%), spinal cord of males (14%) and females (14%), and hippocampus of females (6%) rats exposed to VCR. No significant changes were observed in the hippocampus of male rats and cerebellum of females exposed to VCR in early life.

Enzymes associated with axonal depolarization

Ca²⁺ - ATPase

To evaluate potential disruptions in calcium homeostasis caused by neonatal exposure to VCR, Ca²⁺-ATPase activity was measured in brain tissue

(Table 6 - Supplementary material). We observed that VCR exposure increased Ca^{2+} -ATPase activity in the cerebral cortex of male (175%) and female (115%) rats, the cerebellum of male (115%) and female (90%) rats, the spinal cord of female (817%) rats, and the hippocampus of male (106%) and female (212%) rats. Among all tissues examined, only the spinal cord of males showed no increase in Ca^{2+} -ATPase activity following VCR treatment.

Mg^{2+} - ATPase

To investigate whether neonatal exposure to VCR impacts basic cellular energy metabolism and ionic balance, Mg^{2+} -ATPase activity was assessed in brain tissue (Table 6 - Supplementary material). We found an increase in Mg^{2+} -ATPase activity in the cerebellum of males (39%), the spinal cord of males (67%) and females (67%), the hippocampus of male (47%) and female (106%) rats and the hypothalamus of males (39%) and females (45%) that received VCR. However, in the cerebral cortex of males and females, as well as the cerebellum of females, no statistical changes were observed among animals that received VCR in the neonatal phase regarding Mg^{2+} -ATPase activity.

Histopathological analysis

VCR-induced neurodegeneration with central and peripheral components during early neurodevelopment

Histopathological analysis was conducted to investigate potential structural alterations in the spinal cord after neonatal exposure to VCR (Fig. 12). The images depict the control animals, which are represented in the figures (Fig. 12; Slides 1 and 2). The spinal cords of male and female rats showed bilateral and symmetrical swelling of the periaxonal space in the ventral and lateral funiculi. Occasionally, axonal spheroids were seen in these regions. The myelin

sheaths were swollen, giving the white matter a vacuolar appearance. In some areas, they exhibited large vacuoles of different sizes (Fig. 12; Slide 4) and sometimes presented digestion chambers containing macrophages. The cell bodies of motor neurons exhibited vacuoles (Fig. 12; Slide 3). Males and females showed vacuolization in the white matter of the spinal cord and the nerve roots of the lumbar and sacral segments with moderate intensity. No differences were observed between male and female rats exposed to VCR.

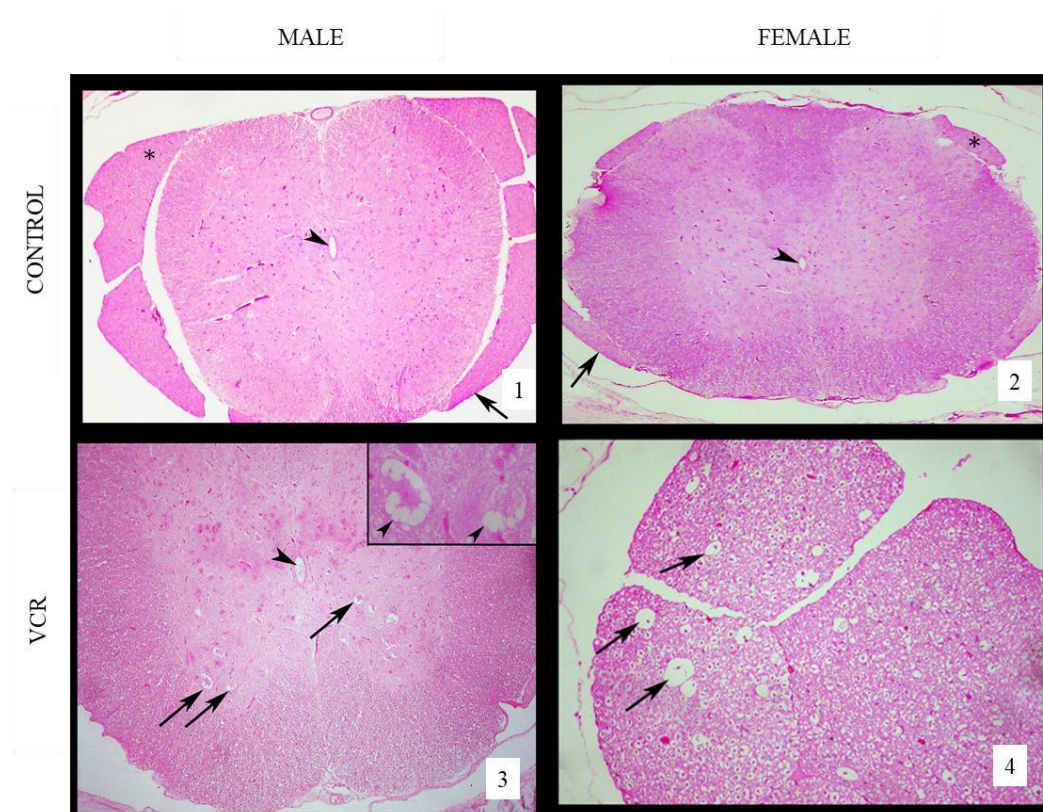


Fig. 12 - Effects of exposure to vincristine sulfate (VCR) ($6 \mu\text{g.kg}^{-1}$, i.p.) on histological analysis of the spinal cord of male and female rats stained with hematoxylin-eosin (HE). (Slide 1) Histological profile of the lumbar spinal cord of control male rats; (*) denotes dorsal nerve root, and (arrow) denotes ventral nerve root (HE; 100X). (Slide 2) Histological profile of the lumbar spinal cord of control female rats; (*) denotes dorsal nerve root; (arrow) denotes ventral nerve root; (arrowhead) denotes ependymal canal of the spinal cord (HE; 100X). (Slide 3)

Histological profile of the sacral spinal cord of male rats exposed to VCR; (arrowhead) ependymal canal of the spinal cord; (arrow) denotes vacuolated motor neurons (HE; 200X). The magnification of the image (arrowhead) denotes motor neurons presenting vacuoles in the cytoplasm (HE; 400X). (Slide 4) Histological profile of the lumbar spinal cord of female rats exposed to VCR; (arrow) denotes nerve root showing vacuolated axons (HE; 200X).

Discussion

VCR is a chemotherapeutic agent well known for inducing neurotoxicity in adult patients; however, it remains the most widely used treatment in pediatric oncology (Gomber; Dewan; Chhonker, 2010b; Schappacher *et al.*, 2019b, 2019c; Triarico *et al.*, 2021a). This experimental study aimed to investigate how early-life exposure to VCR impacts neurological function in neonatal rats by assessing neurodevelopmental milestones, physical growth, mitochondrial function, oxidative stress, and nociceptive sensitivity.

The present findings demonstrate that neonatal exposure to VCR significantly impairs physical development, as evidenced by reduced body weight gain and altered somatic growth parameters. These alterations underscore the disruptive effects of VCR on early postnatal maturation.

The dimensions of the cranial space are directly associated with the development of the central nervous system (CNS); therefore, reductions in the anteroposterior or lateral axes of the skull may indicate brain atrophy or impaired brain growth (Luhmann; Fukuda, 2020; Semple *et al.*, 2013). In rats, the early postnatal period—particularly between PNDs 15 and 20—corresponds developmentally to the human age range of approximately 2 to 3 years (Quinn, 2005; Rudnitskaya *et al.*, 2020). This is a critical window during which

neurogenesis, cell migration, myelination, and the formation of cognitive, motor, and emotional functions are actively occurring (Luhmann; Fukuda, 2020). Notably, this is also the age range in which childhood leukemia most frequently manifests, and VCR remains the primary chemotherapeutic agent used in treatment (Kintossou *et al.*, 2023).

In our study, we found that VCR administration interferes with CNS processes related to cranial development, especially between PNDs 15 and 20. Importantly, the anteroposterior axis of the skull in females exposed to VCR was the only parameter that failed to return to control levels by PND 25, indicating a potential sex-specific vulnerability.

Additionally, the longitudinal axis of the body—an indicator of overall physical growth reflecting nutritional and metabolic status—was significantly affected by VCR treatment, particularly at PNDs 20 and 25. We emphasize once more the greater susceptibility of female rats, both in terms of delayed recovery in longitudinal growth and in the persistent deficits observed in the cranial anteroposterior axis, suggesting combined metabolic and neurodevelopmental impairments induced by early VCR exposure.

Regarding physical development patterns, we also evaluated body weight as a general indicator of somatic growth and metabolic status. Significant weight loss was observed in both male and female rats exposed to VCR at PND 20, followed by a recovery to control levels by PND 25. Body weight is a sensitive marker of developmental toxicity, and transient reductions may reflect systemic metabolic disturbances or delayed growth processes triggered by early chemotherapeutic exposure (Silva, 2020).

Although males and females exposed to VCR demonstrated impaired

growth patterns, we found that females exposed to VCR had greater difficulty in recovering to control patterns in the anteroposterior axis of the skull and in the longitudinal axis of the body. This finding indicates a susceptibility to VCR toxicity unique to females.

In the present study, neonatal exposure to VCR significantly disrupted the ontogeny of key sensorimotor reflexes. Negative geotaxis, which relies on vestibular input and postural coordination, was impaired specifically at PND 20, indicating a transient disruption in the maturation of neural circuits associated with spatial orientation and motor control. This period corresponds to a critical window of cerebellar and brainstem development in rodents, during which axonal growth, synaptogenesis, and myelination are particularly active and vulnerable to neurotoxic insults (Luhmann; Fukuda, 2020).

More strikingly, vibrissae placement reflexes were affected in both male and female pups at PNDs 20 and 25, suggesting a more persistent neurodevelopmental alteration. The execution of this reflex depends on the integrity of cranial nerves (notably the trigeminal nerve), brainstem nuclei, and sensorimotor integration pathways (Costa *et al.*, 2017). VCR, known for its potent antimicrotubule activity via disruption of microtubule dynamics, can interfere with axonal transport, synaptic stabilization, and neurogenesis—mechanisms essential for the functional maturation of these pathways (Schappacher *et al.*, 2019b).

Indeed, these findings align with the histopathological diagnosis observed in our study. Neonatal exposure to VCR induced marked neurodegenerative changes in both male and female rats. Notably, the presence of vacuoles in the motor neuron soma may disrupt the ontogeny of sensorimotor reflexes.

Additionally, macrophages containing digestion chambers suggest an ongoing neurotoxic process within the spinal cord, potentially impairing sensory responses and neurodevelopment. The relevance of this observation is underscored by the central role of the spinal cord as the primary integration center for early reflex responses, including limb withdrawal and nociception. Supporting this evidence, a recent study from our group reported VCR-induced Wallerian degeneration in aged rats, reinforcing the notion that both neonatal and elderly populations exhibit heightened susceptibility to VCR-mediated neurotoxicity (da Motta *et al.*, 2024).

Additionally, VCR has been shown to induce oxidative stress, mitochondrial dysfunction, and glial activation in the developing nervous system (Chen; Wang; Song, 2020; da Motta *et al.*, 2024; Schappacher; Styczynski; Baccei, 2017-; Shao *et al.*, 2024). Such alterations may impair the survival and differentiation of neuronal populations during key developmental stages, leading to lasting behavioral and functional deficits (Chen *et al.*, 2024). The persistence of vibrissae placement impairment until PND 25 supports the hypothesis of a sustained neurotoxic effect, potentially reflecting either delayed neurodevelopment or irreversible structural damage.

These neurodevelopmental impairments are closely associated with the oxidative damage observed in this study. Elevated lipid peroxidation—particularly prominent in the cortex, hippocampus, and hypothalamus of VCR-exposed females, and in the spinal cord of males—suggests a neurotoxic imbalance potentially contributing to disrupted maturation. The significant depletion of NPSH levels following VCR administration further indicates redox imbalance and a state of oxidative stress. Taken together, these findings highlight oxidative stress as a

key pathophysiological mechanism underlying VCR-induced neurotoxicity and developmental impairment (Alenezi, 2023a; Shayesteh *et al.*, 2022b).

Still, these findings align with previous experimental studies indicating that chemotherapeutic agents can impair reflex development and neurobehavioral maturation when administered during early postnatal life (Hathway *et al.*, 2018). Our results extend this evidence by showing that even a single neonatal exposure to VCR is sufficient to alter the trajectory of reflex acquisition and performance, reinforcing the need to monitor subtle neurodevelopmental outcomes in pediatric patients exposed to chemotherapeutic agents during critical windows of CNS development.

Returning to the idea of the damage observed in behavioral tests and linking it to the damage verified through biochemical and histological tests also observed here. In the righting reflex test, neonatal rats exposed to VCR exhibited significant delays in returning to the ventral position on both PND 20 and 25, indicating impaired sensorimotor coordination and neurodevelopmental delay. This reflex, which normally matures rapidly in early postnatal life, depends on the functional integrity of spinal circuits, brainstem pathways, and early myelination processes. Previous studies have demonstrated that VCR interferes with microtubule assembly and axonal transport, leading to neurodevelopmental delays and peripheral neuropathies (Burt *et al.*, 2019; Wang *et al.*, 2000b). Additionally, VCR-induced oxidative stress and mitochondrial dysfunction have been shown to disrupt neuronal signaling during critical developmental windows (Chen; Wang; Song, 2020; Shayesteh *et al.*, 2022b).

The persistent impairment in righting reflex observed in neonatal rats exposed to VCR suggests functional disruption in the maturation of sensorimotor

pathways, likely underpinned by mitochondrial dysfunction. Central to this process is the dysregulation of the *PINK-1/PARKIN* pathway, a key mitochondrial quality control mechanism that mediates mitophagy under conditions of oxidative stress and organellar damage (Eltokhy; Toema; El-Deeb, 2022; Khidr *et al.*, 2023). In healthy mitochondria, *PINK-1* is rapidly imported and degraded; however, under mitochondrial depolarization, *PINK-1* accumulates on the outer mitochondrial membrane, where it phosphorylates and recruits *PARKIN*, promoting the ubiquitination of outer membrane proteins and subsequent mitophagy (Eltokhy; Toema; El-Deeb, 2022). In this study, sex-specific expression patterns of *PINK-1* and *PARKIN* in VCR-exposed neonates reveal differential responses to mitochondrial stress. Notably, the spinal cord of female rats showed a coordinated upregulation of both *PINK-1* and *PARKIN*, suggesting an active and non-disrupted mitophagic response aimed at clearing dysfunctional mitochondria. This finding aligns with elevated TBARS levels, indicating oxidative stress likely originating from mitochondrial sources. Conversely, male neonates exhibited reduced *PINK-1* expression in the spinal cord, which may compromise mitochondrial surveillance and the initiation of mitophagy, potentially exacerbating neurotoxicity. Interestingly, an increase in *PARKIN* expression in the cortex of females was observed despite no concurrent elevation in *PINK-1*, suggesting alternative activation mechanisms of *PARKIN* or a compensatory response to persistent mitochondrial damage. Taken together, these findings highlight a sexually dimorphic regulation of mitophagy under VCR-induced stress and suggest that mitochondrial quality control failure—particularly through impaired *PINK-1* signaling—may contribute to prolonged neural dysfunction in males, while females engage more robust compensatory mechanisms to mitigate

neurotoxicity.

Furthermore, both sexes exhibited a marked downregulation of MCL-1 mRNA in the cortex and spinal cord. As an anti-apoptotic member of the BCL-2 family, MCL-1 plays a pivotal role in maintaining neuronal viability by sequestering pro-apoptotic effectors such as BAX and BAK, thereby preventing mitochondrial outer membrane permeabilization and subsequent cytochrome c release (Tantawy *et al.*, 2023; Wolf *et al.*, 2023). Once released into the cytosol, cytochrome c binds to Apoptotic protease activating factor 1 (Apaf-1) and ATP, promoting the formation of the apoptosome complex, which subsequently recruits and activates caspase-9, thereby initiating the caspase cascade that culminates in apoptotic cell death (Tantawy *et al.*, 2023).

The observed suppression of MCL-1 suggests a diminished anti-apoptotic defense, rendering neurons more susceptible to programmed cell death (Tantawy *et al.*, 2023). This finding, combined with impaired mitophagy signaling via the *PINK-1/PARKIN* axis, indicates that VCR exposure compromises mitochondrial quality control on multiple fronts: (i) by enhancing oxidative stress, initiated through excessive ROS production in the electron transport chain; (ii) by impairing mitochondrial clearance mechanisms, as evidenced by dysregulation of *PINK-1* and *PARKIN*; and (iii) by downregulating survival pathways dependent on *MCL-1*. Altogether, these alterations converge to promote mitochondrial dysfunction and apoptotic susceptibility. Consistent with this, histopathological analysis revealed the presence of macrophages within digestive chambers in the spinal cord, suggesting active phagocytosis amid ongoing neuroinflammation. However, the inhibition of *MCL-1* may also compromise macrophage viability, predisposing these cells to functional exhaustion or apoptosis, thereby

perpetuating ineffective clearance of damaged cells and sustaining the inflammatory milieu characteristic of VCR-induced neurotoxicity.

At PND 25, VCR-exposed neonatal rats of both sexes exhibited marked impairments in specific neurodevelopmental reflexes. Startle response was significantly blunted, suggesting altered sensory processing and motor coordination. Furthermore, deficits in postural reflexes were evident during the free-fall acceleration test, and latency to respond in the cliff aversion test was significantly increased, indicating delayed integration of sensorimotor and protective responses. These findings collectively support the notion that VCR disrupts the maturation of essential reflex pathways involved in environmental perception and motor reaction (Brown; Ross; Belsky, 2025).

Molecular evidence from our study offers mechanistic insight into the behavioral deficits observed following VCR exposure, highlighting a complex interplay between mitochondrial dysfunction, apoptotic signaling, and sex-specific vulnerability. VCR administration resulted in a region- and sex-dependent modulation of apoptosis-related gene expression. Notably, CASPASE-3 mRNA levels were upregulated in the cerebral cortex of females, indicating activation of the executioner phase of apoptosis, while a downregulation in the spinal cord of males may reflect impaired apoptotic clearance or altered compensatory responses. Furthermore, increased expression of BAX in the cortex of both sexes reinforces the engagement of the intrinsic (mitochondria-mediated) apoptotic pathway, as BAX promotes mitochondrial outer membrane permeabilization and the subsequent release of cytochrome c (Li *et al.*, 2018; Zhu *et al.*, 2025). This pro-apoptotic shift was paralleled by the downregulation of *MCL-1*, an essential anti-apoptotic regulator of mitochondrial integrity, in both the cortex and spinal

cord, suggesting a compromised cellular capacity to counteract apoptotic stimuli (elucidated in this study). Importantly, these alterations coincided with a dysregulation of the *PINK-1/PARKIN* mitophagy pathway, particularly in male spinal cords where reduced *PINK-1* expression may hinder mitochondrial quality control. Together, these findings indicate that VCR-induced oxidative stress likely initiates a cascade of mitochondrial damage that overwhelms mitophagy and anti-apoptotic defenses, culminating in enhanced apoptotic susceptibility and neuronal dysfunction.

This mechanistic convergence supports the histopathological and behavioral outcomes observed, and underscores the critical role of mitochondrial integrity in mediating VCR neurotoxicity. The convergence of these molecular alterations with impaired reflexes such as delayed cliff aversion and altered righting responses suggests that VCR-induced neurotoxicity disrupts the refinement of neural circuits necessary for basic survival behavior (Cheon *et al.*, 2017b; Filippi-Chiela *et al.*, 2022). Apoptotic signaling in the cortex may contribute to deficits in environmental perception and higher-order integration, while changes in the spinal cord may impair the relay and execution of motor commands (Guha; Singh; Kumar, 2023a; Sampathkumar *et al.*, 2021). These findings underscore the importance of evaluating sex-specific and region-specific responses to chemotherapeutic agents during critical periods of neurodevelopment, as even subtle gene expression imbalances may translate into profound functional impairments.

It has been reported that VCR can trigger peripheral neuropathy due to the severity of neurotoxicity and, in more advanced cases of neurological and motor damage, it can lead to the worsening and development of motor neuropathy. In

fact, this is a clinical concern that has already been demonstrated in studies with children undergoing chemotherapy based on VCR (Tunjungsari; Gunawan; Ugrasena, 2021). This is because it appears that the sympathetic autonomic system can also be affected in motor neuropathy triggered by VCR (Tunjungsari; Gunawan; Ugrasena, 2021). Therefore, we emphasize that the pathophysiological approach demonstrated here through behavioral, clinical, biochemical and gene expression assays are of utmost importance to elucidate the pathophysiology of neuropathy induced by VCR in pediatric patients.

In this sense, we verified in our study parameters that can be associated with motor neuropathy - gait analysis and rotarod. Both tests indicated that VCR promoted impairments in locomotion, motor skills and coordination in males and females in both rotarod and gait analysis tests. These functional deficits are consistent with motor neuropathy, a condition frequently associated with VCR-induced neurotoxicity (Alenezi, 2022; Geisler, 2021b). Previous clinical reports have demonstrated that children undergoing VCR-based chemotherapy often develop motor neuropathies, with symptoms such as reduced motor control, muscle weakness, and gait abnormalities (Tunjungsari; Gunawan; Ugrasena, 2021; Uittenboogaard *et al.*, 2022). Furthermore, a systematic review conducted by Gilchrist *et al.* (Gilchrist; Tanner, 2016) reinforces these findings, indicating that VCR-induced peripheral neuropathy in children can affect motor, sensory, and autonomic nerves. Motor symptoms include weakness in the extremities, difficulty walking, and deterioration of reflexes and fine motor skills (Alenezi, 2022; van de Velde *et al.*, 2021).

Furthermore, our findings indicate the development of peripheral neuropathy, as evidenced by VCR-induced mechanical and thermal hyperalgesia

in both male and female rats. These results suggest that, despite partial impairments in motor function and reflex responses, nociceptive sensitivity remains heightened, leading to pronounced behavioral reactions to cold and heat stimuli. This hyperalgesic profile may be associated with the neurotoxic effects of VCR on sensory neurons, particularly in the dorsal root ganglia and spinal cord, regions known to be vulnerable to chemotherapeutic agents (Takeda; Takahashi; Matsumoto, 2012; Taves *et al.*, 2013).

In addition, the imbalance in redox homeostasis and mitochondrial dysfunction triggered by VCR, as demonstrated in our biochemical assays, may exacerbate neuronal excitability and pain transmission. Supporting this hypothesis, studies have shown that VCR can upregulate pro-nociceptive mediators, including inflammatory cytokines and ion channels such as TRPV1 and Nav1.7, which are known to enhance pain sensitivity (Starobova; Vetter, 2017a).

One plausible mechanism underlying this hyperalgesic profile is increased neuronal excitability, potentially driven by mitochondrial dysfunction and oxidative imbalance, both of which were evidenced in our biochemical assays. Additionally, our results demonstrate a significant increase in the activity of Ca^{2+} -ATPase and Mg^{2+} -ATPase in key regions of the central nervous system following VCR exposure. Specifically, Ca^{2+} -ATPase activity was elevated in the cerebral cortex, hippocampus, and cerebellum of both sexes, and selectively in the spinal cord of VCR-exposed females. Similarly, Mg^{2+} -ATPase activity was increased in the hippocampus of both sexes, the cerebellum of males, and in the spinal cord and hypothalamus of both sexes. These ATPases are crucial for maintaining ionic gradients and calcium homeostasis, both of which are intimately linked to

neuronal excitability, synaptic transmission, and neuroplasticity (Holliday, 2017).

Dysregulated ATPase activity may contribute to altered intracellular Ca^{2+} levels and membrane potential instability, further amplifying excitatory signaling and promoting central sensitization (Groten; MacVicar, 2022; Guha; Singh; Kumar, 2023b). In this context, the overactivation of ATPases may represent a compensatory response to VCR-induced cytotoxic stress, but paradoxically, it may also facilitate maladaptive neuronal activity and pain hypersensitivity.

To get a sense of the general idea and complexity of the pathophysiological pathway observed here, we can connect the biochemical, histopathological and gene expression findings. The histopathological findings in VCR-treated neonates—particularly the presence of cytoplasmic vacuolization in motor neurons and the infiltration of macrophages containing phagocytic chambers—point to active neurodegeneration and neuronal stress in the spinal cord. These structural alterations are consistent with mitochondrial dysfunction and neuroinflammatory responses (da Motta *et al.*, 2024; Shayesteh *et al.*, 2022b). Corroborating this, the observed dysregulation of mitochondrial-related genes and enzymes reinforces the hypothesis of exacerbated neuronal excitability and apoptotic signaling as central mechanisms in VCR-induced neuropathy. Specifically, we found upregulation of Ca^{2+} - and Mg^{2+} -ATPase activity in multiple CNS regions, which may reflect a compensatory attempt to restore ionic homeostasis under conditions of mitochondrial stress but could also contribute to calcium overload and excitotoxicity. Concurrently, the marked decrease in *MCL-1* mRNA expression—an anti-apoptotic regulator—suggests reduced cellular resilience against programmed cell death, especially in the cortex and spinal cord of both sexes. In parallel, *BAX* expression, a pro-apoptotic

marker, was elevated in the cortex of both male and female rats, indicating enhanced apoptotic drive.

The differential expression of mitophagy markers further supports this scenario: while *PINK-1* expression decreased in males but increased in females within the spinal cord, *PARKIN* expression was elevated exclusively in the cortex and spinal cord of females. This sex-specific dysregulation in the *PINK-1/PARKIN* axis may signal altered mitochondrial quality control mechanisms, contributing to region-specific vulnerabilities and differential neurodegenerative outcomes (Khidr *et al.*, 2023). Collectively, these findings depict a convergent pathophysiological framework in which mitochondrial impairment, oxidative stress, calcium dysregulation, and apoptotic signaling synergistically drive the neurodegenerative process triggered by VCR, manifesting behaviorally as impaired sensorimotor development and increased nociceptive sensitivity (Fig. 13).

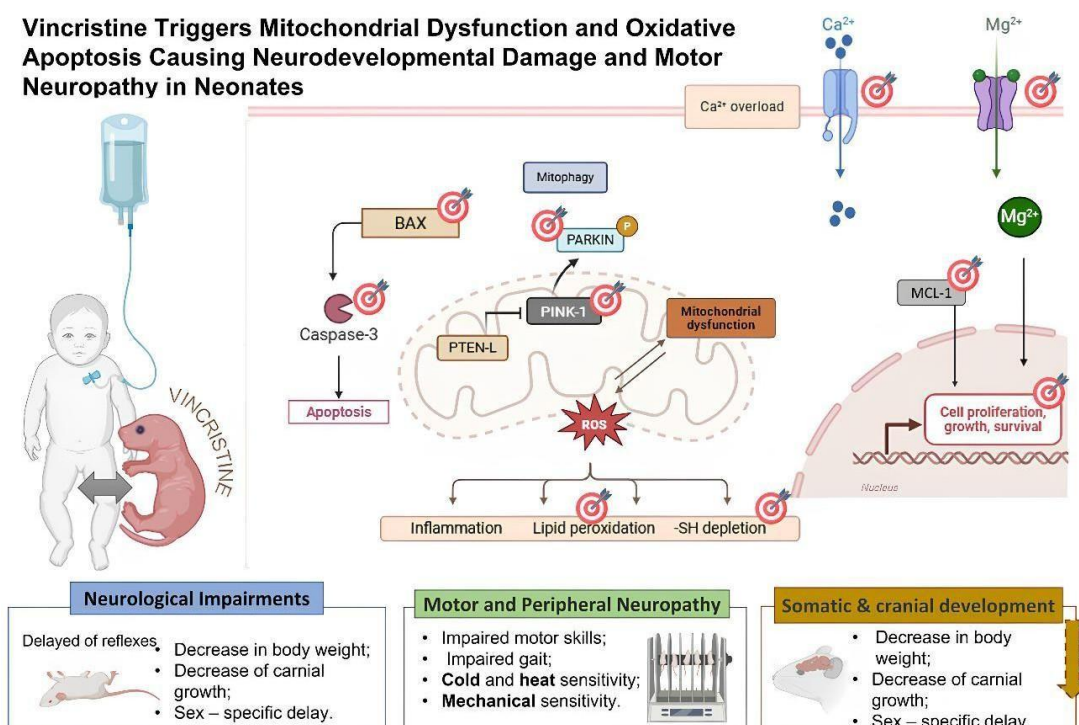


Fig. 13 – Vincristine (VCR) disrupts neurodevelopment by triggering mitochondrial dysfunction, oxidative stress, and apoptosis, leading to reflex delay, motor impairment, and peripheral neuropathy in neonatal rats. VCR administration during early life causes Ca^{2+} overload and Mg^{2+} dysregulation, increasing the activity of Ca^{2+} - and Mg^{2+} -ATPases and contributing to neuronal hyperexcitability. VCR activates BCL2-associated X protein (BAX) and caspase-3, promoting apoptosis, while dysregulation of the PTEN-induced putative kinase 1 (PINK-1)/Parkin RBR E3 ubiquitin protein ligase (PARKIN) pathway impairs mitophagy, resulting in mitochondrial dysfunction and excessive generation of reactive oxygen species (ROS). This oxidative imbalance is evidenced by lipid peroxidation and non-protein sulfhydryl (NPSH) depletion. The consequent neurotoxicity manifests as delayed reflex ontogeny, impaired motor coordination, and peripheral neuropathy characterized by mechanical and thermal hyperalgesia. Histological analysis confirms spinal cord degeneration and inflammation, while reduced myeloid cell leukemia 1 (MCL-1) expression indicates impaired neuronal survival and growth. Together, these effects highlight the risk of neurodevelopmental damage from VCR-based chemotherapy in pediatric patients.

Conclusions

Early-life exposure to VCR disrupts key neurodevelopmental processes, impairing sensorimotor reflexes, motor coordination, and nociceptive responses in neonatal rats. These functional deficits are associated with oxidative stress, neuroinflammation, mitochondrial dysfunction, and apoptosis. Collectively, these findings highlight the neurotoxic risk of VCR during critical windows of brain

development and underscore the need for enhanced neurodevelopmental monitoring in pediatric oncology.

Acknowledgments

The authors gratefully acknowledge the financial support and scholarships provided by the Brazilian funding agencies: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS), and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES). The authors also thank the L'ORÉAL-UNESCO-ABC For Women in Science program for support.

Funding Declaration

This study received financial support and scholarships from the following Brazilian agencies: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) (312747/2020-9, 406118/2021-3, 442284/2023-3), Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS) (RITES 22/2551-0000389-3, PDJ 23/2551-0001861-6; 24/2551-0001948-0). This study was also financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) - Finance Code 001. EAW is a recipient of a CNPq fellowship.

Author contributions

KPM conceived and designed the study. KPM, VMER, APBW, and CARF performed the biochemical and behavioral analyses. JVZE and MPS were

responsible for the histological analysis. KPM and EBB were responsible for the gene expression analysis. KPM and EAW wrote the manuscript. EAW supervised the study. All authors approved the final version of the manuscript.

Data Availability

All datasets generated and analyzed during this study are included in this article. Materials are available upon request.

Declarations

Ethics Approval Animal - care and all experimental procedures were conducted in compliance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH publication no. 80–23, revised in 1996) and in accordance with the Committee on Care and Use of Experimental Animal Resources, Federal University of Pelotas, Brazil (CEUA-UFPeI) (038650/2021-19). All efforts were made to minimize the number of animals used and their suffering.

Consent to Participate - Not applicable.

Consent for Publication - Not applicable.

Conflict of Interest - The authors declare no competing interests

Generative AI and AI-assisted technologies in the writing process - During the preparation of this work, the authors used GPTchat (OpenAI, 2025) to improve readability and language. After using this tool, the authors have reviewed and edited the content as necessary and take full responsibility for the content of the publication.

References

AEBI, H. Catalase in vitro. **Methods in Enzymology**, [s. l.], v. 105, p. 121–126, 1984.

AKSENOV, M. Y.; MARKESBERY, W. R. Changes in thiol content and expression of glutathione redox system genes in the hippocampus and cerebellum in Alzheimer's disease. **Neuroscience Letters**, [s. l.], v. 302, n. 2–3, p. 141–145, 2001.

ALAMRI, F. F. *et al.* Applicability of the grip strength and automated von Frey tactile sensitivity tests in the mouse photothrombotic model of stroke. **Behavioural Brain Research**, [s. l.], v. 336, n. August 2017, p. 250–255, 2018a.

ALAMRI, F. F. *et al.* Applicability of the grip strength and automated von Frey tactile sensitivity tests in the mouse photothrombotic model of stroke. **Behavioural Brain Research**, [s. l.], v. 336, n. August 2017, p. 250–255, 2018b. Disponível em: <http://dx.doi.org/10.1016/j.bbr.2017.09.008>.

ALBENSI, B. C. What Is Nuclear Factor Kappa B (NF-κB) Doing in and to the Mitochondrion?. **Frontiers in Cell and Developmental Biology**, [s. l.], v. 7, 2019a.

ALBENSI, B. C. What Is Nuclear Factor Kappa B (NF-κB) Doing in and to the Mitochondrion?. **Frontiers in Cell and Developmental Biology**, [s. l.], v. 7, 2019b. Disponível em: <https://www.frontiersin.org/article/10.3389/fcell.2019.00154/full>.

ALENEZI, S. K. The Ameliorative Effect of Thymoquinone on Vincristine-Induced Peripheral Neuropathy in Mice by Modulating Cellular Oxidative Stress and Cytokine. **Life**, [s. l.], v. 13, n. 1, p. 101, 2022.

ALENEZI, S. K. The Ameliorative Effect of Thymoquinone on Vincristine-Induced Peripheral Neuropathy in Mice by Modulating Cellular Oxidative Stress and Cytokine. **Life**, [s. l.], v. 13, n. 1, 2023a.

ALENEZI, S. K. The Ameliorative Effect of Thymoquinone on Vincristine-Induced Peripheral Neuropathy in Mice by Modulating Cellular Oxidative Stress and Cytokine. **Life**, [s. l.], v. 13, n. 1, 2023b.

ALWHAIBI, A. M. *et al.* Vincristine-Induced Neuropathy in Patients Diagnosed with Solid and Hematological Malignancies: The Role of Dose Rounding. **Journal of Clinical Medicine**, [s. l.], v. 12, n. 17, p. 5662, 2023.

AN, R. *et al.* Methylcobalamin Protects Melanocytes from H₂O₂-Induced Oxidative Stress by Activating the Nrf2/HO-1 Pathway. **Drug Design, Development and Therapy**, [s. l.], v. Volume 15, p. 4837–4848, 2021.

ANAND, K. J. S.; HICKEY, P. R. Pain and Its Effects in the Human Neonate and Fetus. **New England Journal of Medicine**, [s. l.], v. 317, n. 21, p. 1321–1329, 1987.

ANBALAGAN, M. *et al.* Post-translational modifications of nuclear receptors and human disease. **Nuclear receptor signaling**, [s. l.], v. 10, n. Figure 1, 2012.

ARETI, A. *et al.* Oxidative stress and nerve damage: Role in chemotherapy induced peripheral neuropathy. **Redox Biology**, [s. l.], v. 2, n. 1, p. 289–295, 2014.

BAE, E. H.; GREENWALD, M. K.; SCHWARTZ, A. G. Chemotherapy-Induced Peripheral Neuropathy: Mechanisms and Therapeutic Avenues. **Neurotherapeutics**, [s. l.], v. 18, n. 4, p. 2384–2396, 2021.

BAIG, M. A.; PANCHAL, S. S. Streptozotocin-Induced Diabetes Mellitus in Neonatal Rats: An Insight into its Applications to Induce Diabetic Complications. **Current Diabetes Reviews**, [s. l.], v. 16, n. 1, p. 26–39, 2019.

BAKER, D. W. History of The Joint Commission's Pain Standards. **JAMA**, [s. l.], v. 317,

n. 11, p. 1117, 2017.

BARTH, A. *et al.* 7-Chloro-4-(Phenylselanyl) Quinoline with Memory Enhancer Action in Aging Rats: Modulation of Neuroplasticity, Acetylcholinesterase Activity, and Cholesterol Levels. **Molecular Neurobiology**, [s. l.], 2019a.

BARTH, A. *et al.* 7-Chloro-4-(Phenylselanyl) Quinoline with Memory Enhancer Action in Aging Rats: Modulation of Neuroplasticity, Acetylcholinesterase Activity, and Cholesterol Levels. **Molecular Neurobiology**, [s. l.], 2019b.

BARTLEY, E. J.; FILLINGIM, R. B. Sex differences in pain: a brief review of clinical and experimental findings. **British Journal of Anaesthesia**, [s. l.], v. 111, n. 1, p. 52–58, 2013.

BEJČEK, J. *et al.* Na⁺/K⁺-atpase revisited: On its mechanism of action, role in cancer, and activity modulation. **Molecules**, [s. l.], v. 26, n. 7, 2021.

BENJAMIN, R. S. *et al.* Chemotherapy for Bone Sarcomas in Adults: The MD Anderson Experience. **American Society of Clinical Oncology Educational Book**, [s. l.], n. 35, p. e656–e660, 2015.

BENNETT, M. I. *et al.* Prevalence and aetiology of neuropathic pain in cancer patients: A systematic review. **Pain**, [s. l.], v. 153, n. 2, p. 359–365, 2012.

BEYER, C.; KAROLCZAK, M. Estrogenic stimulation of neurite growth in midbrain dopaminergic neurons depends on cAMP/protein kinase A signalling. **Journal of Neuroscience Research**, [s. l.], v. 59, n. 1, p. 107–116, 2000a.

BEYER, C.; KAROLCZAK, M. Estrogenic stimulation of neurite growth in midbrain dopaminergic neurons depends on cAMP/protein kinase A signalling. **Journal of Neuroscience Research**, [s. l.], v. 59, n. 1, p. 107–116, 2000b.

BHATT, S. *et al.* 5-HT₃ Receptor Antagonism: A Potential Therapeutic Approach for the Treatment of Depression and other Disorders. **Current Neuropharmacology**, [s. l.], v. 19, n. 9, p. 1545–1559, 2020.

BILBERG, A. *et al.* High prevalence of widespread pain in women with early rheumatoid arthritis. **Scandinavian Journal of Rheumatology**, [s. l.], v. 47, n. 6, p. 447–454, 2018. Disponível em: <https://doi.org/10.1080/03009742.2018.1447683>.

BLUETTE, C. T. *et al.* Behavioral, Histopathologic, and Molecular Biological Responses of Nanoparticle- and Solution-Based Formulations of Vincristine in Mice. **International Journal of Toxicology**, [s. l.], v. 40, n. 1, p. 40–51, 2021. Disponível em: <http://journals.sagepub.com/doi/10.1177/1091581820968255>.

BRADFORD, M. M. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. **Analytical biochemistry**, [s. l.], v. 72, n. 1–2, p. 248–254, 1976a.

BRADFORD, M. M. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. **Analytical biochemistry**, [s. l.], v. 72, n. 1–2, p. 248–254, 1976b. Disponível em: <https://www.sciencedirect.com/science/article/abs/pii/0003269776905273>.

BREIVIK, H. *et al.* Cancer-related pain: a pan-European survey of prevalence,

treatment, and patient attitudes. **Annals of Oncology**, [s. l.], v. 20, n. 8, p. 1420–1433, 2009.

BRIGATTE, P. *et al.* Walker 256 Tumor-Bearing Rats as a Model to Study Cancer Pain. **The Journal of Pain**, [s. l.], v. 8, n. 5, p. 412–421, 2007.

BROWN, A. M.; ROSS, A.; BELSKY, J. A. Vincristine-Induced Autonomic Neuropathy Diagnosed via Quantitative Sudomotor Axon Reflex Sweat Test in an Adolescent Patient With Acute Leukemia. **Pediatric Blood & Cancer**, [s. l.], 2025.

BROZOVIĆ, G. Cancer Pain and Therapy. **Acta Clinica Croatica**, [s. l.], 2022.

BUJALSKA, M.; GUMUŁKA, S. W. Effect of cyclooxygenase and nitric oxide synthase inhibitors on vincristine induced hyperalgesia in rats. **Pharmacological Reports**, [s. l.], v. 60, n. 5, p. 735–741, 2008.

BURT, R. *et al.* Activated stromal cells transfer mitochondria to rescue acute lymphoblastic leukemia cells from oxidative stress. **Blood**, [s. l.], v. 134, n. 17, p. 1415–1429, 2019.

BUSCH, C. J.; BINDER, C. J. Malondialdehyde epitopes as mediators of sterile inflammation. **Biochimica et Biophysica Acta - Molecular and Cell Biology of Lipids**, [s. l.], v. 1862, n. 4, p. 398–406, 2017. Disponível em: <http://dx.doi.org/10.1016/j.bbalip.2016.06.016>.

CALIXTO-CAMPOS, C. *et al.* The Ehrlich Tumor Induces Pain-Like Behavior in Mice: A Novel Model of Cancer Pain for Pathophysiological Studies and Pharmacological Screening. **BioMed Research International**, [s. l.], v. 2013, p. 1–12, 2013.

CANTA, A.; POZZI, E.; CAROZZI, V. A. Mitochondrial dysfunction in chemotherapy-induced peripheral neuropathy (CIPN). **Toxics**, [s. l.], v. 3, n. 2, p. 198–223, 2015a.

CANTA, A.; POZZI, E.; CAROZZI, V. A. Mitochondrial dysfunction in chemotherapy-induced peripheral neuropathy (CIPN). **Toxics**, [s. l.], v. 3, n. 2, p. 198–223, 2015b.

CARACENI, A.; SHKODRA, M. Cancer Pain Assessment and Classification. **Cancers**, [s. l.], v. 11, n. 4, p. 510, 2019.

CASSOL, G. *et al.* A role of Na⁺, K⁺ -ATPase in spatial memory deficits and inflammatory/oxidative stress after recurrent concussion in adolescent rats. **Brain Research Bulletin**, [s. l.], v. 180, p. 1–11, 2022a.

CASSOL, G. *et al.* A role of Na⁺, K⁺ -ATPase in spatial memory deficits and inflammatory/oxidative stress after recurrent concussion in adolescent rats. **Brain Research Bulletin**, [s. l.], v. 180, p. 1–11, 2022b. Disponível em: <https://linkinghub.elsevier.com/retrieve/pii/S0361923021003543>.

CAVIEDES, A. *et al.* BDNF/NF-κB Signaling in the Neurobiology of Depression. **Current Pharmaceutical Design**, [s. l.], v. 23, n. 21, 2017a.

CAVIEDES, A. *et al.* BDNF/NF-κB Signaling in the Neurobiology of Depression. **Current Pharmaceutical Design**, [s. l.], v. 23, n. 21, 2017b. Disponível em: <http://www.eurekaselect.com/149163/article>.

CHANCAY, M. G.; GUENDSECHADZE, S. N.; BLANCO, I. Types of pain and their

psychosocial impact in women with rheumatoid arthritis. **Women's Midlife Health**, [s. l.], v. 5, n. 1, p. 1–9, 2019.

CHANTAL, T. *et al.* ACTION OF VINCA ALKALOIDES ON CALCIUM MOVEMENTS THROUGH MITOCHONDRIAL MEMBRANE. **Pharmacological Research Communications**, [s. l.], v. 18, n. 6, p. 519–528, 1986.

CHEN, C. *et al.* Body weight, frailty, and chronic pain in older adults: A cross-sectional study. **BMC Geriatrics**, [s. l.], v. 19, n. 1, p. 1–10, 2019.

CHEN, X. *et al.* Current understanding of the molecular mechanisms of chemotherapy-induced peripheral neuropathy. **Frontiers in Molecular Neuroscience**, [s. l.], v. 17, 2024.

CHEN, S. P. *et al.* Involvement of hippocampal acetylcholinergic receptors in electroacupuncture analgesia in neuropathic pain rats. **Behavioral and Brain Functions**, [s. l.], v. 12, n. 1, p. 1–10, 2016.

CHEN, Q. M. Nrf2 for protection against oxidant generation and mitochondrial damage in cardiac injury. **Free Radical Biology and Medicine**, [s. l.], v. 179, p. 133–143, 2022.

CHEN, X.-J.; WANG, L.; SONG, X.-Y. Mitoquinone alleviates vincristine-induced neuropathic pain through inhibiting oxidative stress and apoptosis via the improvement of mitochondrial dysfunction. **Biomedicine & Pharmacotherapy**, [s. l.], v. 125, p. 110003, 2020.

CHENG, H. *et al.* Case report: Wallerian degeneration: The innate-immune response to adult-onset Still's disease peripheral nerve injury. **Frontiers in Neurology**, [s. l.], v. 13, 2022.

CHEON, J. H. *et al.* P-gp Inhibition by XL019, a JAK2 Inhibitor, Increases Apoptosis of Vincristine-treated Resistant KBV20C Cells with Increased p21 and pH2AX Expression. **Anticancer Research**, [s. l.], v. 37, n. 12, 2017a.

CHEON, J. H. *et al.* P-gp Inhibition by XL019, a JAK2 Inhibitor, Increases Apoptosis of Vincristine-treated Resistant KBV20C Cells with Increased p21 and pH2AX Expression. **Anticancer Research**, [s. l.], v. 37, n. 12, 2017b. Disponível em: <http://ar.iijournals.org/content/37/12/6761.abstract>.

CHIBA, T. *et al.* Vincristine increased spinal cord substance P levels in a peripheral neuropathy rat model. **Drug and Chemical Toxicology**, [s. l.], v. 45, n. 1, p. 393–397, 2022. Disponível em: <https://www.tandfonline.com/doi/full/10.1080/01480545.2019.1706547>.

CHIECHIO, S. *et al.* L-Acetylcarnitine Induces Analgesia by Selectively Up-Regulating mGlu2 Metabotropic Glutamate Receptors. **Molecular Pharmacology**, [s. l.], v. 61, n. 5, p. 989–996, 2002.

CHO, S.-H. *et al.* Anti-inflammatory activity of Echinosophora koreensis nakai root extract in lipopolysaccharides-stimulated RAW 264.7 cells and carrageenan-induced mouse paw edema model. **Journal of Ethnopharmacology**, [s. l.], v. 302, p. 115940, 2023.

CLARK, A. K.; MALCANGIO, M. Microglial signalling mechanisms: Cathepsin S and Fractalkine. **Experimental Neurology**, [s. l.], v. 234, n. 2, p. 283–292, 2012.

- COBB, C. A.; COLE, M. P. Oxidative and nitrative stress in neurodegeneration. **Neurobiology of Disease**, [s. l.], v. 84, p. 4–21, 2015. Disponível em: <http://dx.doi.org/10.1016/j.nbd.2015.04.020>.
- COLUZZI, F. *et al.* Pain management in childhood leukemia: Diagnosis and available analgesic treatments. **Cancers**, [s. l.], v. 12, n. 12, p. 1–13, 2020.
- COLVIN, L. A. Chemotherapy-induced peripheral neuropathy: where are we now?. **Pain**, [s. l.], v. 160, n. 1, p. S1–S10, 2019.
- COOK, K. M. *et al.* Experience of early-life pain in premature infants is associated with atypical cerebellar development and later neurodevelopmental deficits. **BMC Medicine**, [s. l.], v. 21, n. 1, p. 435, 2023.
- COSTA, Y. M. *et al.* Reliability of the nociceptive blink reflex evoked by electrical stimulation of the trigeminal nerve in humans. **Clinical Oral Investigations**, [s. l.], v. 21, n. 8, p. 2453–2463, 2017.
- COX, B. C. *et al.* Transport of multiple nicotinic acetylcholine receptors in the rat optic nerve: High densities of receptors containing $\alpha 6$ and $\beta 3$ subunits. **Journal of Neurochemistry**, [s. l.], v. 105, n. 5, p. 1924–1938, 2008.
- CUREALL FRAMEWORK: WHO GLOBAL INITIATIVE FOR CHILDHOOD CANCER INCREASING ACCESS, ADVANCING QUALITY, SAVING LIVES. . [S. l.: s. n.], [s. d.].
- DA MOTTA, K. P. *et al.* Insights into Vincristine-Induced Peripheral Neuropathy in Aged Rats: Wallerian Degeneration, Oxidative Damage, and Alterations in ATPase Enzymes. **ACS Chemical Neuroscience**, [s. l.], v. 15, n. 21, p. 3954–3969, 2024.
- DA MOTTA, K. P. *et al.* The Antinociceptive Responses of MTDZ to Paclitaxel – Induced Peripheral Neuropathy and Acute Nociception in Mice : Behavioral , Pharmacological , and Biochemical Approaches. **Pharmaceuticals**, [s. l.], v. 16, n. 9, p. 1217, 2023.
- DA ROCHA, V. M. E. *et al.* Structure-Activity Relationship of 7-Chloro-4-(Phenylselanyl) Quinoline: Novel Antinociceptive and Anti-Inflammatory Effects in Mice. **Chemistry & Biodiversity**, [s. l.], v. 22, n. 3, 2025.
- DAGNINO, A. P. A.; CAMPOS, M. M. Chronic Pain in the Elderly: Mechanisms and Perspectives. **Frontiers in Human Neuroscience**, [s. l.], v. 16, p. 1–11, 2022.
- DANG, X. *et al.* Alantolactone suppresses inflammation, apoptosis and oxidative stress in cigarette smoke-induced human bronchial epithelial cells through activation of Nrf2/HO-1 and inhibition of the NF- κ B pathways. **Respiratory Research**, [s. l.], v. 21, n. 1, p. 95, 2020.
- DAVIS, R. L. *et al.* Effects of mechanistically distinct NF- κ B inhibitors on glial inducible nitric-oxide synthase expression. **Nitric Oxide**, [s. l.], v. 12, n. 4, p. 200–209, 2005.
- DE FREITAS COUTO, S. *et al.* 7-chloro-4-(phenylselanyl) quinoline prevents dopamine depletion in a *Drosophila melanogaster* model of Parkinson's-like disease. **Journal of Trace Elements in Medicine and Biology**, [s. l.], v. 54, p. 232–243, 2019a. Disponível em: <https://linkinghub.elsevier.com/retrieve/pii/S0946672X1830405X>.

DE FREITAS COUTO, S. *et al.* 7-chloro-4-(phenylselanyl) quinoline prevents dopamine depletion in a *Drosophila melanogaster* model of Parkinson's-like disease. **Journal of Trace Elements in Medicine and Biology**, [s. l.], v. 54, p. 232–243, 2019b.

DE OLIVEIRA, R. L. *et al.* Prospecting for a quinoline containing selenium for comorbidities depression and memory impairment induced by restriction stress in mice. **Psychopharmacology**, [s. l.], v. 239, n. 1, p. 59–81, 2022a. Disponível em: <https://doi.org/10.1007/s00213-021-06039-8>.

DE OLIVEIRA, R. L. *et al.* Prospecting for a quinoline containing selenium for comorbidities depression and memory impairment induced by restriction stress in mice. **Psychopharmacology**, [s. l.], v. 239, n. 1, p. 59–81, 2022b.

DEL RIO, D.; STEWART, A. J.; PELLEGRINI, N. A review of recent studies on malondialdehyde as toxic molecule and biological marker of oxidative stress. **Nutrition, Metabolism and Cardiovascular Diseases**, [s. l.], v. 15, n. 4, p. 316–328, 2005.

DENG, G. Integrative Medicine Therapies for Pain Management in Cancer Patients. **The Cancer Journal**, [s. l.], v. 25, n. 5, p. 343–348, 2019.

DESFORGES, A. D. *et al.* Treatment and diagnosis of chemotherapy-induced peripheral neuropathy: An update. **Biomedicine & Pharmacotherapy**, [s. l.], v. 147, p. 112671, 2022.

DIOUF, B. *et al.* Association of an inherited genetic variant with vincristine-related peripheral neuropathy in children with acute lymphoblastic leukemia Critical revision of the manuscript for important intellectual content: Barthelemy Diouf; HHS Public Access. **Jama**, [s. l.], v. 313, n. 8, p. 815–823, 2015.

DOBRETISOV, M. Neuronal function and alpha3 isoform of the Na/K-ATPase. **Frontiers in Bioscience**, [s. l.], v. 10, n. 1–3, p. 2373, 2005a.

DOBRETISOV, M. Neuronal function and alpha3 isoform of the Na/K-ATPase. **Frontiers in Bioscience**, [s. l.], v. 10, n. 1–3, p. 2373, 2005b. Disponível em: <https://imrpess.com/journal/FBL/10/3/10.2741/1704>.

DOS SANTOS, L. M. *et al.* Methionine and methionine sulfoxide treatment induces M1/classical macrophage polarization and modulates oxidative stress and purinergic signaling parameters. **Molecular and Cellular Biochemistry**, [s. l.], v. 424, n. 1–2, p. 69–78, 2017.

DUARTE, L. F. B. *et al.* A simple method for the synthesis of 4-arylselanyl-7-chloroquinolines used as in vitro acetylcholinesterase inhibitors and in vivo memory improvement. **Tetrahedron Letters**, [s. l.], v. 58, n. 33, p. 3319–3322, 2017a.

DUARTE, L. F. B. *et al.* Organoselenium compounds from purines: Synthesis of 6-arylselanylpurines with antioxidant and anticholinesterase activities and memory improvement effect. **Bioorganic & Medicinal Chemistry**, [s. l.], v. 25, n. 24, p. 6718–6723, 2017b.

DUPUIS, L. L. *et al.* Anxiety, pain, and nausea during the treatment of standard-risk childhood acute lymphoblastic leukemia: A prospective, longitudinal study from the Children's Oncology Group. **Cancer**, [s. l.], v. 122, n. 7, p. 1116–1125, 2016.

DZIECHCIAŻ, M.; BALICKA-ADAMIK, L.; FILIP, R. The problem of pain in old age.

Annals of agricultural and environmental medicine : AAEM, [s. l.], v. . 1, n. 1, p. 35–38, 2013.

EDINOFF, A. N. *et al.* Selective Serotonin Reuptake Inhibitors and Adverse Effects: A Narrative Review. **Neurology International**, [s. l.], v. 13, n. 3, p. 387–401, 2021.

EDWARDS, R. R. *et al.* The role of psychosocial processes in the development and maintenance of chronic pain disorders. **Pain**, [s. l.], v. 176, n. 1, p. 70–92, 2017.

EIDE, S.; FENG, Z. P. Doxorubicin chemotherapy-induced “chemo-brain”: Meta-analysis. **European Journal of Pharmacology**, [s. l.], v. 881, n. July 2019, p. 173078, 2020.

EL HACHEM, G. *et al.* Advances in pain management for older patients with cancer. **ecancermedicalsecience**, [s. l.], v. 13, 2019.

ELDUFANI, J.; BLAISE, G. The role of acetylcholinesterase inhibitors such as neostigmine and rivastigmine on chronic pain and cognitive function in aging: A review of recent clinical applications. **Alzheimer's and Dementia: Translational Research and Clinical Interventions**, [s. l.], v. 5, p. 175–183, 2019.

ELLMAN, G. L. Tissue Sulfhydryl Groups. **Archives of biochemistry and biophysics**, [s. l.], v. 82, n. 1, p. 70–77, 1959.

ELTOKHY, A. K.; TOEMA, O.; EL-DEEB, O. S. The Correlation Between PINK-1/Parkin Mediated Mitophagy, Endoplasmic Reticulum Stress and Total Polyamines in Pediatric Bronchial Asthma: An Integrated Network of Pathways. **Molecular Biology Reports**, [s. l.], v. 49, n. 1, p. 227–235, 2022.

EVENEPOEL, M. *et al.* Pain Prevalence During Cancer Treatment: A Systematic Review and Meta-Analysis. **Journal of Pain and Symptom Management**, [s. l.], v. 63, n. 3, p. e317–e335, 2022.

FANE, M.; WEERARATNA, A. T. How the ageing microenvironment influences tumour progression. **Nature Reviews Cancer**, [s. l.], v. 20, n. 2, p. 89–106, 2020.

FANG, J. *et al.* Expression Dynamics of Heme Oxygenase-1 in Tumor Cells and the Host Contributes to the Progression of Tumors. **Journal of Personalized Medicine**, [s. l.], v. 11, n. 12, p. 1340, 2021.

FILIPPI-CHIELA, E. C. *et al.* Vincristine promotes differential levels of apoptosis, mitotic catastrophe, and senescence depending on the genetic background of glioblastoma cells. **Toxicology in Vitro**, [s. l.], v. 85, p. 105472, 2022.

FISKE, B. C. H.; SUBBAROW, Y. The colorimetric determination of phosphorus. **The Journal of Biological Chemistry**, [s. l.], v. 66, n. september, p. 375–400, 1925a.

FISKE, B. C. H.; SUBBAROW, Y. The colorimetric determination of phosphorus. **The Journal of Biological Chemistry**, [s. l.], v. 66, n. september, p. 375–400, 1925b.

FITZMAURICE, C. *et al.* Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study Global Burden . **JAMA Oncology**, [s. l.], v. 3, n. 4, p. 524–548, 2017.

FLATTERS, S. J. L.; DOUGHERTY, P. M.; COLVIN, L. A. Clinical and preclinical perspectives on Chemotherapy-Induced Peripheral Neuropathy (CIPN): A narrative review. **British Journal of Anaesthesia**, [s. l.], v. 119, n. 4, p. 737–749, 2017.

FRANÇOIS, A. *et al.* The Low-Threshold Calcium Channel Cav3.2 Determines Low-Threshold Mechanoreceptor Function. **Cell Reports**, [s. l.], v. 10, n. 3, p. 370–382, 2015.

GAUTHIER, I.; TARR, M. J. Visual Object Recognition: Do We (Finally) Know More Now Than We Did?. **Annual Review of Vision Science**, [s. l.], v. 2, n. 1, p. 377–396, 2016.

GEŖGOTEK, A.; SKRZYDLEWSKA, E. Biological effect of protein modifications by lipid peroxidation products. **Chemistry and Physics of Lipids**, [s. l.], v. 221, n. February, p. 46–52, 2019.

GEŖGOTEK, A.; SKRZYDLEWSKA, E. Lipid peroxidation products' role in autophagy regulation. **Free Radical Biology and Medicine**, [s. l.], v. 212, p. 375–383, 2024.

GEISLER, S. Vincristine- and bortezomib-induced neuropathies – from bedside to bench and back. **Experimental Neurology**, [s. l.], v. 336, p. 113519, 2021a.

GEISLER, S. Vincristine- and bortezomib-induced neuropathies – from bedside to bench and back. **Experimental Neurology**, [s. l.], v. 336, p. 113519, 2021b. Disponível em: <https://doi.org/10.1016/j.expneurol.2020.113519>.

GEORGE, E. B.; GLASS, J. D.; GRIFFIN, J. W. Axotomy-induced axonal degeneration is mediated by calcium influx through ion-specific channels. **Journal of Neuroscience**, [s. l.], v. 15, n. 10, p. 6445–6452, 1995.

GILCHRIST, L. S.; MARAIS, L.; TANNER, L. Comparison of two chemotherapy-induced peripheral neuropathy measurement approaches in children. **Supportive Care in Cancer**, [s. l.], v. 22, n. 2, p. 359–366, 2014.

GILCHRIST, L.; TANNER, L. Gait Patterns in Children With Cancer and Vincristine Neuropathy. **Pediatric Physical Therapy**, [s. l.], v. 28, n. 1, p. 16–22, 2016.

GLOBAL CANCER BURDEN GROWING, AMIDST MOUNTING NEED FOR SERVICES. **Saudi medical journal**, [s. l.], v. 45, n. 3, p. 326–327, 2024.

GOESLING, J.; LIN, L. A.; CLAUW, D. J. Psychiatry and Pain Management: at the Intersection of Chronic Pain and Mental Health. **Current Psychiatry Reports**, [s. l.], v. 20, n. 2, 2018.

GOLCHIN, L. *et al.* Pistachio supplementation attenuates motor and cognition impairments induced by cisplatin or vincristine in rats. **Advanced Biomedical Research**, [s. l.], v. 4, n. 1, p. 92, 2015.

GOMBER, S.; DEWAN, P.; CHHONKER, D. Vincristine induced neurotoxicity in cancer patients. **Indian Journal of Pediatrics**, [s. l.], v. 77, n. 1, p. 97–100, 2010a.

GOMBER, S.; DEWAN, P.; CHHONKER, D. Vincristine induced neurotoxicity in cancer patients. **Indian Journal of Pediatrics**, [s. l.], v. 77, n. 1, p. 97–100, 2010b.

GÓMEZ, V. *et al.* Breast cancer–associated macrophages promote tumorigenesis by

suppressing succinate dehydrogenase in tumor cells. **Science Signaling**, [s. l.], v. 13, n. 652, 2020.

GOUVEIA, D. N. *et al.* α -Terpineol reduces cancer pain via modulation of oxidative stress and inhibition of iNOS. **Biomedicine & Pharmacotherapy**, [s. l.], v. 105, p. 652–661, 2018.

GRANT, C. H. *et al.* Multimorbidity and analgesic-related harms: a systematic review. **British Journal of Anaesthesia**, [s. l.], v. 134, n. 6, p. 1717–1745, 2025.

GROTEN, C. J.; MACVICAR, B. A. Mitochondrial Ca^{2+} uptake by the MCU facilitates pyramidal neuron excitability and metabolism during action potential firing. **Communications Biology**, [s. l.], v. 5, n. 1, p. 900, 2022.

GU, C. *et al.* Cancer Cells Promote Immune Regulatory Function of Macrophages by Upregulating Scavenger Receptor MARCO Expression. **The Journal of Immunology**, [s. l.], v. 211, n. 1, p. 57–70, 2023.

GUHA, L.; SINGH, N.; KUMAR, H. Different Ways to Die: Cell Death Pathways and Their Association With Spinal Cord Injury. **Neurospine**, [s. l.], v. 20, n. 2, p. 430–448, 2023a.

GUHA, L.; SINGH, N.; KUMAR, H. Different Ways to Die: Cell Death Pathways and Their Association With Spinal Cord Injury. **Neurospine**, [s. l.], v. 20, n. 2, p. 430–448, 2023b.

HABIF, M. *et al.* Early Long-Term Memory Impairment and Changes in the Expression of Synaptic Plasticity-Associated Genes, in the McGill-R-Thy1-APP Rat Model of Alzheimer's-Like Brain Amyloidosis. **Frontiers in Aging Neuroscience**, [s. l.], v. 12, 2021. Disponível em: <https://www.frontiersin.org/articles/10.3389/fnagi.2020.585873/full>.

HABIG, W. H.; JAKOBY, M. J. P.; B., W. J. Glutathione S-Transferases: The first enzymatic step in mercapturic acid formation. **THE JOURNAL OF BIOLOGICAL CHEMISTRY**, [s. l.], v. 249, n. 22, p. 7130–7139, 1974.

HARRIS, J. C. *et al.* Sustained delivery of vincristine inside an orthotopic mouse sarcoma model decreases tumor growth. **Journal of Pediatric Surgery**, [s. l.], v. 51, n. 12, p. 2058–2062, 2016.

HASHMI, J. A.; DAVIS, K. D. Women experience greater heat pain adaptation and habituation than men. **Pain**, [s. l.], v. 145, n. 3, p. 350–357, 2009a.

HASHMI, J. A.; DAVIS, K. D. Women experience greater heat pain adaptation and habituation than men. **Pain**, [s. l.], v. 145, n. 3, p. 350–357, 2009b. Disponível em: <http://dx.doi.org/10.1016/j.pain.2009.07.002>.

HATHWAY, G. J. *et al.* Cancer Chemotherapy in Early Life Significantly Alters the Maturation of Pain Processing. **Neuroscience**, [s. l.], v. 387, p. 214–229, 2018.

HE, X.; SUN, J.; HUANG, X. Expression of caspase-3, Bax and Bcl-2 in hippocampus of rats with diabetes and subarachnoid hemorrhage. **Experimental and Therapeutic Medicine**, [s. l.], 2017.

HODAPP, J. W.; ALI, S.; DRENDEL, A. L. Bringing It All Together: A Review of the

Challenges in Measuring Children's Satisfaction as a Key Component of Acute Pain Management. **Children**, [s. l.], v. 7, n. 11, p. 243, 2020.

HOLLIDAY, L. S. Vacuolar H⁺-ATPases (V-ATPases) as therapeutic targets: a brief review and recent developments. **Biotarget**, [s. l.], v. 1, n. 7, p. 18–18, 2017.

HONE, A. J.; MCINTOSH, J. M. **Nicotinic Acetylcholine Receptors in Neuropathic and Inflammatory Pain**. [S. l.: s. n.], 2018-. ISSN 1751553X.v. 592

HOOGEN, N. J. van den *et al.* Neonatal Plasticity of the Nociceptive System: Mechanisms, Effects, and Treatment of Repetitive Painful Procedures During NICU Admittance. **Current Pharmaceutical Design**, [s. l.], v. 23, n. 38, p. 5902–5910, 2018.

HORIE, K.; MA, J.; UMEZAWA, K. Inhibition of Canonical NF- κ B Nuclear Localization by (–)-DHMEQ via Impairment of DNA Binding. **Oncology Research Featuring Preclinical and Clinical Cancer Therapeutics**, [s. l.], v. 22, n. 2, p. 105–115, 2015.

HOU, Y. *et al.* Ageing as a risk factor for neurodegenerative disease. **Nature Reviews Neurology**, [s. l.], v. 15, n. 10, p. 565–581, 2019.

HUANG, Y. L. *et al.* Chronic pain and use of analgesics in the elderly: A nationwide population-based study. **Archives of Medical Science**, [s. l.], v. 16, n. 2, p. 627–634, 2020.

ISAKSEN, T. J.; LYKKE-HARTMANN, K. Insights into the Pathology of the α 2-Na⁺/K⁺-ATPase in Neurological Disorders; Lessons from Animal Models. **Frontiers in Physiology**, [s. l.], v. 7, 2016a.

ISAKSEN, T. J.; LYKKE-HARTMANN, K. Insights into the Pathology of the α 2-Na⁺/K⁺-ATPase in Neurological Disorders; Lessons from Animal Models. **Frontiers in Physiology**, [s. l.], v. 7, 2016b. Disponível em: <http://journal.frontiersin.org/Article/10.3389/fphys.2016.00161/abstract>.

JAGANJAC, M. *et al.* The relevance of pathophysiological alterations in redox signaling of 4-hydroxynonenal for pharmacological therapies of major stress-associated diseases. **Free Radical Biology and Medicine**, [s. l.], v. 157, p. 128–153, 2020.

JIANG, K.; SHI, Jinshan; SHI, Jing. Morin Alleviates Vincristine-Induced Neuropathic Pain via Nerve protective Effect and Inhibition of NF- κ B Pathway in Rats. **Cellular and Molecular Neurobiology**, [s. l.], v. 39, n. 6, p. 799–808, 2019a.

JIANG, K.; SHI, Jinshan; SHI, Jing. Morin Alleviates Vincristine-Induced Neuropathic Pain via Nerve protective Effect and Inhibition of NF- κ B Pathway in Rats. **Cellular and Molecular Neurobiology**, [s. l.], v. 39, n. 6, p. 799–808, 2019b. Disponível em: <https://doi.org/10.1007/s10571-019-00679-3>.

JIN, T.; LENG, B. Cynaropicrin Averts the Oxidative Stress and Neuroinflammation in Ischemic/Reperfusion Injury Through the Modulation of NF- κ B. **Applied Biochemistry and Biotechnology**, [s. l.], v. 195, n. 9, p. 5424–5438, 2023.

JOSEPH, E. K.; LEVINE, J. D. Mitochondrial electron transport in models of neuropathic and inflammatory pain. **Pain**, [s. l.], v. 121, n. 1–2, p. 105–114, 2006.

KAI, K. *et al.* Species and Sex Differences in Susceptibility to Olfactory Lesions Among the Mouse, Rat and Monkey Following an Intravenous Injection of Vincristine Sulphate.

Toxicologic Pathology, [s. l.], v. 34, n. 3, p. 223–231, 2006.

KAKATKAR, S.; NARAYAN, A.; BALKRISHNAN, R. Prescription analgesic overuse in older adults: Can we mitigate this growing problem?. **AGING MEDICINE**, [s. l.], v. 5, n. 4, p. 294–296, 2022.

KALTSCHMIDT, B.; KALTSCHMIDT, C. NF-KappaB in Long-Term Memory and Structural Plasticity in the Adult Mammalian Brain. **Frontiers in Molecular Neuroscience**, [s. l.], v. 8, 2015.

KANG, L. *et al.* Oxaliplatin-induced peripheral neuropathy: clinical features, mechanisms, prevention and treatment. **Journal of Neurology**, [s. l.], n. 0123456789, 2020. Disponível em: <https://doi.org/10.1007/s00415-020-09942-w>.

KANZAKI, H. *et al.* Disabling the Nuclear Translocalization of RelA/NF- κ B by a Small Molecule Inhibits Triple-Negative Breast Cancer Growth. **Breast Cancer: Targets and Therapy**, [s. l.], v. Volume 13, p. 419–430, 2021.

KASAI, S. *et al.* Regulation of Nrf2 by Mitochondrial Reactive Oxygen Species in Physiology and Pathology. **Biomolecules**, [s. l.], v. 10, n. 2, p. 320, 2020.

KATSUYAMA, S. *et al.* Antinociceptive Effects of the Serotonin and Noradrenaline Reuptake Inhibitors Milnacipran and Duloxetine on Vincristine-Induced Neuropathic Pain Model in Mice. **ISRN Pain**, [s. l.], v. 2014, p. 1–7, 2014.

KAZARYAN, S. *et al.* Oxidative stress and histopathological changes in several organs of mice injected with biogenic silver nanoparticles. **Artificial Cells, Nanomedicine, and Biotechnology**, [s. l.], v. 50, n. 1, p. 331–342, 2022.

KESZTYÜS, D. *et al.* Use of Infrared Thermography in Medical Diagnosis, Screening, and Disease Monitoring: A Scoping Review. **Medicina**, [s. l.], v. 59, n. 12, p. 2139, 2023.

KHALILZADEH, M. *et al.* Aripiprazole prevents from development of vincristine-induced neuropathic nociception by limiting neural NOS overexpression and NF- κ B hyperactivation. **Cancer Chemotherapy and Pharmacology**, [s. l.], v. 86, n. 3, p. 393–404, 2020a.

KHALILZADEH, M. *et al.* Aripiprazole prevents from development of vincristine-induced neuropathic nociception by limiting neural NOS overexpression and NF- κ B hyperactivation. **Cancer Chemotherapy and Pharmacology**, [s. l.], v. 86, n. 3, p. 393–404, 2020b. Disponível em: <https://doi.org/10.1007/s00280-020-04127-8>.

KHIDR, H. Y. *et al.* Formoterol attenuated mitochondrial dysfunction in rotenone-induced Parkinson's disease in a rat model: Role of PINK-1/PARKIN and PI3K/Akt/CREB/BDNF/TrkB axis. **International Immunopharmacology**, [s. l.], v. 125, p. 111207, 2023.

KIGUCHI, N. *et al.* The critical role of invading peripheral macrophage-derived interleukin-6 in vincristine-induced mechanical allodynia in mice. **European Journal of Pharmacology**, [s. l.], v. 592, n. 1–3, p. 87–92, 2008.

KIM, S. J. *et al.* Antitumor Effects of Selenium. **International Journal of Molecular Sciences**, [s. l.], v. 22, n. 21, p. 11844, 2021.

KIM, Y. S. *et al.* Assessment of pain in the elderly: A literature review. **National Medical Journal of India**, [s. l.], v. 30, n. 4, p. 203–207, 2017a.

KIM, Y. S. *et al.* Assessment of pain in the elderly: A literature review. **National Medical Journal of India**, [s. l.], v. 30, n. 4, p. 203–207, 2017b.

KIM, S. H. *et al.* Regulation of P21-Activated Kinase-4 by Progesterone and Tumor Necrosis Factor- α in Human Endometrium and Its Increased Expression in Advanced-Stage Endometriosis. **The Journal of Clinical Endocrinology & Metabolism**, [s. l.], v. 98, n. 2, p. E238–E248, 2013a.

KIM, S. H. *et al.* Regulation of P21-Activated Kinase-4 by Progesterone and Tumor Necrosis Factor- α in Human Endometrium and Its Increased Expression in Advanced-Stage Endometriosis. **The Journal of Clinical Endocrinology & Metabolism**, [s. l.], v. 98, n. 2, p. E238–E248, 2013b. Disponível em: <https://academic.oup.com/jcem/article-lookup/doi/10.1210/jc.2012-2969>.

KIM, J.; SHARMA, R. P. Calcium-mediated activation of c-Jun NH2-terminal kinase (JNK and apoptosis in response to cadmium in murine macrophages. **Toxicological Sciences**, [s. l.], v. 81, n. 2, p. 518–527, 2004.

KINOSHITA, P. F. *et al.* The influence of Na⁺, K⁺-ATPase on glutamate signaling in neurodegenerative diseases and senescence. **Frontiers in Physiology**, [s. l.], v. 7, n. JUN, p. 1–19, 2016.

KINTOSSOU, A. K. *et al.* Early Life Nutrition Factors and Risk of Acute Leukemia in Children: Systematic Review and Meta-Analysis. **Nutrients**, [s. l.], v. 15, n. 17, p. 3775, 2023.

KOHNO, T. *et al.* Peripheral nerve injury alters excitatory synaptic transmission in laminal II of the rat dorsal horn. **Journal of Physiology**, [s. l.], v. 548, n. 1, p. 131–138, 2003.

KOSTIĆ, M.; MARJANOVIĆ, J.; DIVAC, V. Organoselenium transition metal complexes as promising candidates in medicine area. **JBIC Journal of Biological Inorganic Chemistry**, [s. l.], v. 29, n. 6, p. 555–571, 2024.

KREMER, M. *et al.* How to study anxiety and depression in rodent models of chronic pain?. **European Journal of Neuroscience**, [s. l.], v. 53, n. 1, p. 236–270, 2021.

KUPPUSAMY, P. *et al.* Targeting metabolic pathways alleviates bortezomib-induced neuropathic pain without compromising anticancer efficacy in a sex-specific manner. **Frontiers in Pain Research**, [s. l.], v. 5, 2024.

LAFORGIA, M. *et al.* Peripheral Neuropathy under Oncologic Therapies: A Literature Review on Pathogenetic Mechanisms. **International Journal of Molecular Sciences**, [s. l.], v. 22, n. 4, p. 1980, 2021.

LAURITZEN, M. *et al.* Clinical Relevance of Cortical Spreading Depression in Neurological Disorders: Migraine, Malignant Stroke, Subarachnoid and Intracranial Hemorrhage, and Traumatic Brain Injury. **Journal of Cerebral Blood Flow & Metabolism**, [s. l.], v. 31, n. 1, p. 17–35, 2011a.

LAURITZEN, M. *et al.* Clinical Relevance of Cortical Spreading Depression in Neurological Disorders: Migraine, Malignant Stroke, Subarachnoid and Intracranial

Hemorrhage, and Traumatic Brain Injury. **Journal of Cerebral Blood Flow & Metabolism**, [s. l.], v. 31, n. 1, p. 17–35, 2011b. Disponível em: <http://journals.sagepub.com/doi/10.1038/jcbfm.2010.191>.

LAW, A. Y. S. *et al.* Histone deacetylase inhibitor-induced cellular apoptosis involves stanniocalcin-1 activation. **Experimental Cell Research**, [s. l.], v. 314, n. 16, p. 2975–2984, 2008.

LEE, S. J. *et al.* Fetal Pain. **JAMA**, [s. l.], v. 294, n. 8, p. 947, 2005.

LEE, J. Y. *et al.* The Antiallodynic Effect of Nefopam on Vincristine-Induced Neuropathy in Mice. **Journal of Pain Research**, [s. l.], v. Volume 13, p. 323–329, 2020. Disponível em: <https://www.dovepress.com/the-antiallodynic-effect-of-nefopam-on-vincristine-induced-neuropathy-peer-reviewed-article-JPR>.

LEE, B. Y.; HUR, E. M. A role of microtubules in oligodendrocyte differentiation. **International Journal of Molecular Sciences**, [s. l.], v. 21, n. 3, 2020.

LEGAKIS, L. P.; BIGBEE, J. W.; NEGUS, S. S. Lack of paclitaxel effects on intracranial Self-Stimulation in male and female rats: Comparison to mechanical sensitivity. **Behavioural Pharmacology**, [s. l.], v. 29, p. 290–298, 2018.

LEMOS, B. B. *et al.* ROLE OF 7-CHLORO-4- (PHENYLSELANYL) QUINOLINE IN THE TREATMENT. **Canadian physiology and pharmacology**, [s. l.], v. 99(4), n. 378–388, p. 1–50, 2021a.

LEMOS, B. B. *et al.* ROLE OF 7-CHLORO-4- (PHENYLSELANYL) QUINOLINE IN THE TREATMENT. **Canadian physiology and pharmacology**, [s. l.], v. 99(4), n. 378–388, p. 1–50, 2021b.

LI, H. *et al.* Adipocyte Fatty Acid-Binding Protein Promotes Palmitate-Induced Mitochondrial Dysfunction and Apoptosis in Macrophages. **Frontiers in Immunology**, [s. l.], v. 9, 2018.

LI, G. zhou *et al.* CaMKII and CaV3.2 T-type calcium channel mediate Connexin-43-dependent inflammation by activating astrocytes in vincristine-induced neuropathic pain. **Cell Biology and Toxicology**, [s. l.], p. 679–702, 2021a.

LI, G. zhou *et al.* CaMKII and CaV3.2 T-type calcium channel mediate Connexin-43-dependent inflammation by activating astrocytes in vincristine-induced neuropathic pain. **Cell Biology and Toxicology**, [s. l.], p. 679–702, 2021b.

LI, T. *et al.* Characterising vincristine-induced peripheral neuropathy in adults: symptom development and long-term persistent outcomes. **Supportive Care in Cancer**, [s. l.], v. 32, n. 5, p. 278, 2024.

LI, Y. *et al.* Dorsal root ganglion neurons become hyperexcitable and increase expression of voltage-gated T-type calcium channels (Cav3.2) in paclitaxel-induced peripheral neuropathy. **Pain**, [s. l.], v. 158, n. 3, p. 417–429, 2017.

LI, W. *et al.* Ibrutinib alleviates LPS-induced neuroinflammation and synaptic defects in a mouse model of depression. **Brain, Behavior, and Immunity**, [s. l.], v. 92, p. 10–24, 2021.

LI, G. zhou *et al.* Vincristine-induced peripheral neuropathy: A mini-review.

NeuroToxicology, [s. l.], v. 81, p. 161–171, 2020a.

LI, G. zhou *et al.* Vincristine-induced peripheral neuropathy: A mini-review. **NeuroToxicology**, [s. l.], v. 81, p. 161–171, 2020b.

LIU, J. *et al.* Glutamatergic Neurons in the Amygdala Are Involved in Paclitaxel-Induced Pain and Anxiety. **Frontiers in Psychiatry**, [s. l.], v. 13, n. April, p. 1–11, 2022.

LIU, J. *et al.* Na/K-ATPase signaling and salt sensitivity: The role of oxidative stress. **Antioxidants**, [s. l.], v. 6, n. 1, p. 12–14, 2017a.

LIU, J. *et al.* Na/K-ATPase signaling and salt sensitivity: The role of oxidative stress. **Antioxidants**, [s. l.], v. 6, n. 1, p. 12–14, 2017b.

LIU, J.; LILLY, M. N.; SHAPIRO, J. I. Targeting Na/K-ATPase Signaling: A New Approach to Control Oxidative Stress. **Current Pharmaceutical Design**, [s. l.], v. 24, n. 3, p. 359–364, 2018a.

LIU, J.; LILLY, M. N.; SHAPIRO, J. I. Targeting Na/K-ATPase Signaling: A New Approach to Control Oxidative Stress. **Current Pharmaceutical Design**, [s. l.], v. 24, n. 3, p. 359–364, 2018b. Disponível em: <https://www.eurekaselect.com/158913/article>.

LIVAK, K. J.; SCHMITTGEN, T. D. Analysis of Relative Gene Expression Data Using Real-Time Quantitative PCR and the 2- $\Delta\Delta$ CT Method. **Methods**, [s. l.], v. 25, n. 4, p. 402–408, 2001a.

LIVAK, K. J.; SCHMITTGEN, T. D. Analysis of relative gene expression data using real-time quantitative PCR and the 2- $\Delta\Delta$ CT method. **Methods**, [s. l.], v. 25, n. 4, p. 402–408, 2001b.

LOWRY, Oliver H. *et al.* PROTEIN MEASUREMENT WITH THE FOLIN PHENOL REAGENT. **Journal of Biological Chemistry**, [s. l.], v. 193, n. 1, p. 265–275, 1951.

LUHMANN, H. J.; FUKUDA, A. Can we understand human brain development from experimental studies in rodents?. **Pediatrics International**, [s. l.], v. 62, n. 10, p. 1139–1144, 2020.

MACDONALD, A. D.; WOOLFE, G. Analgesic action of pethidine derivatives and related compounds. **British journal of pharmacology and chemotherapy**, [s. l.], v. 1, p. 4–14, 1946.

MADSEN, M. L. *et al.* Aspects of vincristine-induced neuropathy in hematologic malignancies: a systematic review. **Cancer Chemotherapy and Pharmacology**, [s. l.], v. 84, n. 3, p. 471–485, 2019. Disponível em: <https://doi.org/10.1007/s00280-019-03884-5>.

MAGEE, J. C.; GRIENBERGER, C. Synaptic Plasticity Forms and Functions. **Annual Review of Neuroscience**, [s. l.], v. 43, n. 1, p. 95–117, 2020a.

MAGEE, J. C.; GRIENBERGER, C. Synaptic Plasticity Forms and Functions. **Annual Review of Neuroscience**, [s. l.], v. 43, n. 1, p. 95–117, 2020b. Disponível em: <https://www.annualreviews.org/doi/10.1146/annurev-neuro-090919-022842>.

MALDONADO, L. A. G. *et al.* Influence of tumor cell-derived TGF- β on macrophage

phenotype and macrophage-mediated tumor cell invasion. **The International Journal of Biochemistry & Cell Biology**, [s. l.], v. 153, p. 106330, 2022.

MALONEYHUSS, M. A. *et al.* Efficacy and toxicity of mustargen, vincristine, procarbazine and prednisone (MOPP) for the treatment of relapsed or resistant lymphoma in cats. **Journal of Feline Medicine and Surgery**, [s. l.], v. 22, n. 4, p. 299–304, 2020.

MARKOVIC, T. *et al.* Pain induces adaptations in ventral tegmental area dopamine neurons to drive anhedonia-like behavior. **Nature Neuroscience**, [s. l.], v. 24, n. 11, p. 1601–1613, 2021.

MASKO, M. *et al.* A novel approach to thermographic images analysis of equine thoracolumbar region: the effect of effort and rider's body weight on structural image complexity. **BMC Veterinary Research**, [s. l.], v. 17, n. 1, p. 99, 2021.

MCCALLUM, J. B. *et al.* Loss of T-type calcium current in sensory neurons of rats with neuropathic pain. **Anesthesiology**, [s. l.], v. 98, n. 1, p. 209–216, 2003.

MCILWAIN, K. L. *et al.* The use of behavioral test batteries: Effects of training history. **Physiology & Behavior**, [s. l.], v. 73, n. 5, p. 705–717, 2001.

MCKELVEY, R. *et al.* Neuropathic pain is constitutively suppressed in early life by anti-inflammatory neuroimmune regulation. **Journal of Neuroscience**, [s. l.], v. 35, n. 2, p. 457–466, 2015.

MEFFERT, M. K. *et al.* NF- κ B functions in synaptic signaling and behavior. **Nature Neuroscience**, [s. l.], v. 6, n. 10, p. 1072–1078, 2003.

MELÉNDEZ, D. M. *et al.* Spatial memory deficits after vincristine-induced lesions to the dorsal hippocampus. **PLoS ONE**, [s. l.], v. 15, n. 4, p. 1–16, 2020.

MESTDAGH, F.; STEYAERT, A.; LAVAND'HOMME, P. Cancer Pain Management: A Narrative Review of Current Concepts, Strategies, and Techniques. **Current Oncology**, [s. l.], v. 30, n. 7, p. 6838–6858, 2023.

MICLESCU, A. A. *et al.* Association between systemic inflammation and experimental pain sensitivity in subjects with pain and painless neuropathy after traumatic nerve injuries. **Scandinavian Journal of Pain**, [s. l.], v. 7, 2022.

MINJ, E.; UPADHAYAY, S.; MEHAN, S. Nrf2/HO-1 Signaling Activator Acetyl-11-keto-beta Boswellic Acid (AKBA)-Mediated Neuroprotection in Methyl Mercury-Induced Experimental Model of ALS. **Neurochemical Research**, [s. l.], v. 46, n. 11, p. 2867–2884, 2021.

MISRA, H. P.; FRIDOVICH, I. The role of superoxide anion in the autoxidation of epinephrine and a simple assay for superoxide dismutase. **Journal of Biological Chemistry**, [s. l.], v. 247, n. 10, p. 3170–3175, 1972.

MOJARAD-JABALI, S. *et al.* Comparison of three synthetic transferrin mimetic small peptides to promote the blood–brain barrier penetration of vincristine liposomes for improved glioma targeted therapy. **International Journal of Pharmaceutics**, [s. l.], v. 613, p. 121395, 2022.

MOK, C. C.; LOK, E. Y. C.; CHEUNG, E. F. C. Concurrent psychiatric disorders are

associated with significantly poorer quality of life in patients with rheumatoid arthritis. **Scandinavian Journal of Rheumatology**, [s. l.], v. 41, n. 4, p. 253–259, 2012.

MONTAGUE, K. *et al.* A novel interaction between CX 3 CR 1 and CCR 2 signalling in monocytes constitutes an underlying mechanism for persistent vincristine-induced pain. **Journal of Neuroinflammation**, [s. l.], v. 15, n. 1, p. 1–15, 2018.

MONTAGUE-CARDOSO, K.; MALCANGIO, M. Changes in blood–spinal cord barrier permeability and neuroimmune interactions in the underlying mechanisms of chronic pain. **Pain Reports**, [s. l.], v. 6, n. 1, p. 1–7, 2021.

MORA, E. *et al.* Vincristine-induced peripheral neuropathy in pediatric cancer patients. **American Journal of Cancer Research**, [s. l.], v. 6, n. 11, p. 2416–2430, 2016.

MORTAZAVI, H. Balance training as a promising intervention for reducing the risk of fall in elderly patients with chemotherapy-induced peripheral neuropathy. **Journal of Cancer Research and Therapeutics**, [s. l.], v. 15, n. 5, p. 1192, 2019.

MOSCHETTI, G. *et al.* Prokineticin 2 promotes and sustains neuroinflammation in vincristine treated mice: Focus on pain and emotional like behavior. **Brain, Behavior, and Immunity**, [s. l.], v. 82, n. September, p. 422–431, 2019a.

MOSCHETTI, G. *et al.* Prokineticin 2 promotes and sustains neuroinflammation in vincristine treated mice: Focus on pain and emotional like behavior. **Brain, Behavior, and Immunity**, [s. l.], v. 82, n. September, p. 422–431, 2019b.

MOSELEY, A. E. *et al.* Deficiency in Na,K-ATPase α isoform genes alters spatial learning, motor activity, and anxiety in mice. **Journal of Neuroscience**, [s. l.], v. 27, n. 3, p. 616–626, 2007.

MOTTA, K. P. da *et al.* **7-Chloro-4- (phenylselanyl) quinoline reduces renal oxidative stress induced by oxaliplatin in mice.** [S. l.: s. n.], 2021a.

MOTTA, K. P. da *et al.* 7-Chloro-4- (phenylselanyl) quinoline reduces renal oxidative stress induced by oxaliplatin in mice. **Canadian physiology and pharmacology**, [s. l.], p. 1–37, 2021b.

MOTTA, K. P. da *et al.* 7-Chloro-4- (phenylselanyl) quinoline reduces renal oxidative stress induced by oxaliplatin in mice. **Canadian physiology and pharmacology**, [s. l.], p. 1–37, 2021c.

MOTTA, K. P. da *et al.* Target enzymes in oxaliplatin-induced peripheral neuropathy in Swiss mice: A new acetylcholinesterase inhibitor as therapeutic strategy. **Chemico-Biological Interactions**, [s. l.], v. 352, n. November 2021, p. 109772, 2022. Disponível em: <https://doi.org/10.1016/j.cbi.2021.109772>.

MOWLAVI, A. *et al.* Increased cutaneous nerve fibers in female specimens. **Plastic and Reconstructive Surgery**, [s. l.], v. 116, n. 5, p. 1407–1410, 2005.

MUSSBACHER, M. *et al.* NF- κ B in monocytes and macrophages – an inflammatory master regulator in multitasked immune cells. **Frontiers in Immunology**, [s. l.], v. 14, 2023a.

MUSSBACHER, M. *et al.* NF- κ B in monocytes and macrophages – an inflammatory master regulator in multitasked immune cells. **Frontiers in Immunology**, [s. l.], v. 14,

2023b. Disponível em:

<https://www.frontiersin.org/articles/10.3389/fimmu.2023.1134661/full>.

NAGAI, J.; GOSHIMA, Y.; OHSHIMA, T. CRMP4 mediates MAG-induced inhibition of axonal outgrowth and protection against Vincristine-induced axonal degeneration.

Neuroscience Letters, [s. l.], v. 519, n. 1, p. 56–61, 2012a. Disponível em:

<http://dx.doi.org/10.1016/j.neulet.2012.05.020>.

NAGAI, J.; GOSHIMA, Y.; OHSHIMA, T. CRMP4 mediates MAG-induced inhibition of axonal outgrowth and protection against Vincristine-induced axonal degeneration.

Neuroscience Letters, [s. l.], v. 519, n. 1, p. 56–61, 2012b.

NGO, V.; DUENNWALD, M. L. Nrf2 and Oxidative Stress: A General Overview of Mechanisms and Implications in Human Disease. **Antioxidants**, [s. l.], v. 11, n. 12, p. 2345, 2022.

NOGUEIRA, C. W.; ROCHA, J. B. T. Toxicology and pharmacology of selenium: Emphasis on synthetic organoselenium compounds. **Archives of Toxicology**, [s. l.], v. 85, n. 11, p. 1313–1359, 2011.

NOGUEIRA, C. W.; ZENI, G.; ROCHA, J. B. T. Organoselenium and organotellurium compounds: Toxicology and pharmacology. **Chemical Reviews**, [s. l.], v. 104, n. 12, p. 6255–6285, 2004.

NOVELLE, M. G.; CAMACHO-MORALES, A.; MARTÍNEZ DE MORENTIN, P. B. Editorial: Role of estrogens as key regulators of energy homeostasis. **Frontiers in Endocrinology**, [s. l.], v. 14, 2023.

OHKAWA, H.; OHISHI, N.; YAGI, K. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. **Analytical Biochemistry**, [s. l.], v. 95, n. 2, p. 351–358, 1979.

OLD, E. A. *et al.* Monocytes expressing CX3CR1 orchestrate the development of vincristine-induced pain. **Journal of Clinical Investigation**, [s. l.], v. 124, n. 5, p. 2023–2036, 2014a.

OLD, E. A. *et al.* Monocytes expressing CX3CR1 orchestrate the development of vincristine-induced pain. **Journal of Clinical Investigation**, [s. l.], v. 124, n. 5, p. 2023–2036, 2014b.

O'ROURKE, S. A.; SHANLEY, L. C.; DUNNE, A. The Nrf2-HO-1 system and inflammaging. **Frontiers in Immunology**, [s. l.], v. 15, 2024.

PAICE, J. A. *et al.* Management of Chronic Pain in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. **Journal of Clinical Oncology**, [s. l.], v. 34, n. 27, p. 3325–3345, 2016.

PALTIAN, J. J. *et al.* 7-chloro-4-(phenylselanyl) quinoline incorporation into polymeric nanocapsules improves its pharmacological action: Physicochemical, toxicological, and behavioral studies. **International Journal of Pharmaceutics**, [s. l.], v. 673, p. 125370, 2025.

PALTIAN, J. J. *et al.* 7-Chloro-4-(Phenylselanyl) Quinoline Is a Novel Multitarget Therapy to Combat Peripheral Neuropathy and Comorbidities Induced by Paclitaxel in Mice. **Molecular Neurobiology**, [s. l.], n. 0123456789, 2022a. Disponível em:

<https://doi.org/10.1007/s12035-022-02991-4>.

PALTIAN, J. J. *et al.* 7-Chloro-4-(Phenylselenyl) Quinoline Is a Novel Multitarget Therapy to Combat Peripheral Neuropathy and Comorbidities Induced by Paclitaxel in Mice. **Molecular Neurobiology**, [s. l.], n. 0123456789, 2022b.

PALTIAN, J. J. *et al.* The anxiolytic effect of a promising quinoline containing selenium with the contribution of the serotonergic and GABAergic pathways: Modulation of parameters associated with anxiety in mice. **Behavioural Brain Research**, [s. l.], v. 393, n. June, p. 112797, 2020a. Disponível em: <https://doi.org/10.1016/j.bbr.2020.112797>.

PALTIAN, J. J. *et al.* The anxiolytic effect of a promising quinoline containing selenium with the contribution of the serotonergic and GABAergic pathways: Modulation of parameters associated with anxiety in mice. **Behavioural Brain Research**, [s. l.], v. 393, n. June, p. 112797, 2020b.

PATIL, M. J. *et al.* Ginger Constituent 6-Shogaol Attenuates Vincristine-Induced Activation of Mouse Gastroesophageal Vagal Afferent C-Fibers. **Molecules**, [s. l.], v. 27, n. 21, 2022.

PAUWELS, B. *et al.* Comparison of the sulforhodamine B assay and the clonogenic assay for in vitro chemoradiation studies. **Cancer Chemotherapy and Pharmacology**, [s. l.], v. 51, n. 3, p. 221–226, 2003.

PEDRA, N. S. *et al.* Impact of gallic acid on tumor suppression: Modulation of redox homeostasis and purinergic response in in vitro and a preclinical glioblastoma model. **The Journal of Nutritional Biochemistry**, [s. l.], v. 110, p. 109156, 2022.

PELLOW, S. *et al.* Validation of open : closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. **Journal of Neuroscience Methods**, [s. l.], v. 14, n. 3, p. 149–167, 1985.

PÉREZ-GONZÁLEZ, M. Z. *et al.* Anti-inflammatory, antioxidant, and acute toxicity of Brugmansia arborea extracts from wild plants and shoots obtained by indirect organogenesis. A thermographic assay to anti-inflammatory evaluation. **Biomedicine & Pharmacotherapy**, [s. l.], v. 186, p. 117972, 2025.

PIETROBON, D.; MOSKOWITZ, M. A. Pathophysiology of Migraine. **Annual Review of Physiology**, [s. l.], v. 75, n. 1, p. 365–391, 2013a.

PIETROBON, D.; MOSKOWITZ, M. A. Pathophysiology of Migraine. **Annual Review of Physiology**, [s. l.], v. 75, n. 1, p. 365–391, 2013b. Disponível em: <https://www.annualreviews.org/doi/10.1146/annurev-physiol-030212-183717>.

PINZ, M. *et al.* 4-Phenylselenyl-7-chloroquinoline, a new quinoline derivative containing selenium, has potential antinociceptive and anti-inflammatory actions. **European Journal of Pharmacology**, [s. l.], v. 780, p. 122–128, 2016a. Disponível em: <http://dx.doi.org/10.1016/j.ejphar.2016.03.039>.

PINZ, M. *et al.* 4-Phenylselenyl-7-chloroquinoline, a new quinoline derivative containing selenium, has potential antinociceptive and anti-inflammatory actions. **European Journal of Pharmacology**, [s. l.], v. 780, p. 122–128, 2016b.

PINZ, M. P. *et al.* Current advances of pharmacological properties of 7-chloro-4-

(phenylselenyl) quinoline: Prevention of cognitive deficit and anxiety in Alzheimer's disease model. **Biomedicine and Pharmacotherapy**, [s. l.], v. 105, n. June, p. 1006–1014, 2018a. Disponível em: <https://doi.org/10.1016/j.biopha.2018.06.049>.

PINZ, M. P. *et al.* Current advances of pharmacological properties of 7-chloro-4-(phenylselenyl) quinoline: Prevention of cognitive deficit and anxiety in Alzheimer's disease model. **Biomedicine and Pharmacotherapy**, [s. l.], v. 105, n. June, p. 1006–1014, 2018b.

PURSER, M. J.; JOHNSTON, D. L.; MCMILLAN, H. J. Chemotherapy-induced Peripheral Neuropathy Among Paediatric Oncology Patients. **Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques**, [s. l.], v. 41, n. 4, p. 442–447, 2014.

QUEIROZ, M. P. *et al.* Effect of Conjugated Linoleic Acid on Memory and Reflex Maturation in Rats Treated During Early Life. **Frontiers in Neuroscience**, [s. l.], v. 13, 2019.

QUEIROZ, K. F. F. da C.; DE CÁSSIA FERNANDES DE LIMA, R. Smart screening system for breast cancer: the use of thermographic images, evolutionary algorithms, and oversampling. **Biomedical Physics & Engineering Express**, [s. l.], v. 9, n. 5, p. 055027, 2023.

QUINES, C. B. *et al.* Involvement of the serotonergic system in the anxiolytic-like effect of 2-phenylethynyl butyltellurium in mice. **Behavioural Brain Research**, [s. l.], v. 277, p. 221–227, 2015.

QUINN, R. Comparing rat's to human's age: How old is my rat in people years? **Nutrition**, [s. l.], v. 21, n. 6, p. 775–777, 2005.

QUITON, R. L.; GREENSPAN, J. D. Sex differences in endogenous pain modulation by distracting and painful conditioning stimulation. **Pain**, [s. l.], p. 132–149, 2007.

RAASING, L. R. M. *et al.* Current View of Diagnosing Small Fiber Neuropathy. **Journal of Neuromuscular Diseases**, [s. l.], v. 8, n. 2, p. 185–207, 2021.

REIS, A. S. *et al.* 4-phenylselenyl-7-chloroquinoline, a novel multitarget compound with anxiolytic activity: Contribution of the glutamatergic system. **Journal of Psychiatric Research**, [s. l.], v. 84, p. 191–199, 2017a.

REIS, A. S. *et al.* 4-phenylselenyl-7-chloroquinoline, a novel multitarget compound with anxiolytic activity: Contribution of the glutamatergic system. **Journal of Psychiatric Research**, [s. l.], v. 84, p. 191–199, 2017b.

REIS, A. S. *et al.* 4-phenylselenyl-7-chloroquinoline, a novel multitarget compound with anxiolytic activity: Contribution of the glutamatergic system. **Journal of Psychiatric Research**, [s. l.], v. 84, p. 191–199, 2017c. Disponível em: <https://linkinghub.elsevier.com/retrieve/pii/S0022395616304976>.

REIS, A. S. *et al.* Advances in the Understanding of Oxaliplatin-Induced Peripheral Neuropathy in Mice: 7-Chloro-4-(Phenylselenyl) Quinoline as a Promising Therapeutic Agent. **Molecular Neurobiology**, [s. l.], v. 57, n. 12, p. 5219–5234, 2020a.

REIS, A. S. *et al.* Advances in the Understanding of Oxaliplatin-Induced Peripheral Neuropathy in Mice: 7-Chloro-4-(Phenylselenyl) Quinoline as a Promising Therapeutic

Agent. **Molecular Neurobiology**, [s. l.], v. 57, n. 12, p. 5219–5234, 2020b.

REIS, A. S. *et al.* Interface of Aging and Acute Peripheral Neuropathy Induced by Oxaliplatin in Mice: Target-Directed Approaches for Na⁺, K⁺—ATPase, Oxidative Stress, and 7-Chloro-4-(phenylselanyl) quinoline Therapy. **Molecular Neurobiology**, [s. l.], v. 59, n. 3, p. 1766–1780, 2022. Disponível em: <https://doi.org/10.1007/s12035-021-02659-5>.

REIS, A. S. *et al.* Pharmacological modulation of Na⁺, K⁺-ATPase as a potential target for OXA-induced neurotoxicity: Correlation between anxiety and cognitive decline and beneficial effects of 7-chloro-4-(phenylselanyl) quinoline. **Brain Research Bulletin**, [s. l.], v. 162, n. June, p. 282–290, 2020c.

REIS, A. S. *et al.* Pharmacological modulation of Na⁺, K⁺-ATPase as a potential target for OXA-induced neurotoxicity: Correlation between anxiety and cognitive decline and beneficial effects of 7-chloro-4-(phenylselanyl) quinoline. **Brain Research Bulletin**, [s. l.], v. 162, n. June, p. 282–290, 2020d.

REIS, A. S. *et al.* Platinum Deposition in the Central Nervous System: A Novel Insight into Oxaliplatin-induced Peripheral Neuropathy in Young and Old Mice. **Molecular Neurobiology**, [s. l.], v. 62, n. 3, p. 3712–3729, 2025.

REZENDE, A. A. *et al.* Anti-Tumor Efficiency of Perillylalcohol/ β -Cyclodextrin Inclusion Complexes in a Sarcoma S180-Induced Mice Model. **Pharmaceutics**, [s. l.], v. 13, n. 2, p. 245, 2021.

RODRIGUES, K. C. *et al.* The neurotherapeutic role of a selenium-functionalized quinoline in hypothalamic obese rats. **Psychopharmacology**, [s. l.], v. 238, n. 7, p. 1937–1951, 2021a.

RODRIGUES, K. C. *et al.* The neurotherapeutic role of a selenium-functionalized quinoline in hypothalamic obese rats. **Psychopharmacology**, [s. l.], v. 238, n. 7, p. 1937–1951, 2021b.

ROHN, T. T.; HINDS, T. R.; VINCENZI, F. F. Ion transport ATPases as targets for free radical damage. **Biochemical Pharmacology**, [s. l.], v. 46, n. 3, p. 525–534, 1993.

RUAN, Y. *et al.* An effective and concise device for detecting cold allodynia in mice. **Scientific Reports**, [s. l.], v. 8, n. 1, 2018.

RUBIO, M. *et al.* The immunosuppressive effect of vincristine on allostimulatory potential of human dendritic cells interferes with their function and survival. **International Journal of Oncology**, [s. l.], 2004.

RUDNITSKAYA, E. A. *et al.* Features of Postnatal Hippocampal Development in a Rat Model of Sporadic Alzheimer's Disease. **Frontiers in Neuroscience**, [s. l.], v. 14, 2020.

RUHEE, R. T. *et al.* Organosulfur Compounds: A Review of Their Anti-inflammatory Effects in Human Health. **Frontiers in Nutrition**, [s. l.], v. 7, 2020.

SAGALAJEV, B. *et al.* Bidirectional amygdaloid control of neuropathic hypersensitivity mediated by descending serotonergic pathways acting on spinal 5-HT₃ and 5-HT_{1A} receptors. **Behavioural Brain Research**, [s. l.], v. 282, p. 14–24, 2015.

SAHRANAVARD, S. *et al.* Hydroethanolic extract of *Lavandula angustifolia* ameliorates vincristine-induced peripheral neuropathy in rats. **Research in Pharmaceutical Sciences**, [s. l.], v. 17, n. 3, p. 265, 2022. Disponível em: <https://journals.lww.com/10.4103/1735-5362.343080>.

SALAT, K.; FILIPEK, B. Antinociceptive activity of transient receptor potential channel TRPV1, TRPA1, and TRPM8 antagonists in neurogenic and neuropathic pain models in mice. **Journal of Zhejiang University-SCIENCE B**, [s. l.], v. 16, n. 3, p. 167–178, 2015.

SAMPATHKUMAR, V. *et al.* Integration of signals from different cortical areas in higher order thalamic neurons. **Proceedings of the National Academy of Sciences**, [s. l.], v. 118, n. 30, 2021.

SANTOS, G. J. L. *et al.* *Himatanthus drasticus* (Apocynaceae) latex reduces oxidative stress and modulates CD4+, CD8+, FoxP3+ and HSP-60+ expressions in Sarcoma 180-bearing mice. **Journal of Ethnopharmacology**, [s. l.], v. 220, p. 159–168, 2018.

SAVEGNAGO, L. *et al.* Synthesis and antioxidant properties of novel quinoline-chalcogenium compounds. **Tetrahedron Letters**, [s. l.], v. 54, n. 1, p. 40–44, 2013a.

SAVEGNAGO, L. *et al.* Synthesis and antioxidant properties of novel quinoline-chalcogenium compounds. **Tetrahedron Letters**, [s. l.], v. 54, n. 1, p. 40–44, 2013b. Disponível em: <http://dx.doi.org/10.1016/j.tetlet.2012.10.067>.

SCHAPPACHER, K. A. *et al.* Neonatal vincristine administration modulates intrinsic neuronal excitability in the rat dorsal root ganglion and spinal dorsal horn during adolescence. **Pain**, [s. l.], v. 160, n. 3, p. 645–657, 2019a.

SCHAPPACHER, K. A. *et al.* Neonatal vincristine administration modulates intrinsic neuronal excitability in the rat dorsal root ganglion and spinal dorsal horn during adolescence. **Pain**, [s. l.], v. 160, n. 3, p. 645–657, 2019b.

SCHAPPACHER, K. A. *et al.* Neonatal vincristine administration modulates intrinsic neuronal excitability in the rat dorsal root ganglion and spinal dorsal horn during adolescence. **Pain**, [s. l.], v. 160, n. 3, p. 645–657, 2019c.

SCHAPPACHER, K. A.; STYCZYNSKI, L.; BACCEI, M. L. **Early life vincristine exposure evokes mechanical pain hypersensitivity in the developing rat.** [S. l.: s. n.], 2017-. ISSN 18726623.v. 158

SEKERES, M. J.; WINOCUR, G.; MOSCOVITCH, M. The hippocampus and related neocortical structures in memory transformation. **Neuroscience Letters**, [s. l.], v. 680, p. 39–53, 2018.

SEMPLE, B. D. *et al.* Brain development in rodents and humans: Identifying benchmarks of maturation and vulnerability to injury across species. **Progress in Neurobiology**, [s. l.], v. 106–107, p. 1–16, 2013.

SENGUPTA, S. *et al.* Adverse Neonatal Outcomes Associated With Early-Term Birth. **JAMA Pediatrics**, [s. l.], v. 167, n. 11, p. 1053, 2013.

SHABANI, M. *et al.* Profound destructive effects of adolescent exposure to Vincristine accompanied with some sex differences in motor and memory performance. **Canadian Journal of Physiology and Pharmacology**, [s. l.], v. 90, n. 4, p. 379–386, 2012a.

SHABANI, M. *et al.* Profound destructive effects of adolescent exposure to Vincristine accompanied with some sex differences in motor and memory performance. **Canadian Journal of Physiology and Pharmacology**, [s. l.], v. 90, n. 4, p. 379–386, 2012b.

SHAO, Y. *et al.* Morin Regulates M1/M2 Microglial Polarization via NF- κ B p65 to Alleviate Vincristine-Induced Neuropathic Pain. **Drug Design, Development and Therapy**, [s. l.], v. Volume 18, p. 3143–3156, 2024.

SHAYESTEH, S. *et al.* Dapsone improves the vincristine-induced neuropathic nociception by modulating neuroinflammation and oxidative stress. **DARU, Journal of Pharmaceutical Sciences**, [s. l.], v. 30, n. 2, p. 303–310, 2022a.

SHAYESTEH, S. *et al.* Dapsone improves the vincristine-induced neuropathic nociception by modulating neuroinflammation and oxidative stress. **DARU, Journal of Pharmaceutical Sciences**, [s. l.], v. 30, n. 2, p. 303–310, 2022b. Disponível em: <https://doi.org/10.1007/s40199-022-00448-6>.

SHEN, Y. *et al.* Exogenous induction of HO-1 alleviates vincristine-induced neuropathic pain by reducing spinal glial activation in mice. **Neurobiology of Disease**, [s. l.], v. 79, p. 100–110, 2015a.

SHEN, Y. *et al.* Exogenous induction of HO-1 alleviates vincristine-induced neuropathic pain by reducing spinal glial activation in mice. **Neurobiology of Disease**, [s. l.], v. 79, p. 100–110, 2015b. Disponível em: <http://dx.doi.org/10.1016/j.nbd.2015.04.012>.

SHINWARI, Z. *et al.* Vincristine and lomustine induce apoptosis and p21WAF1 up-regulation in medulloblastoma and normal human epithelial and fibroblast cells. **Journal of Neuro-Oncology**, [s. l.], v. 87, n. 2, p. 123–132, 2008.

SILVA, A. V. Associations between clinical signs and pathological findings in toxicity testing. **ALTEX**, [s. l.], 2020.

SILVA, V. D. G. *et al.* Further analysis of acute antinociceptive and anti-inflammatory actions of 4-phenylselenyl-7-chloroquinoline in mice. **Fundamental and Clinical Pharmacology**, [s. l.], v. 31, n. 5, p. 513–525, 2017a.

SILVA, V. D. G. *et al.* Further analysis of acute antinociceptive and anti-inflammatory actions of 4-phenylselenyl-7-chloroquinoline in mice. **Fundamental and Clinical Pharmacology**, [s. l.], v. 31, n. 5, p. 513–525, 2017b.

SIMÃO, D. A. da S. *et al.* Chemotherapy-induced peripheral neuropathy: review for clinical practice. **Revista Dor**, [s. l.], v. 16, n. 3, p. 215–220, 2015.

ŞİMŞEK, Ş.; OYMAK SOYSAL, A. N.; KAŞ ÖZDEMİR, A. Association between Pain Intensity, Pain Belief, and Coping Strategies in Older Adults. **Experimental Aging Research**, [s. l.], v. 49, n. 3, p. 244–251, 2023a. Disponível em: <https://doi.org/10.1080/0361073X.2022.2101304>.

ŞİMŞEK, Ş.; OYMAK SOYSAL, A. N.; KAŞ ÖZDEMİR, A. Association between Pain Intensity, Pain Belief, and Coping Strategies in Older Adults. **Experimental Aging Research**, [s. l.], v. 49, n. 3, p. 244–251, 2023b.

SINGH, G. *et al.* Bergapten Ameliorates Vincristine-Induced Peripheral Neuropathy by Inhibition of Inflammatory Cytokines and NF κ B Signaling. research-article. **ACS**

Chemical Neuroscience, [s. l.], v. 10, n. 6, p. 3008–3017, 2019a.

SINGH, G. *et al.* Bergapten Ameliorates Vincristine-Induced Peripheral Neuropathy by Inhibition of Inflammatory Cytokines and NF κ B Signaling. research-article. **ACS Chemical Neuroscience**, [s. l.], v. 10, n. 6, p. 3008–3017, 2019b.

SMART, J. L.; DOBBING, J. Vulnerability of developing brain. II. Effects of early nutritional deprivation on reflex ontogeny and development of behaviour in the rat. **Brain Research**, [s. l.], v. 28, n. 1, p. 85–95, 1971.

SMITH, E. M. L. *et al.* Predictors of duloxetine response in patients with oxaliplatin-induced painful chemotherapy-induced peripheral neuropathy (CIPN): a secondary analysis of randomised controlled trial – CALGB/alliance 170601. **European Journal of Cancer Care**, [s. l.], v. 26, n. 2, 2017.

SNIJDDERS, R. *et al.* Update on Prevalence of Pain in Patients with Cancer 2022: A Systematic Literature Review and Meta-Analysis. **Cancers**, [s. l.], v. 15, n. 3, p. 591, 2023.

SONG, B. *et al.* Inhibitory phosphorylation of GSK-3 by CaMKII couples depolarization to neuronal survival. **Journal of Biological Chemistry**, [s. l.], v. 285, n. 52, p. 41122–41134, 2010.

SORIANO, D. *et al.* Chemotherapy-induced neuropathy and pain in pediatric oncology patients: impact of combination therapies. **European Journal of Pediatrics**, [s. l.], v. 183, n. 9, p. 3749–3756, 2024.

SOYOCAK, A. *et al.* Tannic acid exhibits anti-inflammatory effects on formalin-induced paw edema model of inflammation in rats. **Human & Experimental Toxicology**, [s. l.], v. 38, n. 11, p. 1296–1301, 2019.

STANGHERLIN, E. C.; ROCHA, J. B. T.; NOGUEIRA, C. W. Diphenyl ditelluride impairs short-term memory and alters neurochemical parameters in young rats. **Pharmacology Biochemistry and Behavior**, [s. l.], v. 91, n. 3, p. 430–435, 2009.

STAROBOVA, H. *et al.* Minocycline prevents the development of mechanical allodynia in mouse models of vincristine-induced peripheral neuropathy. **Frontiers in Neuroscience**, [s. l.], v. 13, n. JUN, p. 1–10, 2019.

STAROBOVA, H.; VETTER, I. Pathophysiology of chemotherapy-induced peripheral neuropathy. **Frontiers in Molecular Neuroscience**, [s. l.], v. 10, n. May, p. 1–21, 2017a.

STAROBOVA, H.; VETTER, I. Pathophysiology of chemotherapy-induced peripheral neuropathy. **Frontiers in Molecular Neuroscience**, [s. l.], v. 10, n. May, p. 1–21, 2017b.

STEEL, A. *et al.* A network linking scene perception and spatial memory systems in posterior cerebral cortex. **Nature Communications**, [s. l.], v. 12, n. 1, p. 2632, 2021.

STERU, L. *et al.* The tail suspension test: A new method for screening antidepressants in mice. **Psychopharmacology**, [s. l.], v. 85, n. 3, p. 367–370, 1985.

STYCZYNSKI, L. M.; SCHAPPACHER, K. A.; BACCEI, M. L. Early life vincristine fails to prime developing pain pathways. **Neuroscience Letters**, [s. l.], v. 720, n. January,

p. 134764, 2020. Disponível em: <https://doi.org/10.1016/j.neulet.2020.134764>.

SU, H. *et al.* Regulation of the Nrf2/HO-1 axis by mesenchymal stem cells-derived extracellular vesicles: implications for disease treatment. **Frontiers in Cell and Developmental Biology**, [s. l.], v. 12, 2024.

SU, Y.-C. *et al.* Survivors of Non-Hodgkin's Lymphoma: A Comparative Study on Patients With Vincristine-Induced Neuropathy and Their Quality of Life. **Journal of Nursing Research**, [s. l.], v. 33, n. 3, p. e393, 2025.

SUN, J. *et al.* Hemoprotein Bach1 regulates enhancer availability of heme oxygenase-1 gene. **The EMBO Journal**, [s. l.], v. 21, n. 19, p. 5216–5224, 2002.

SUN, G. *et al.* Temporal pain processing in the primary somatosensory cortex and anterior cingulate cortex. **Molecular Brain**, [s. l.], v. 16, n. 1, p. 3, 2023.

SUNG, J. Y. *et al.* Sensory axonal dysfunction in cervical radiculopathy. **Journal of Neurology, Neurosurgery and Psychiatry**, [s. l.], v. 86, n. 6, p. 640–645, 2015a.

SUNG, J. Y. *et al.* Sensory axonal dysfunction in cervical radiculopathy. **Journal of Neurology, Neurosurgery and Psychiatry**, [s. l.], v. 86, n. 6, p. 640–645, 2015b.

SWARM, R. A. *et al.* Adult Cancer Pain. **Journal of the National Comprehensive Cancer Network**, [s. l.], v. 11, n. 8, p. 992–1022, 2013.

SY, A. *et al.* Heterozygosity for CMT Type 4 Predicts a Severe Vincristine-induced Polyneuropathy Phenotype: A Case Report and Review of Literature. **Journal of Pediatric Hematology/Oncology**, [s. l.], v. 41, n. 1, p. E41–E43, 2019a.

SY, A. *et al.* Heterozygosity for CMT Type 4 Predicts a Severe Vincristine-induced Polyneuropathy Phenotype: A Case Report and Review of Literature. **Journal of Pediatric Hematology/Oncology**, [s. l.], v. 41, n. 1, p. E41–E43, 2019b.

TAKEDA, M.; TAKAHASHI, M.; MATSUMOTO, S. Suppression of neurokinin-1 receptor in trigeminal ganglia attenuates central sensitization following inflammation. **Journal of the Peripheral Nervous System**, [s. l.], v. 17, n. 2, p. 169–181, 2012.

TANTAWY, S. I. *et al.* Targeting MCL-1 protein to treat cancer: opportunities and challenges. **Frontiers in Oncology**, [s. l.], v. 13, 2023.

TAVES, S. *et al.* Microglia and Spinal Cord Synaptic Plasticity in Persistent Pain. **Neural Plasticity**, [s. l.], v. 2013, p. 1–10, 2013. Disponível em: <http://www.hindawi.com/journals/np/2013/753656/>.

TAY, N. *et al.* Chemotherapy-induced peripheral neuropathy in children and adolescent cancer patients. **Frontiers in Molecular Biosciences**, [s. l.], v. 9, 2022.

TAY, S. Y. *et al.* Pediatric Oncology Patients With Vincristine-Induced Recurrent Laryngeal Nerve Palsy: Two Case Reports and a Brief Review of Literature. **Ear, Nose and Throat Journal**, [s. l.], v. 100, n. 10, p. NP459–NP463, 2021a.

TAY, S. Y. *et al.* Pediatric Oncology Patients With Vincristine-Induced Recurrent Laryngeal Nerve Palsy: Two Case Reports and a Brief Review of Literature. **Ear, Nose and Throat Journal**, [s. l.], v. 100, n. 10, p. NP459–NP463, 2021b.

TIMMINS, H. C. *et al.* The impact of obesity on neuropathy outcomes for paclitaxel- and oxaliplatin-treated cancer survivors. **Journal of Cancer Survivorship**, [s. l.], v. 16, n. 2, p. 223–232, 2022.

TINNIRELLO, A.; MAZZOLENI, S.; SANTI, C. Chronic Pain in the Elderly: Mechanisms and Perspectives. **Biomolecules**, [s. l.], v. 11, n. March, p. 1256, 2021.

TOWER, J.; POMATTO, L. C. D.; DAVIES, K. J. A. Sex differences in the response to oxidative and proteolytic stress. **Redox Biology**, [s. l.], v. 31, p. 101488, 2020.

TREEDE, R. D. The International Association for the Study of Pain definition of pain: As valid in 2018 as in 1979, but in need of regularly updated footnotes. **Pain Reports**, [s. l.], v. 3, n. 2, p. 1–3, 2018.

TREVISAN, G. *et al.* Antinociceptive Effects of 14-Membered Cyclopeptide Alkaloids. **Journal of natural products**, [s. l.], v. 72, p. 608–612, 2009.

TRIARICO, S. *et al.* Vincristine-induced peripheral neuropathy (Vipn) in pediatric tumors: Mechanisms, risk factors, strategies of prevention and treatment. **International Journal of Molecular Sciences**, [s. l.], v. 22, n. 8, 2021a.

TRIARICO, S. *et al.* Vincristine-induced peripheral neuropathy (Vipn) in pediatric tumors: Mechanisms, risk factors, strategies of prevention and treatment. **International Journal of Molecular Sciences**, [s. l.], v. 22, n. 8, 2021b.

TRIARICO, S. *et al.* Vincristine-Induced Peripheral Neuropathy (VIPN) in Pediatric Tumors: Mechanisms, Risk Factors, Strategies of Prevention and Treatment. **International Journal of Molecular Sciences**, [s. l.], v. 22, n. 8, p. 4112, 2021c.

TUCKER, M. H.; TIWARI, P.; CARTER, B. S. The physiology, assessment, and treatment of neonatal pain. **Seminars in Fetal and Neonatal Medicine**, [s. l.], v. 28, n. 4, p. 101465, 2023.

TUMMALA, R. *et al.* Expression of Na,K-ATPase- β 1 subunit increases uptake and sensitizes carcinoma cells to oxaliplatin. **Cancer Chemotherapy and Pharmacology**, [s. l.], v. 64, n. 6, p. 1187–1194, 2009.

TUNJUNGSARI, D. A.; GUNAWAN, P. I.; UGRASENA, I. D. G. RISK FACTORS OF VINCRIStINE-INDUCED PERIPHERAL NEUROPATHY IN ACUTE LYMPHOBLASTIC LEUKAEMIA CHILDREN. **The Journal of Medical Investigation**, [s. l.], v. 68, n. 3.4, p. 232–237, 2021.

TURCU-STIOLICA, A. *et al.* Diagnostic Accuracy of Machine-Learning Models on Predicting Chemo-Brain in Breast Cancer Survivors Previously Treated with Chemotherapy: A Meta-Analysis. **International Journal of Environmental Research and Public Health**, [s. l.], v. 19, n. 24, p. 16832, 2022.

UITTENBOOGAARD, A. *et al.* Pharmacogenomics of Vincristine-Induced Peripheral Neuropathy in Children with Cancer: A Systematic Review and Meta-Analysis. **Cancers**, [s. l.], v. 14, n. 3, p. 612, 2022.

UMANA, I. C. *et al.* **Nicotinic modulation of descending pain control circuitry**. [S. l.: s. n.], 2017-. ISSN 18726623.v. 158

VAN DE VELDE, M. E. *et al.* The association between vincristine-induced peripheral

neuropathy and health-related quality of life in children with cancer. **Cancer Medicine**, [s. l.], v. 10, n. 22, p. 8172–8181, 2021.

VAN DE VELDE, M. E. *et al.* Vincristine-induced peripheral neuropathy in children with cancer: A systematic review. **Critical Reviews in Oncology/Hematology**, [s. l.], v. 114, p. 114–130, 2017a. Disponível em: <https://doi.org/10.1016/j.critrevonc.2017.04.004>.

VAN DE VELDE, M. E. *et al.* Vincristine-induced peripheral neuropathy in children with cancer: A systematic review. **Critical Reviews in Oncology/Hematology**, [s. l.], v. 114, p. 114–130, 2017b.

VAN DEN BEUKEN-VAN EVERDINGEN, M. H. J. *et al.* Prevalence of pain in patients with cancer: a systematic review of the past 40 years. **Annals of Oncology**, [s. l.], v. 18, n. 9, p. 1437–1449, 2007.

VEGA-AVELAIRA, D.; MOSS, A.; FITZGERALD, M. Age-related changes in the spinal cord microglial and astrocytic response profile to nerve injury. **Brain, Behavior, and Immunity**, [s. l.], v. 21, n. 5, p. 617–623, 2007.

VOGT, A. G. *et al.* Organoselenium group is critical for antioxidant activity of 7-chloro-4-phenylselenyl-quinoline. **Chemico-Biological Interactions**, [s. l.], v. 282, p. 7–12, 2018a. Disponível em: <https://doi.org/10.1016/j.cbi.2018.01.003>.

VOGT, A. G. *et al.* Organoselenium group is critical for antioxidant activity of 7-chloro-4-phenylselenyl-quinoline. **Chemico-Biological Interactions**, [s. l.], v. 282, p. 7–12, 2018b.

VOSS, G. T. *et al.* Therapeutic and technological potential of 7-chloro-4-phenylselenyl quinoline for the treatment of atopic dermatitis-like skin lesions in mice. **Materials Science and Engineering C**, [s. l.], v. 84, n. August 2017, p. 90–98, 2017a. Disponível em: <https://doi.org/10.1016/j.msec.2017.11.026>.

VOSS, G. T. *et al.* Therapeutic and technological potential of 7-chloro-4-phenylselenyl quinoline for the treatment of atopic dermatitis-like skin lesions in mice. **Materials Science and Engineering C**, [s. l.], v. 84, n. August 2017, p. 90–98, 2017b.

WALKER, J. L. *et al.* Gait-stance duration as a measure of injury and recovery in the rat sciatic nerve model. **Journal of Neuroscience Methods**, [s. l.], v. 52, n. 1, p. 47–52, 1994.

WALSH, R. N.; CUMMINS, R. A. The open-field test: A critical review. **Psychological Bulletin**, [s. l.], v. 83, n. 3, p. 482–504, 1976.

WANG, F. *et al.* Influence of blood-brain barrier efflux pumps on the distribution of vincristine in brain and brain tumors. **Neuro-Oncology**, [s. l.], v. 12, n. 10, p. 1043–1049, 2010.

WANG, X. *et al.* Observation of Acetylcholinesterase in Stress-Induced Depression Phenotypes by Two-Photon Fluorescence Imaging in the Mouse Brain. **Journal of the American Chemical Society**, [s. l.], v. 141, n. 5, p. 2061–2068, 2019.

WANG, M. S. *et al.* Pathogenesis of axonal degeneration: Parallels between Wallerian degeneration and vincristine neuropathy. **Journal of Neuropathology and Experimental Neurology**, [s. l.], v. 59, n. 7, p. 599–606, 2000a.

WANG, M. S. *et al.* Pathogenesis of axonal degeneration: Parallels between Wallerian degeneration and vincristine neuropathy. **Journal of Neuropathology and Experimental Neurology**, [s. l.], v. 59, n. 7, p. 599–606, 2000b.

WANG, J. H. *et al.* Relationship between prescribed opioids, pain management satisfaction, and pain intensity in oncology outpatients. **Supportive Care in Cancer**, [s. l.], v. 30, n. 4, p. 3233–3240, 2022. Disponível em: <https://doi.org/10.1007/s00520-021-06722-8>.

WANG, L.; AHN, Y. J.; ASMIS, R. Sexual dimorphism in glutathione metabolism and glutathione-dependent responses. **Redox Biology**, [s. l.], v. 31, p. 101410, 2020.

WEEKS, J. C.; LEVINE, R. B. Steroid hormone effects on neurons subserving behavior. **Current Opinion in Neurobiology**, [s. l.], v. 5, n. 6, p. 809–815, 1995.

WHITE, D. *et al.* Targeting translation: A review of preclinical animal models in the development of treatments for chemotherapy-induced peripheral neuropathy. **Journal of the Peripheral Nervous System**, [s. l.], v. 28, n. 2, p. 179–190, 2023.

WIESKOPF, J. S. *et al.* The nicotinic $\alpha 6$ subunit gene determines variability in chronic pain sensitivity via cross-inhibition of P2X2/3 receptors. **Science Translational Medicine**, [s. l.], v. 7, n. 287, 2015.

WILHELM, E. A. *et al.* Antioxidant effect of quinoline derivatives containing or not selenium: Relationship with antinociceptive action quinolines are antioxidant and antinociceptive. **Anais da Academia Brasileira de Ciencias**, [s. l.], v. 89, n. 1, p. 457–467, 2017.

WILLIAMS, M. D.; LASCELLES, B. D. X. Early Neonatal Pain—A Review of Clinical and Experimental Implications on Painful Conditions Later in Life. **Frontiers in Pediatrics**, [s. l.], v. 8, 2020a.

WILLIAMS, M. D.; LASCELLES, B. D. X. Early Neonatal Pain—A Review of Clinical and Experimental Implications on Painful Conditions Later in Life. **Frontiers in Pediatrics**, [s. l.], v. 8, 2020b.

WOLF, E. *et al.* Innate Conformational Dynamics Drive Binding Specificity in Anti-Apoptotic Proteins Mcl-1 and Bcl-2. **Biochemistry**, [s. l.], v. 62, n. 11, p. 1619–1630, 2023.

WOOLF, C. J. Pain modulation in the spinal cord. **Frontiers in Pain Research**, [s. l.], v. 3, 2022.

WOOLFE, G.; MACDONALD, A. D. The Evaluation of the analgesic action of pethidine hydrochloride (demerol). **Journal of Pharmacology and Experimental Therapeutics**, [s. l.], v. 80, n. 3, p. 300–307, 1944.

WORLD HEALTH ORGANIZATION (WHO). **Global cancer burden growing, amidst mounting need for services**. [S. l.: s. n.], 2024. Disponível em: : <https://www.who.int/news/item/01-02-2024-global-cancer-burden-growing--amidstmounting-need-for-services>. Acesso em: 14 jul. 2025.

XIAOHONG, G. *et al.* [Effects of glucocorticoid receptor agonists on hyperalgesia of rats with neuropathic pain and its mechanisms]. **Chinese Journal of Applied**

Physiology, [s. l.], v. 38, n. 5, p. 470–474, 2022.

XU, T. *et al.* Epigenetic upregulation of CXCL12 expression mediates antitubulin chemotherapeutics-induced neuropathic pain. **Pain**, [s. l.], v. 158, n. 4, p. 637–648, 2017a.

XU, T. *et al.* Epigenetic upregulation of CXCL12 expression mediates antitubulin chemotherapeutics-induced neuropathic pain. **Pain**, [s. l.], v. 158, n. 4, p. 637–648, 2017b.

XU, J. *et al.* Longer versus Shorter Schedules of Vincristine, Irinotecan, and Temozolomide (VIT) for Relapsed or Refractory Ewing Sarcoma: A Randomized Controlled Phase 2 Trial. **Clinical Cancer Research**, [s. l.], v. 29, n. 6, p. 1040–1046, 2023.

XUE, V. W. *et al.* Transforming Growth Factor- β : A Multifunctional Regulator of Cancer Immunity. **Cancers**, [s. l.], v. 12, n. 11, p. 3099, 2020.

YOHN, C. N.; GERGUES, M. M.; SAMUELS, B. A. The role of 5-HT receptors in depression Tim Bliss. **Molecular Brain**, [s. l.], v. 10, n. 1, p. 1–12, 2017.

YOON, S. Y.; OH, J. Neuropathic cancer pain: Prevalence, pathophysiology, and management. **Korean Journal of Internal Medicine**, [s. l.], v. 33, n. 6, p. 1058–1069, 2018.

ZAJĄCZKOWSKA, R. *et al.* Mechanisms of Chemotherapy-Induced Peripheral Neuropathy. **International Journal of Molecular Sciences**, [s. l.], v. 20, n. 6, p. 1451, 2019.

ŽARKOVIĆ, N. *et al.* Spontaneous Regression of Cancer: Revealing Granulocytes and Oxidative Stress as the Crucial Double-edge Sword. **Frontiers in Bioscience-Landmark**, [s. l.], v. 27, n. 4, 2022.

ZHAN, X.; LI, J.; ZHOU, T. Targeting Nrf2-Mediated Oxidative Stress Response Signaling Pathways as New Therapeutic Strategy for Pituitary Adenomas. **Frontiers in Pharmacology**, [s. l.], v. 12, 2021.

ZHANG, H. Cancer Pain Management—New Therapies. **Current Oncology Reports**, [s. l.], v. 24, n. 2, p. 223–226, 2022.

ZHANG, S. Chemotherapy-induced peripheral neuropathy and rehabilitation: A review. **Seminars in Oncology**, [s. l.], v. 48, n. 3, p. 193–207, 2021.

ZHAO, J. Y. *et al.* DNA methyltransferase DNMT3a contributes to neuropathic pain by repressing Kcna2 in primary afferent neurons. **Nature Communications**, [s. l.], v. 8, n. May 2016, p. 1–15, 2017.

ZHAO, B. *et al.* Supplementation of lycopene attenuates oxidative stress induced neuroinflammation and cognitive impairment via Nrf2/NF- κ B transcriptional pathway. **Food and Chemical Toxicology**, [s. l.], v. 109, p. 505–516, 2017a.

ZHAO, B. *et al.* Supplementation of lycopene attenuates oxidative stress induced neuroinflammation and cognitive impairment via Nrf2/NF- κ B transcriptional pathway. **Food and Chemical Toxicology**, [s. l.], v. 109, p. 505–516, 2017b. Disponível em: <https://doi.org/10.1016/j.fct.2017.09.050>.

ZHENG, S. *et al.* TNF- α Impairs Pericyte-Mediated Cerebral Microcirculation via the NF- κ B/iNOS Axis after Experimental Traumatic Brain Injury. **Journal of Neurotrauma**, [s. l.], v. 40, n. 3–4, p. 349–364, 2023a.

ZHENG, S. *et al.* TNF- α Impairs Pericyte-Mediated Cerebral Microcirculation via the NF- κ B/iNOS Axis after Experimental Traumatic Brain Injury. **Journal of Neurotrauma**, [s. l.], v. 40, n. 3–4, p. 349–364, 2023b. Disponível em: <https://www.liebertpub.com/doi/10.1089/neu.2022.0016>.

ZHU, Y. *et al.* Inhibition of PINK1 senses ROS signaling to facilitate neuroblastoma cell pyroptosis. **Autophagy**, [s. l.], p. 1–20, 2025.

ZHU, M. *et al.* Na⁺/K⁺-ATPase-dependent autophagy protects brain against ischemic injury. **Signal Transduction and Targeted Therapy**, [s. l.], v. 5, n. 1, p. 55, 2020.

ZHU, S. *et al.* Roles of tumor-associated macrophages in tumor progression: implications on therapeutic strategies. **Experimental Hematology & Oncology**, [s. l.], v. 10, n. 1, p. 60, 2021.

ZHU, J. *et al.* The neuroprotective effect of oxytocin on vincristine-induced neurotoxicity in mice. **Toxicology Letters**, [s. l.], v. 340, p. 67–76, 2021. Disponível em: <https://linkinghub.elsevier.com/retrieve/pii/S0378427421000096>.

Supplementary material

Vincristine-Induced Disruption of Sensorimotor Ontogeny and Neural Integrity in Neonatal Rats: Behavioral, Histopathological and Molecular Insights

Ketlyn P. da Motta^a, Vanessa M. E. da Rocha^a, Eduardo B. Blödorn^a, Ana Paula B. Wille^a, Caren Aline R. da Fonseca^a, Joanna V. Z. Echenique^b, Mauro P. Soares^b, and Ethel A. Wilhelm^{a*}

^a *Postgraduate Program in Biochemistry and Bioprospecting, Laboratory of Preclinical and Translational Research in Pain and Chronic Disease, Center for Chemical, Pharmaceutical and Food Sciences, Federal University of Pelotas, Box 354. CEP 96010-900. Pelotas, RS, Brazil*

^b *Regional Diagnostic Laboratory Faculty of Veterinary Medicine, Federal University of Pelotas (UFPel), Pelotas, CEP 96010-900. RS, Brazil*

Table 1 - Primers used for one-step RT-qPCR reaction. Listed are the forward and reverse primer sequences used to amplify each target gene, as well as the B-actin, used as endogenous control.

Primer Name	Sequence	Reference
Bax Forward	5' CGGCGAATTGGAGATGAACTGG 3'	[1]
Bax Reverse	5' CTAGCAAAGTAGAAGAGGGCAACC 3'	
CASPASE-3 Forward	5' GTGGAAGTACGATGATATGGC 3'	[1]
CASPASE-3 Reverse	5' CGCAAAGTGAAGTGGATGAACC 3'	
MCL-1 Forward	5' CATGTTTGGCCTTCGGAGAA 3'	[2]
MCL-1 Reverse	5' GCATGTAGTTGGTGGCTGGAG 3'	
PINK-1 Forward	5' CCAAACACCTTGGCCTTCTA 3'	[3]
PINK-1 Reverse	5' CTGCCGAGATATTCCACATCAT 3'	
Parkin Forward	5' CTGGAAGTGTGGCTGTGAGTGGAA 3'	[4]
Parkin Reverse	5' AGAAGAAGAAATGGCTAACAAAGGTAGGAG 3'	
B-actin Forward	5' ACCCGCGAGTACAACCTTCT 3'	[5]
B-actin Reverse	5' ATACCCACCATCACACCCTGG 3'	

Table 2 – Adjusted p-values from Tukey's post hoc test following one-way ANOVA, indicating pairwise group comparisons.

	P-values		t, df	
	MALE	FEMALE	MALE	FEMALE
Startle	0.0060	0.0022	t=3.333. df=12	t=3.873. df=12
Response				
Acceleration	0.0007	0.0005	t=4.500. df=12	t=4.768, df=12
Cliff aversion	0.0016	0.0032	t=4.062. df=12	t=3.667, df=12
Test with digital anesthesiometer (DA)	<0.0001	<0.0001	t=20.55. df=12	t=22.31, df=12
Hot plate test	<0.0001	<0.0001	t=17.30. df=12	t=21.00. df=12
Cold plate test	<0.0001	<0.0001	t=5.944. df=12	t=6.041, df=12
Rotarod test	0.0029	0.0002	t=3.808, df=11	t=5.422. df=12
Gait analysis	<0.0001	<0.0001	t=10.16, df=12	t=8.006, df=12

Table 3 –Results from Tukey's post hoc test following two-way ANOVA. Values represent the F statistic and corresponding p-values for pairwise group comparisons.

Analysis male versus females		
Day 5		
	F statistic	P-values
Lateral axis (cranial width)	F (1, 24) = 1.022	P=0.3221
Anteroposterior axis (cranial length)	F (1, 24) = 0.4839	P=0.4934
Body length	F (1, 24) = 1.022	P=0.3221
Weight body	F (1, 24) = 0.2918	P=0.5940
Day 10		
Lateral axis (cranial width)	F (1, 24) = 0.2988	P=0.5897
Anteroposterior axis (cranial length)	F (1, 24) = 0.1967	P=0.6614
Body length	F (1, 24) = 0.2988	P=0.5897
Weight body	F (1, 24) = 0.7126	P=0.4069
Day 15		
Lateral axis (cranial width)	F (1, 24) = 1.951	P=0.1753
Anteroposterior axis (cranial length)	F (1, 24) = 0.1200	P=0.7321
Body length	F (1, 24) = 1.951	P=0.1753
Weight body	F (1, 24) = 0.1975	P=0.6607
Day 20		
Lateral axis (cranial width)	F (1, 24) = 0.2895	P=0.5955
Anteroposterior axis (cranial length)	F (1, 24) = 0.1524	P=0.6997
Body length	F (1, 24) = 0.2895	P=0.5955
Weight body	F (1, 24) = 0.1630	P=0.6900
Day 25		
Lateral axis (cranial width)	F (1, 24) = 1.629	P=0.2141
Anteroposterior axis (cranial length)	F (1, 24) = 6.425	P=0.0182
Body length	F (1, 24) = 1.629	P=0.2141
Weight body	F (1, 24) = 1.066	P=0.3122

Table 4 – Results from Tukey's post hoc test following two-way ANOVA. Values represent the F statistic and corresponding p-values for pairwise group comparisons.

Analysis male versus females		
Day 5		
	F statistic	P-values
Negative geotaxis	$F(1, 24) = 1.241$	$P=0.2762$
Recovery from decubitus	$F(1, 24) = 0.1667$	$P=0.6867$
Vibrissae placement	$F(1, 24) = 0.000$	$P>0.9999$
Day 10		
Negative geotaxis	$F(1, 24) = 0.2727$	$P=0.6063$
Recovery from decubitus	$F(1, 24) = 0.3333$	$P=0.5691$
Vibrissae placement	$F(1, 24) = 0.000$	$P>0.9999$
Day 15		
Negative geotaxis	$F(1, 24) = 0.2222$	$P=0.6416$
Recovery from decubitus	$F(1, 24) = 0.8000$	$P=0.3800$
Vibrissae placement	$F(1, 24) = 0.6429$	$P=0.4305$
Day 20		
Negative geotaxis	$F(1, 24) = 0.000$	$P>0.9999$
Recovery from decubitus	$F(1, 24) = 0.02474$	$P=0.8763$
Vibrissae placement	$F(1, 24) = 1.000$	$P=0.3273$
Day 25		
Negative geotaxis	$F(1, 24) = 0.8727$	$P=0.3595$
Recovery from decubitus	$F(1, 24) = 0.2727$	$P=0.6063$
Vibrissae placement	$F(1, 24) = 0.6279$	$P=0.4359$

Table 5 – Results of unpaired t-test. Values represent the t statistic, degrees of freedom (df), and corresponding p-values, assuming a Gaussian distribution.

	P-values		t, df	
	MALE	FEMALE	MALE	FEMALE
Cerebral cortex				
BAX	0.0162	0.0150	t=2.885, df=10	t=2.931, df=10
Caspase-3	0.0527	0.0051	t=2.197, df=10	t=3.573, df=10
MCL-1	0.0366	0.0432	t=2.379, df=11	t=2.314, df=10
PINK-1	0.1897	0.0563	t=1,407, df=10	t=2.661, df=4
Parkin	0.3771	0.0269	t=0.9242, df=10	t=2.591, df=10
TBARS levels	0.0064	0.0037	t=3.295, df=12	t=3.593, df=12
NPSH levels	0.0368	0.0339	t=2.348, df=12	t=2.394, df=12
Ca ²⁺ -ATPase	0.0278	0.0103	t=2.503, df=12	t=3.039, df=12
Mg ²⁺ -ATPase	0.7496	0.4097	t=0.3266, df=12	t=0.8543, df=12
Spinal cord				
BAX	0.8344	0.2260	t=0.2145, df=10	t=1,290, df=10
Caspase-3	0.0005	0.0506	t=4.524, df=14	t=2.221, df=10
MCL-1	0.0244	0.0375	t=2.648, df=10	t=2.396, df=10
PINK-1	0.0005	0.0417	t=5.011, df=10	t=2.334, df=10
Parkin	0.1902	0.0113	t=1,405, df=10	t=3.096, df=10
TBARS levels	0.0213	0.0874	t=2.648, df=12	t=1.861, df=12
NPSH levels	0.0252	0.0190	t=2.556, df=12	t=2.709, df=12
Ca ²⁺ -ATPase	0.7107	<0.0001	t=0.3807, df=11	t=5.951, df=12
Mg ²⁺ -ATPase	0.0214	0.0214	t=2.645, df=12	t=2.645, df=12
Hippocampus				
TBARS levels	0.0243	0.0149	t=2.576, df=12	t=2.839, df=12
NPSH levels	0.0707	0.0203	t=1.983, df=12	t=2.673, df=12
Ca ²⁺ -ATPase	0.0112	0.0003	t=2.992, df=12	t=5.043, df=12
Mg ²⁺ -ATPase	0.0035	0.0130	t=3.629, df=12	t=2.915, df=12
Cerebellum				
TBARS levels	0.0928	0.2182	t=1,826, df=12	t=1.299, df=12
NPSH levels	0.0013	0.1208	t=4.160, df=12	t=1.670, df=12
Ca ²⁺ -ATPase	0.0004	0.0096	t=4.800, df=12	t=3.076, df=12
Mg ²⁺ -ATPase	0.0134	0.4227	t=2.899, df=12	t=0.8301, df=12
Hypothalamus				
TBARS levels	0.0414	0.0128	t=2.284, df=12	t=2.923, df=12
NPSH levels	0.0414	0.0128	t=2.284, df=12	t=2.923, df=12
Mg ²⁺ -ATPase	0.0237	0.0057	t=2.588, df=12	t=3.355, df=12

Table 6 - Effects of vincristine sulfate (VCR) ($6 \mu\text{g.kg}^{-1}$, i.p.) on Thiobarbituric Acid Reactive Species (TBARS) and Non-protein Thiol Levels (NPSH) levels and Ca^{2+} - ATPase and Mg^{2+} - ATPase activities.

Parameter	Tissue	Sex	Group	Mean $\pm$ S.E.M
TBARS ^a	Cerebral cortex	Male	Control	99.05 $\pm$ 17.78
			VCR	183.65 $\pm$ 25.11
		Female	Control	77.14 $\pm$ 11.74
			VCR	194.69 $\pm$ 30.21**
	Cerebellum	Male	Control	34.85 $\pm$ 5.19
			VCR	52.45 $\pm$ 8.14
		Female	Control	21.67 $\pm$ 2.45
			VCR	34.88 $\pm$ 9.83
	Spinal Cord	Male	Control	505.35 $\pm$ 49.67
			VCR	763.75 $\pm$ 105.55*
		Female	Control	319.16 $\pm$ 42.68
			VCR	487.84 $\pm$ 85.00
	Hippocampus	Male	Control	295.36 $\pm$ 17.15
			VCR	416.83 $\pm$ 40.83*
		Female	Control	229.86 $\pm$ 25.20
			VCR	343.79 $\pm$ 30.66*
	Hypothalamus	Male	Control	276.87 $\pm$ 41.90
			VCR	419.46 $\pm$ 46.22*
		Female	Control	280.48 $\pm$ 59.74
			VCR	497.75 $\pm$ 46.87 *
NPSH ^b	Cerebral cortex	Male	Control	2.07 $\pm$ 0.15
			VCR	1.70 $\pm$ 0.04*
		Female	Control	1.90 $\pm$ 0.08
			VCR	1.69 $\pm$ 0.02*
	Cerebellum	Male	Control	1.36 $\pm$ 0.02
			VCR	1.17 $\pm$ 0.04**
		Female	Control	1.59 $\pm$ 0.17
			VCR	1.30 $\pm$ 0.04
	Spinal Cord	Male	Control	1.54 $\pm$ 0.07
			VCR	1.33 $\pm$ 0.04*
		Female	Control	1.50 $\pm$ 0.06
			VCR	1.31 $\pm$ 0.03*
	Hippocampus	Male	Control	1.82 $\pm$ 0.07
			VCR	1.67 $\pm$ 0.01
		Female	Control	1.55 $\pm$ 0.02
			VCR	1.46 $\pm$ 0.02*
Ca^{2+} -ATPase ^c	Cerebral cortex	Male	Control	37.07 $\pm$ 8.65
			VCR	101.90 $\pm$ 19.35*

Mg ²⁺ -ATPase ^c	Cerebellum	Female	Control	68.68 ± 6.74
			VCR	148.03 ± 25.15*
		Male	Control	6.97 ± 0.87
			VCR	14.99 ± 1.43***
	Spinal Cord	Female	Control	11.32 ± 1.83
			VCR	21.57 ± 2.73**
		Male	Control	3.91 ± 1.02
			VCR	4.34 ± 1.20
	Hippocampus	Female	Control	3.80 ± 0.52
			VCR	34.86 ± 6.22****
		Male	Control	62.25 ± 12.93
			VCR	128.49 ± 22.73*
		Female	Control	22.58 ± 3.79
			VCR	70.46 ± 8.59***
	Cerebral cortex	Male	Control	113.58 ± 9.59
			VCR	109.23 ± 8.80
		Female	Control	129.62 ± 7.81
			VCR	138.33 ± 6.45
	Cerebellum	Male	Control	266.66 ± 8.53
			VCR	371.61 ± 38.17*
		Female	Control	242.82 ± 24.10
			VCR	272.46 ± 24.92
	Spinal Cord	Male	Control	15.80 ± 0.57
			VCR	26.37 ± 3.56*
		Female	Control	9.03 ± 0.34
			VCR	15.07 ± 2.09*
	Hippocampus	Male	Control	22.64 ± 1.54
			VCR	33.26 ± 2.41**
		Female	Control	21.87 ± 1.37
			VCR	45.13 ± 7.85*
	Hypothalamus	Male	Control	25.32 ± 2.85
			VCR	35.12 ± 2.38*
		Female	Control	28.74 ± 1.72
			VCR	41.60 ± 3.29**

Results are reported as means ± standard error of the mean (S.E.M.) of 7 animals in each group. (*) P < 0.05. (**) P < 0.01, (***) P < 0.001 and (****) P < 0.0001 denote significance levels when comparing the VCR group to the control group. Data were analyzed statistically using Unpaired-parametric T-test.

^a Data are expressed as the nmol MDA/mg protein;

^b Data are expressed as the nmol NPSH/g of tissue;

^c Data are expressed as the nmol Pi/mg protein/min.

References

1. He, X.; Sun, J.; Huang, X. Expression of Caspase-3, Bax and Bcl-2 in Hippocampus of Rats with Diabetes and Subarachnoid Hemorrhage. *Exp Ther Med* **2017**, doi:10.3892/etm.2017.5438.
2. Chang, S.-H.; Hwang, C.-S.; Yin, J.-H.; Chen, S.-D.; Yang, D.-I. Oncostatin M-Dependent Mcl-1 Induction Mediated by JAK1/2-STAT1/3 and CREB Contributes to Bioenergetic Improvements and Protective Effects against Mitochondrial Dysfunction in Cortical Neurons. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research* **2015**, 1853, 2306–2325. doi:10.1016/j.bbamcr.2015.05.014.
3. Yu, J.; Li, Y.; Liu, X.; Ma, Z.; Michael, S.; Orgah, J.O.; Fan, G.; Zhu, Y. Mitochondrial Dynamics Modulation as a Critical Contribution for Shenmai Injection in Attenuating Hypoxia/Reoxygenation Injury. *J Ethnopharmacol* **2019**, 237, 9–19, doi:10.1016/j.jep.2019.03.033.
4. Chen, Z.; Wang, J.; He, J.; Fan, H.; Hou, S.; Lv, Q. Myoglobin Mediates Autophagy of NRK-52E in Rat Renal Tubular Epithelial Cells Via the Pink1/Parkin Signaling Pathway. *Medical Science Monitor* **2020**, 26, doi:10.12659/MSM.923045.
5. Amidfar, M.; Kim, Y.-K.; Wiborg, O. Effectiveness of Memantine on Depression-like Behavior, Memory Deficits and Brain mRNA Levels of BDNF and TrkB in Rats Subjected to Repeated Unpredictable Stress. *Pharmacological Reports* **2018**, 70, 600–606, doi:10.1016/j.pharep.2017.12.007.

4.5. Capítulo 5 – Manuscrito 4

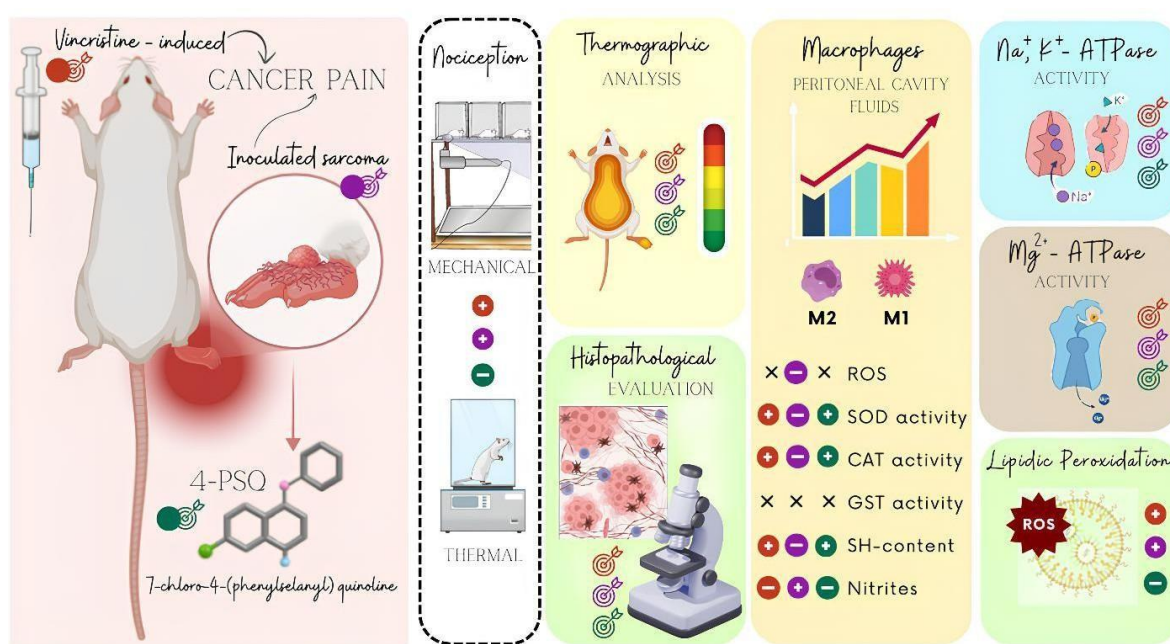
Eficácia terapêutica da 7-cloro-4-(fenilselanil)quinolina contra a dor oncológica induzida pela progressão tumoral e tratamento com vincristina

Levando em consideração os efeitos antitumorais *in vitro* do 4-PSQ e o efeito antinociceptivo apresentado em diferentes frentes da NPIV, elaboramos esta quinta etapa. O conjunto de dados descritos no estudo abaixo apresentou um modelo novo e translacional relevante de dor oncológica, combinando a nocicepção induzida por S180 com a neurotoxicidade induzida por VCR, recapitulando assim os estados mistos de dor experimentados por pacientes com câncer. Sendo assim, o manuscrito 4 teve como objetivo verificar *in vivo* os efeitos antitumorais do 4-PSQ observando a dor oncológica perante a progressão tumoral em um modelo de sarcoma e a NPIV. Ainda, o estudo contou com a avaliação histopatológica afim de confirmar o tecido tumoral de sarcoma; análise inflamatória por meio de avaliação termogênica e investigação de macrófagos peritoneais; e análise bioquímica da atividade de ATPases e peroxidação lipídica.

O sarcoma 180 (S180) e VCR induziram hiperalgesia significativa – característica da dor oncológica. Paralelamente, foram observados durante o protocolo experimental indicando a formação de edema tumoral e hipertermia local, os quais foram atenuados por 4-PSQ, particularmente em combinação com VCR. A histologia confirmou a massa tumoral e a infiltração inflamatória. Macrófagos peritoneais de camundongos portadores de S180 mostraram maior viabilidade, mas proliferação reduzida, refletindo desregulação funcional; o 4-PSQ restaurou ambos. O sarcoma também induziu desequilíbrio oxidativo e níveis elevados de nitrito no perfil de macrófagos peritoneais observados, enquanto 4-PSQ normalizou esses biomarcadores. Nas análises bioquímicas observamos que o sarcoma e/ou VCR prejudicaram as atividades das Na^+ , K^+ e Mg^{2+} -ATPases em regiões cerebrais, com o 4-PSQ revertendo as disfunções. Esses achados demonstraram robustos efeitos antinociceptivos, antioxidantes e imunomoduladores do 4-PSQ, destacando seu potencial como terapia adjuvante para dor oncológica e neuropatia induzida por quimioterapia.

MANUSCRITO 4

Os resultados do Capítulo 5 da tese estão apresentados sob a forma de manuscrito científico, o qual se encontra assim organizado. Os itens Materiais e Métodos, Resultados, Discussão dos Resultados e Referências Bibliográficas encontram-se no próprio artigo. O manuscrito científico encontra-se submetido na revista *Brain, Behavior and Immunity*.



Therapeutic Efficacy of 7-chloro-4-(phenylselanyl)quinoline Against Oncological Pain Induced by Tumor Progression and Vincristine Treatment

Ketlyn P. da Motta^a, Vanessa M. E. da Rocha^a, Bruna S. Pacheco^b, Tiago V. Collares ^b, Fabiana K. Seixas^b, Joanna V.Z. Echenique^c, Mauro P. Soares^c, Rhayane Tavares^d, Diego Alves^d, Nathalia S. Pedra^e, Natália P. Bona^e, Roselia M. Spanevello^e, Juliano S. Barin^f, Pricila N. Pinheiro^{ag}, Marcia F. Mesko^g and Ethel A. Wilhelm ^{a*}

^a Graduate Program in Biochemistry and Bioprospecting, Preclinical and Translational Research Group on Pain and Chronic Diseases, Center for Chemical, Pharmaceutical, and Food Science, Federal University of Pelotas (UFPel), 96010-900, Pelotas, RS, Brazil. ^b Cellular and Molecular Oncology Research Group (GPO), CDTec, Federal University of Pelotas (UFPel), 96010-900, Pelotas, RS, Brazil. ^c Regional Diagnostic Laboratory Faculty of Veterinary Medicine, Federal University of Pelotas, Pelotas, RS, Brazil. ^d Graduate Program in Chemistry, Clean Organic Synthesis Laboratory, Federal University of Pelotas (UFPel), Pelotas, RS, Brazil. ^e Graduate Program in Biochemistry and Bioprospecting, Laboratory of Neurochemistry, Inflammation and Cancer, Pelotas, RS, Brazil. ^f Department of Food Science and Technology, Federal University of Santa Maria, 97105-900, Santa Maria, RS, Brazil. ^g Contaminant Control Laboratory in Biomaterials (LCCBio Federal University of Pelotas (UFPel), 96010-900, Pelotas, RS, Brazil.

*Address for Correspondence:

Ethel Antunes Wilhelm; e-mail: ethelwilhelm@yahoo.com.br / Phone: +55-53-32757360
Graduate Program in Biochemistry and Bioprospecting (PPGBBio), Center for Chemical, Pharmaceutical and Food Sciences, Federal University of Pelotas (UFPel), Capão do Leão Campus, Pelotas, Zip Code 96010-900, RS, Brazil.

Abstract

Cancer pain is a complex and multifactorial condition, often exacerbated by tumor progression and chemotherapeutic neurotoxicity. This study investigated the therapeutic potential of 7-chloro-4-(phenylselanyl)quinoline (4-PSQ) in a model of cancer pain induced by intraplantar inoculation of Sarcoma 180 (S180) cells and vincristine (VCR)-induced peripheral neuropathy. Male mice were randomly divided into five groups: Control, S180, S180+VCR, S180+4-PSQ, and S180+VCR+4-PSQ. On day 1, groups II–V received an intraplantar injection of 25 μ L of a suspension containing 10^6 S180 cells, whereas group I received vehicle. From days 2 to 6, groups III and V were treated with VCR (0.1 mg/kg, intraperitoneally). From days 8 to 17, animals were treated daily with 4-PSQ (1 mg/kg, orally). Nociceptive behavior was assessed on days 0, 7, 11, and 17, and tumor progression was monitored every two days by paw morphometry and thermography. On day 18, tissues were collected for histopathological, immunological, redox, and neurochemical analyses. S180 and VCR induced significant hyperalgesia, tumor edema, and local hyperthermia, all attenuated by 4-PSQ, particularly in combination with VCR. Histology confirmed a tumor mass and inflammatory infiltration. Peritoneal macrophages from S180-bearing mice showed increased viability but reduced proliferation, reflecting functional dysregulation; 4-PSQ restored both. S180 induced oxidative imbalance and elevated nitrite levels, while 4-PSQ normalized these biomarkers. Finally, S180 and/or VCR impaired Na^+ , K^+ , and Mg^{2+} -ATPase activities in cerebral regions, with 4-PSQ reversing dysfunctions. These findings demonstrate robust antinociceptive, antioxidant, and immunomodulatory effects of 4-PSQ, highlighting its potential as an adjuvant therapy for cancer pain and chemotherapy-induced neuropathy.

Keywords: cancer pain, macrophages, sarcoma, thermographic analysis, tumor progression.

Introduction

Oncological pain is a complex and debilitating condition that significantly reduces the quality of life for cancer patients (Evenepoel *et al.*, 2022; Yoon; Oh, 2018; Zhang, 2022). A recent epidemiological study by Snijders *et al.* (2023) found that, on average, 44.5% of patients experience cancer-related pain, increasing to 54.6% among those in advanced or terminal stages. Although initially thought to result from tumor growth and local invasion, cancer pain actually involves a much more intricate pathophysiology, including ongoing inflammation, nerve injury, and side effects from treatments, especially chemotherapy (Evenepoel *et al.*, 2022; Zhang, 2022).

Chemotherapeutic agents, although essential for controlling tumors, can paradoxically exacerbate nociceptive processes. Vincristine (VCR), a vinca alkaloid commonly used in cancer treatments because of its strong ability to inhibit cell division, is effective against a wide range of cancers (Li, G. Zhou *et al.*, 2021a; Uittenboogaard *et al.*, 2022). However, up to 90% of patients treated with VCR develop chemotherapy-induced peripheral neuropathy, a chronic, dose-limiting side effect characterized by axonal degeneration, neuroinflammation, and intense neuropathic pain (Purser; Johnston; McMillan, 2014; Tay *et al.*, 2022). These effects not only reduce treatment adherence but also create a significant clinical burden, with few therapeutic options available to address them.

To promote an understanding of the multifactorial mechanisms involved in the modulation and triggering of oncological pain conditions, an experimental investigation of patterns that encompass both the pain associated with tumor development and tissue compression by the tumor, as well as with chemotherapy treatment, is necessary. Therefore, in experimental settings, intraplantar

inoculation of Sarcoma 180 (S180) cells in rodents has emerged as a well-characterized model to recapitulate cancer-induced pain (Brigatte *et al.*, 2007; Gouveia *et al.*, 2018). This model mimics the main pathological characteristics of tumor progression, including tissue remodeling, inflammatory cell infiltration, and peripheral sensitization (Brigatte *et al.*, 2007; Gouveia *et al.*, 2018; Rezende *et al.*, 2021).

Despite the availability of pharmacological options such as opioids, antidepressants (duloxetine), and calcium channel modulators (pregabalin), current treatments are hindered by limited efficacy, tolerance development, and adverse side effects, often leading to treatment-resistant pain (Smith *et al.*, 2017; Wang *et al.*, 2022). In this therapeutic gap, selenium-based compounds have gained attention for their redox-modulating and neuroprotective properties. Among these, the organoselenium compound 7-chloro-4-phenylselenanylquinoline (4-PSQ) has demonstrated promising preclinical efficacy. Previous studies have demonstrated that 4-PSQ exerts significant effects against neuropathic pain caused by chemotherapy. The pharmacological potential of 4-PSQ is linked to its antioxidant effects, modulation of ATP-dependent enzymes involved in neuronal excitability (including Ca^{2+} , Mg^{2+} , and Na^+/K^+ -ATPases), and displays neuroprotective potential (Barth *et al.*, 2019a; Motta *et al.*, 2021c; Paltian *et al.*, 2022a; Reis *et al.*, 2020a, 2020c, 2022; Vogt *et al.*, 2018a). Its antinociceptive properties are likely mediated through anti-inflammatory pathways, including downregulation of pro-inflammatory cytokines (TNF- α , IL-1 β), restoration of Nrf2 and NF- κ B signaling, and attenuation of mitochondrial dysfunction (Pinz *et al.*, 2016a; Reis *et al.*, 2020c, 2022; Voss *et al.*, 2017a).

In this study, we aimed to evaluate the antinociceptive potential of 4-PSQ

in a murine model of cancer pain induced by S180 tumor inoculation and potentiated by VCR-induced neuropathy. Using a multimodal experimental approach, including behavioral pain assays (mechanical and thermal sensitivities), thermographic imaging, histopathological tumor validation, peritoneal macrophage cytotoxicity analysis, oxidative stress profiling, and enzymatic evaluation of Na^+ , K^+ -ATPase and Mg^{2+} -ATPase activities in distinct regions of the central nervous system, we sought to elucidate both peripheral and central mechanisms of 4-PSQ's pharmacological action. Our findings offer novel insights into the potential of 4-PSQ as a candidate adjuvant therapy for managing cancer- and chemotherapy-induced pain.

Materials and Methods

S180 sarcoma mouse model

S180 cells were obtained from the Rio de Janeiro Cell Bank (APABCAM, Federal University of Rio de Janeiro, Brazil). The cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum, 1% penicillin-streptomycin and 1% amphotericin B. Cultures were maintained at 37 °C in a humidified incubator with 5% CO_2 . Cell counts were performed using a Neubauer hemocytometer and the Trypan Blue dye exclusion method. For in vivo experiments, animals were inoculated with 20 μL of a suspension containing 1×10^6 tumor cells.

Animals

Experiments were conducted on 60-day-old male Swiss mice. The animals were kept under controlled environmental conditions (temperature: $22 \pm 2^\circ\text{C}$;

humidity: 20–80%) and a 12-hour light/dark cycle, with free access to standard laboratory food and water. All procedures received approval from the Institutional Animal Care and Use Committee of the Federal University of Pelotas, Brazil (protocol no. CEEA 24440-2019) and were performed in accordance with established ethical guidelines.

Drugs

The compound 4-PSQ (Fig. 1) was synthesized and structurally characterized by the Clean Organic Synthesis Laboratory (LASOL) at the Federal University of Pelotas. Structural elucidation was performed using proton and carbon-13 nuclear magnetic resonance spectroscopy (^1H and ^{13}C NMR). Compound purity was assessed via gas chromatography–mass spectrometry (GC–MS), confirming a purity level of 99.9% (Duarte *et al.*, 2017b; Savegnago *et al.*, 2013b). VCR sulfate was obtained from INTAS Pharmaceuticals® (Batch No. M2103904) and stored at 4°C.

The 4-PSQ was prepared at a dose of 1 mg/kg in canola oil (10 mg/mL) and administered orally via gavage (p.o.), considering its lipophilic nature. VCR was prepared at a dose of 0.1 mg/kg in 0.9% saline (10 mg/mL) and administered intraperitoneally (i.p.), following established protocols. All other reagents used for biochemical assays were of high analytical grade and obtained from Sigma-Aldrich (St. Louis, MO, USA).

Design Experimental for Oncological Pain

This study aimed to assess cancer pain caused by both VCR and tumor

growth using a well-established sarcoma model. Male mice were randomly divided into five experimental groups.

- Group I – Control: received an intraplantar (i.pl.) injection of 25 μ L of PBS solution, intraperitoneal (i.p.) injection of 0.9% saline solution (10 mL/kg), and oral administration of canola oil (10 mL/kg).
- Group II – S180: received an injection of 25 μ L (i.pl.) of a suspension containing S180 tumor cells, 0.9% saline solution i.p. (10 mL/kg), and oral administration of canola oil (10 mL/kg).
- Group III – S180 + VCR: received S180 cell inoculation (25 μ L; i.pl.), VCR was induced at 0.1 mg/kg (i.p.), and oral canola oil (10 mL/kg).
- Group IV – S180 + 4-PSQ: received S180 cell inoculation (25 μ L; i.pl.), 0.9% saline i.p. (10 mL/kg), and 4-PSQ treatment at a dose of 1 mg/kg (p.o.).
- Group V – S180 + VCR + 4-PSQ: received S180 cell inoculation (25 μ L; i.pl.), VCR at 0.1 mg/kg (i.p.), and 4-PSQ treatment at 1 mg/kg (p.o.).

Baseline nociceptive thresholds were set on day 0. Tumor induction was carried out on day 1 in groups II–V, while group I received only the vehicle. VCR (0.1 mg/kg, intraperitoneally) was administered once daily from days 2 to 6 in groups III and V; the other groups received isotonic saline as a vehicle control. Oral administration of 4-PSQ (1 mg/kg) occurred once daily from days 8 to 17 in groups IV and V, while the remaining groups received the canola oil vehicle (10 mL/kg) orally.

Nociceptive responses, mechanical allodynia, and thermal hyperalgesia were assessed on days 0, 7, 11, and 17. Tumor progression was monitored over time

through volumetric measurements of the affected paw every 48 hours. On day 18, animals underwent infrared thermographic imaging, followed by euthanasia. Tumor-inoculated tissues were excised for histopathological examination. Central nervous system regions (cerebral cortex, spinal cord, cerebellum, and hippocampus) were harvested for subsequent biochemical analyses, and peritoneal exudates were collected for immunophenotyping of macrophage populations. Figure 2 illustrates the experimental design clearly and structurally, aiding understanding of the temporal sequence and interventions.

Assessment of Tumor Progression

Tumor growth was monitored every 48 hours by measuring paw dimensions using a calibrated digital caliper. The S180 Sarcoma cells were previously inoculated into the plantar surface of the left hind paw, and measurements were taken throughout the experimental period to assess tumor progression. Two anatomical parameters were evaluated: *paw width* – defined as the lateral distance across the paw, corresponding to the frontal (coronal) plane, measured from the medial to the lateral margins; and *paw depth* – defined as the dorsoplantar distance, corresponding to the sagittal plane, measured from the plantar (ventral) surface to the dorsal aspect of the paw.

All measurements were taken with the animals gently restrained to reduce stress and movement. Data were recorded in centimeters (cm) and shown as average values for each time point. Progressive increases in paw size were seen as signs of tumor growth and related swelling, enabling a non-invasive, ongoing assessment of tumor burden in live subjects.

Assessment of Tumor-Associated Edema

To measure tumor-associated edema, a postmortem analysis was conducted after euthanasia on day 18 of the protocol. The left and right hind paws were surgically removed at the ankle joint immediately after sacrifice and weighed using a precision analytical balance (± 0.0001 g accuracy).

Edema was assessed by calculating the difference in tissue mass between the tumor-bearing (left) paw and the contralateral, non-inoculated (right) paw of the same animal, serving as an internal control. This method enables individualized normalization and reduces inter-animal variability caused by baseline anatomical differences. The following formula was used to estimate the extent of edema:

$$Paw\ Edema\ (mg) = Weight_{Left\ Paw\ (tumor)} - Weight_{Right\ Paw\ (control)}$$

This mass differential reflects the contribution of both tumor growth and associated inflammatory edema, providing a robust endpoint for comparative analysis of treatment efficacy.

Thermographic analysis

Thermographic imaging was performed using a long-wave infrared camera (7.5-13.0 μ m, FLIR E60, FLIR Systems, USA) with a resolution of 320 $\times$ 240 pixels and a frame rate of 30 Hz. Images were recorded and processed using ResearchIR software (version 3.5, FLIR Systems). Anesthetized mice were imaged at a distance of 0.15 m in a temperature-controlled room ($20 \pm 1^\circ\text{C}$). Thermal analysis was conducted using three approaches: (i) temperature range ($^\circ\text{C}$) across the entire body, including dorsal and ventral surfaces; (ii) temperature gradient ($^\circ\text{C}$) from the ankle to the tip of the left paw (tumor local); and (iii) point

temperature (°C) at the paw center for control animals and at the tumor center for experimental animals.

Behavior tests

Assessment of Mechanical Nociceptive Threshold

Mechanical sensitivity was evaluated on days 0, 7, 11, and 17 using a modified version of the method originally described by Alamri et al. (2018b). To ensure consistency and reduce environmental stress, mice were individually acclimated for at least 30 minutes in transparent acrylic enclosures placed over an elevated wire mesh platform, providing unobstructed access to the plantar surface of the hind paws. All procedures were performed in a temperature-controlled, noise-free environment.

Mechanical nociceptive thresholds were evaluated using a digital handheld force transducer (Digital Analgesimeter; Insight®, São Paulo, Brazil), equipped with a blunt polypropylene tip. A gradually increasing force was applied perpendicularly to the central region of the plantar surface of the hind paw until a reflexive withdrawal response was elicited. The force required to induce paw withdrawal was automatically recorded in grams (g) and considered the mechanical withdrawal threshold.

For each time point, the mechanical threshold was determined based on ten consecutive measurements per animal, performed in a rotating sequence across groups of up to 12 animals housed simultaneously within the testing apparatus. The procedure involved applying the stimulus to each animal in turn and then repeating the sequence until a total of ten rounds were completed. This design ensured consistent interstimulus intervals, minimizing habituation or

sensitization effects. The mean withdrawal threshold from the ten measurements was calculated for each animal and used for subsequent statistical analysis. Data were presented as line graphs depicting the temporal profile of mechanical hypersensitivity across experimental conditions.

Assessment of Thermal Hyperalgesia

Thermal nociception was evaluated using a modified version of the hot plate test originally described by Woolfe and MacDonald (1946). This assay is widely recognized as a reliable behavioral paradigm for assessing supraspinal nociceptive responses in rodents. Evaluations were conducted on experimental days 0, 7, 11, and 17 to monitor the development of thermal hyperalgesia over time.

Mice were individually placed in a transparent acrylic box positioned on a heated metal surface maintained at a constant temperature of 52 ± 1 °C. The latency to the first nociceptive response, characterized by hind paw licking, withdrawal, or jumping, was recorded in seconds and used as an index of thermal sensitivity. To prevent tissue damage, a maximum cut-off time of 45 seconds was enforced for all animals. Shortened response latencies were interpreted as indicative of increased thermal sensitivity. Each animal was tested only once per session, and all measurements were performed in a quiet, temperature-controlled room to minimize external stressors. Results were expressed as paw withdrawal latency (seconds) and analyzed to determine treatment-induced changes in thermal nociceptive thresholds.

Ex vivo analysis

On day 18 of the experimental protocol, animals were euthanized, and tissue samples were systematically collected for comprehensive multi-parametric analyses. Peritoneal fluid was first harvested to characterize macrophage phenotypes, evaluate cytotoxic functions, and assess oxidative damage profiles. Subsequently, hind paws were excised, weighed to quantify edema, and processed for detailed histopathological evaluation. Additionally, discrete regions of the central nervous system, including the cerebral cortex, spinal cord, cerebellum, and hippocampus, were dissected for biochemical assays measuring ATPase activities (Na^+/K^+ -ATPase and Mg^{2+} -ATPase) and lipid peroxidation marker. These analyses aimed to elucidate biochemical alterations associated with Sarcoma- and VCR-induced oncological pain, as well as to characterize the therapeutic effects of 4-PSQ.

Primary Culture of Peritoneal Macrophages

Primary cultures of peritoneal macrophages were established following the protocol described by Dos Santos et al. (2017), with minor modifications. Briefly, macrophages were harvested by lavage of the peritoneal cavity using 5 mL of sterile RPMI 1640 medium devoid of fetal bovine serum (FBS). The recovered cell suspension was centrifuged and washed twice with sterile phosphate-buffered saline (PBS) to remove residual contaminants, followed by resuspension in serum-free RPMI 1640 medium. Cells were then seeded into 6-, 48-, or 96-well culture plates and incubated at 37°C in a humidified atmosphere containing 5% CO_2 for 30 minutes to facilitate selective adherence of macrophages. Subsequently, non-adherent cells were gently removed by washing with serum-free RPMI 1640 medium. The remaining adherent cell population, enriched in

peritoneal macrophages, was utilized for downstream functional assays.

Cytotoxicity

Cell Viability Assay

To evaluate cell viability and proliferative capacity, peritoneal macrophages were seeded in 96-well plates at a density of 1×10^6 cells per well and incubated for 18 hours under standard culture conditions. Cell metabolic activity was subsequently assessed using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, a colorimetric technique based on the enzymatic reduction of the yellow tetrazolium salt MTT to insoluble purple formazan crystals by mitochondrial dehydrogenases in viable cells.

MTT reagent was added to each well at a final concentration of 0.5 mg/mL, and the plates were incubated for 90 minutes at 37 °C. Following incubation, the supernatant was carefully aspirated, and formazan crystals were solubilized in dimethyl sulfoxide (DMSO) with gentle agitation. Absorbance was quantified at 492 nm using a microplate spectrophotometer (SpectraMax 190, Molecular Devices, San Jose, CA, USA).

Cell viability was calculated relative to untreated controls according to the following formula:

$$\text{Cell viability rate (\%)} = \frac{OD_{treated}}{OD_{control}} \times 100\%$$

Results were presented as percentage viability relative to control cells.

Cell Proliferation Assay

Cell proliferation was evaluated using the sulforhodamine B (SRB) assay,

a colorimetric method that quantifies cellular protein content as an indirect measure of cell density and proliferation. The procedure was performed according to the protocol described by Pauwels et al. (2003), with minor modifications. Following 18 hours of treatment, macrophage cultures were gently washed with phosphate-buffered saline (PBS) and fixed by the addition of ice-cold 50% trichloroacetic acid (TCA) for 45 minutes at 4 °C to precipitate cellular proteins.

After fixation, the plates were thoroughly rinsed five times with distilled water to remove residual TCA. Cells were then stained with 0.4% (w/v) sulforhodamine B solution prepared in 1% acetic acid and incubated at room temperature, protected from light, for 30 minutes. Excess unbound dye was removed by washing the wells five times with 1% acetic acid. The protein-bound SRB dye was subsequently solubilized in 10 mM Tris base (pH ~10.5), and absorbance was measured at 530 nm using a microplate reader (SpectraMax 190, Molecular Devices, San Jose, CA, USA).

Proliferation rates were expressed as a percentage of the untreated control group according to the formula:

$$\text{Cell viability rate (\%)} = \frac{OD_{treated}}{OD_{control}} \times 100\%$$

Preparation of lysates for oxidative stress assays

After 18 hours of incubation, the cultures were washed twice with sterile water, and lysates were prepared manually using a cell scraper. Then, the collected sample was centrifuged at 1000 rpm for 10 minutes. The pellet was discarded, and the supernatant was used for analysis of oxidative parameter (Pedra et al., 2022). Protein determination was carried out according to Lowry et

al. (1951), using bovine serum albumin as a standard.

Oxidative stress analysis

Quantification of Reactive Oxygen Species (ROS)

Intracellular ROS levels were measured using the DCFH-DA (2',7'-dichlorodihydrofluorescein diacetate) assay, following the procedure described by Dos Santos et al. (2017), with slight modifications. Macrophage cultures were incubated with 1 μ M DCFH-DA for 30 minutes at 37 °C in the dark. Upon cellular uptake, DCFH-DA is deacetylated by intracellular esterases and oxidized by ROS to form the fluorescent compound DCF. Fluorescence intensity was then measured using a microplate reader (SpectraMax190) with excitation at 485 nm and emission at 520 nm. ROS levels were normalized to the total protein content and expressed as micromoles of DCF per milligram of protein.

Total sulfhydryl (SH) content

The SH content in cell lysates was determined using the 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB) assay, as previously described by Aksenov and Markesbery (2001), with minor modifications. This colorimetric method is based on the reaction between free thiol groups and DTNB, resulting in the formation of the yellow chromophore 5-thio-2-nitrobenzoic acid (TNB), which absorbs light at 412 nm. Briefly, cell lysates were diluted in phosphate-buffered saline (PBS, pH 7.4) containing 1 mM EDTA. The reaction was initiated by adding DTNB, and after sufficient incubation, the absorbance was recorded at 412 nm using a spectrophotometer (SpectraMax190). The concentration of SH groups was calculated using a standard curve of TNB and expressed as nanomoles of TNB per milligram of protein.

Superoxide dismutase (SOD) activity

The activity of SOD was assessed based on the method established by Misra and Fridovich (1972), which involves the inhibition of adrenaline auto-oxidation by superoxide radicals. In this assay, cell lysates were first treated with catalase to eliminate potential interference from hydrogen peroxide (H_2O_2). Subsequently, glycine buffer (pH 10.2) and adrenaline were added to initiate the reaction. The formation of adrenochrome, resulting from the oxidation of adrenaline, was monitored by measuring the absorbance at 480 nm using a microplate reader (SpectraMax 190). The enzyme activity was calculated based on the inhibition rate of adrenaline oxidation and expressed as units per milligram of protein.

Catalase (CAT) activity

CAT activity was determined following the protocol described by Aebi (1984), which is based on the decomposition of H_2O_2 in a potassium phosphate buffer (pH 7.0). Briefly, the reaction was initiated by adding H_2O_2 to the cell lysates prepared in phosphate buffer. The breakdown of H_2O_2 was monitored by measuring the decrease in absorbance at 240 nm at 37 °C using a microplate reader (SpectraMax 190). Enzyme activity was calculated from the rate of H_2O_2 decomposition and expressed as units per milligram of protein.

Glutathione S-transferase (GST) activity

GST activity was determined using 1-chloro-2,4-dinitrobenzene (CDNB) as the substrate, following a previously established protocol (Habig; Jakoby; B., 1974). The reaction mixture consisted of 1 mM CDNB (dissolved in ethanol), 10 mM reduced glutathione (GSH), 20 mM potassium phosphate buffer (pH 6.5), and 20 μL of the sample. The formation of the GS-DNB conjugate was monitored spectrophotometrically (SpectraMax 190). Enzyme activity was expressed as micromoles of GS-DNB formed per minute per milligram of protein ($\mu\text{mol}/\text{min}/\text{mg}$ protein).

Histopathological Evaluation

The posterior hind paws were collected postmortem and fixed by immersion in 10% neutral-buffered formalin for 24 hours. Following fixation, samples were decalcified in an 8% solution composed of equal parts hydrochloric acid and formic acid (1:1 ratio) for approximately 5 days. Decalcified tissues were then transversely sectioned, routinely processed, embedded in paraffin, and cut into sections 3–4 μm thick. Histological slides were stained with hematoxylin and eosin (H&E) and examined under light microscopy by two independent and blinded pathologists.

Skeletal muscle lesions were semi-quantitatively scored based on the extent of myofiber necrosis and accompanying inflammatory infiltration. The grading criteria were defined as follows:

- Mild (+): up to 33% of muscle fibers showing necrosis, with multifocal inflammatory cell infiltrates interspersed among preserved fibers;
- Moderate (++) : 34–66% of muscle fibers affected, with multifocal to coalescing inflammatory infiltrates;
- Severe (+++) : more than 66% of muscle fibers exhibiting necrosis, with diffuse and widespread inflammatory infiltration throughout the muscle tissue.

This grading system enabled a consistent and reproducible assessment of tumor-associated muscle damage across experimental groups.

Biochemical Assays

Tissue preparation

On the day of euthanasia, samples from the cerebral cortex, spinal cord, cerebellum, and hippocampus were dissected. The collected tissues were immediately frozen and stored at -80°C in an ultra-low-temperature freezer. For the biochemical assays, samples were homogenized in 50 mM Tris-HCl buffer (pH 7.4) and subsequently centrifuged at $900 \times g$ for 10 minutes to obtain the supernatant (S1). Protein concentration was determined spectrophotometrically at 595 nm using the Bradford assay (Bradford, 1976b), with bovine serum

albumin (BSA) serving as the standard. Protein concentrations were expressed as mg/mL. These values were used for normalization in subsequent biochemical analyses.

TBARS levels

TBARS levels were used as an indirect method to quantify the presence of malondialdehyde (MDA), one of the products formed during lipid peroxidation. The measurement of TBARS levels followed the protocol described by Ohkawa et al. (1979). An aliquot of S1 was added to a reaction mixture containing thiobarbituric acid (0.8%), sodium dodecyl sulfate (8.1%), and acetic acid (pH 3.4), and then incubated at 95°C for 2 hours. Subsequently, the absorbance was measured at 532 nm using a spectrophotometer. The results were reported as nmol MDA/mg protein.

Na⁺ K⁺ - ATPase and Mg²⁺ - ATPase activities

The reaction mixture consisted of S1, 3 mM MgCl₂, 125 mM NaCl, 20 mM KCl, and 50 mM Tris/HCl (pH 7.4), with a final volume of 500 µL. The reaction was initiated by adding ATP to a final concentration of 3.0 mM. Control samples were prepared under the same conditions with the addition of 0.1 mM ouabain. Ouabain is an inhibitor of the Na⁺, K⁺ pump, and its inclusion allowed the observation of enzyme activity related to the Mg²⁺ pump. To determine the Mg²⁺-ATPase activity, 1 mM ouabain was added to the reaction medium. The reactions were initiated by adding ATP and stopped after 30 minutes of incubation by the addition of 10% TCA.

The samples were further incubated at 37 °C for 30 minutes and the

incubation was halted by adding 10% TCA with 10 mM HgCl₂. Enzyme activity was calculated by measuring the difference in inorganic phosphate (Pi) levels between incubations conducted in the absence and presence of ouabain. The quantification of released inorganic phosphate (Pi) was performed using the method described by Fiske and Subbarow (1925a). The color reaction was spectrophotometrically analyzed at 650 nm. Results were expressed as nmol Pi/mg protein/min.

Statistical Analysis

Statistical analysis was performed using one-way ANOVA followed by Tukey's post-hoc test when appropriate. Data were presented as mean $\pm$ standard error of the mean (S.E.M.). Differences were considered significant at $P < 0.05$, using GraphPad Prism 9.5.0 and 8.0.1 software (GraphPad Prism, San Diego, USA).

Results

Assessment of Tumor Progression

Tumor progression in the Sarcoma-induced cancer pain model was quantitatively assessed by monitoring changes in paw width and depth every 48 hours (Fig. 3). These morphometric parameters, measured with a digital caliper, served as indirect indicators of tumor growth and local edema after intraplantar inoculation of S180 cells and systemic VCR administration. Figure 3A shows tumor progression by measuring the lateral width (latero-lateral dimension) of the animals' left hind paw. From day 3 to day 17 of the experiment, inoculation of S180 cells caused a steady increase in paw width across all groups receiving tumor induction (S180, S180 + VCR, S180 + 4-PSQ, and S180 + VCR + 4-PSQ). Notably, the S180 group showed significant increases in paw width compared to

the control group, with percentage differences of approximately 6% on day 3, 28% on day 5, 64% on day 7, 56% on day 9, 77% on day 11, 104% on day 13, 86% on day 15, and 66% on day 17.

VCR administration attenuated tumor-induced paw swelling on days 7, 11, and 13. Treatment with 4-PSQ alone (S180 + 4-PSQ group) significantly reduced paw width compared to the S180 group on days 11 and 15. Moreover, the combined treatment (S180 + VCR + 4-PSQ) resulted in a sustained reduction in paw width compared to the S180 group on days 7, 11, 13, 15, and 17. When comparing the S180 + VCR group to the S180 + VCR + 4-PSQ group, the addition of 4-PSQ enhanced the therapeutic effect, with greater reductions observed on days 13, 15, and 17.

Figure 3B shows tumor growth through depth measurements of the left hind paw during the experiment. From day 3 to day 17, intraplantar inoculation with S180 cells caused a steady and significant rise in paw depth among all tumor-bearing groups (S180, S180 + VCR, S180 + 4-PSQ, and S180 + VCR + 4-PSQ). Importantly, the S180 group showed notable increases in paw depth compared to the control group, with percentage differences reaching about 14% on day 3, 30% on day 5, 85% on day 7, 94% on day 9, 97% on day 11, 108% on day 13, 137% on day 15, and 125% on day 17.

VCR monotherapy attenuated tumor-induced paw swelling at early time points, with significant reductions observed on days 3, 7, and 9. Treatment with 4-PSQ alone (S180 + 4-PSQ) led to a significant reduction in paw depth only on day 13 compared to the S180 group. Importantly, the combination therapy (S180 + VCR + 4-PSQ) produced a sustained reduction in paw depth from day 13 onward, with significant differences observed on days 13, 15, and 17. Moreover,

when comparing the S180 + VCR group to the S180 + VCR + 4-PSQ group, the addition of 4-PSQ enhanced the therapeutic effect on paw depth, reaching statistical significance on day 9.

Assessment of Tumor-Associated Edema

Paw edema was assessed on day 18 of the experimental protocol, immediately following euthanasia, serving as a terminal endpoint for evaluating tumor-associated inflammatory swelling. As illustrated in Figure 3C, intraplantar inoculation with S180 Sarcoma cells resulted in marked edema formation and tumor development, evidenced by a substantial increase in the weight of the left hind paw (approximately 1850% relative to the contralateral paw). Monotherapy with either VCR or 4-PSQ, as well as the combined treatment (VCR + 4-PSQ), significantly attenuated paw swelling and contributed to a reduction in tumor burden.

Thermographic analysis

As Fig. 4 shows thermographic images with infrared profiles of representative left paws from animals in each group, while Table 1 presents the comparison of mean temperatures by group for the whole animal, the left paws (gradient), and the tumor.

Table 1. Comparison of mean temperatures (°C) of the whole animal, left paws, and tumors for each group (mean ± SD).

Group	Whole animal	Whole paw	Tumor*
Control	33.2 ± 0.4 ^A	23.4 ± 1.5 ^b	23.2 ± 0.7 ^c
S180	33.0 ± 0.7 ^A	28.3 ± 2.2 ^a	28.2 ± 1.6 ^{a.b}
S180 + VCR	33.8 ± 0.4 ^A	28.1 ± 1.8 ^a	29.8 ± 3.3 ^a
S180 + 4PSQ	32.7 ± 0.7 ^A	27.3 ± 1.8 ^a	27.1 ± 2.0 ^{ab}
S180 + VCR + 4PSQ	31.7 ± 0.7 ^A	26.0 ± 1.2 ^{a.b}	25.4 ± 0.9 ^{bc}

*Central point measurement of the left paw

A, a, b, c Superscript letters indicate statistical similarity or difference (One-Way ANOVA, test of Tukey, confidence level of 95%).

Following statistical analysis of the results presented in Table 1, no significant differences were observed in the mean temperatures of whole animals across all groups. However, this pattern was not observed for the mean temperatures of the paws and tumors. Both for the whole paw and tumor measurements, a significant difference was found between the control group and the other tumor-bearing groups, with the exception of the “S180 + VCR + 4PSQ” group, which consisted of tumor-bearing animals receiving both the chemotherapeutic agent and the test drug.

Regarding the measurements of the whole paw, the “S180 + VCR + 4PSQ” group showed temperatures statistically similar to the control group, while not differing significantly from the other tumor-bearing groups. For the point temperature measurements in tumors, this same group also displayed results statistically similar to the control group, and significantly different from the “S180 + VCR” group. Additionally, no significant differences were observed between the “S180 + VCR + 4PSQ” group and the “S180” or “S180 + 4PSQ” groups, likely due to a trend of slightly lower tumor site temperatures in the latter two groups compared to the chemotherapeutic-treated group. These findings may suggest that while the chemotherapeutic agent increases tumor site temperature, the test drug could contribute to its reduction.

Behavior tests

Assessment of Mechanical Nociceptive Threshold

The intraplantar inoculation of S180 cells induced a pronounced mechanical hyperalgesia at all assessed time points, day 7 (45%), day 11 (40%), and day 17 (43%), when compared to baseline values (Fig. 5A). The group receiving S180 in combination with VCR (S180 + VCR) exhibited an exacerbation of mechanical hypersensitivity relative to the S180 group, with increased nociceptive responses observed on day 7 (27%), day 11 (34%), and day 17 (40%). Treatments with either VCR or 4-PSQ alone, as well as their combined administration, did not fully restore mechanical sensitivity to control levels. However, beginning on day 11, animals treated with 4-PSQ, whether in the S180 + 4-PSQ or S180 + VCR + 4-PSQ groups, exhibited a significant reduction in mechanical hyperalgesia, indicating a potential antinociceptive effect of 4-PSQ in both tumor- and chemotherapy-associated pain conditions.

Assessment of Thermal Hyperalgesia

Intraplantar inoculation of S180 cells induced a marked increase in thermal sensitivity at all evaluated time points, day 7 (29%), day 11 (49%), and day 17 (27%), compared to the control group (Fig. 5B). Co-administration of VCR with S180 (S180 + VCR group) further exacerbated thermal hyperalgesia, with a significant increase in nociceptive responses observed on day 7 (54%) relative to the S180 group.

Treatment with 4-PSQ (S180 + 4-PSQ) effectively restored thermal sensitivity to control levels on days 11 and 17. Furthermore, when 4-PSQ was combined with VCR and tumor induction (S180 + VCR + 4-PSQ group), it significantly reversed the increased thermal hyperalgesia caused by the

combined effects of VCR and S180. Notably, the combination treatment showed a longer-lasting antinociceptive effect, with a marked decrease in thermal hypersensitivity maintained between days 11 and 17, exceeding the effectiveness observed in the S180 + 4-PSQ group.

Ex vivo analysis

Primary Culture of Peritoneal Macrophages

Cytotoxicity

To investigate the immunological impact of tumor progression and therapeutic interventions, cytotoxicity and proliferation assays were performed on peritoneal macrophages collected at the endpoint of the experimental protocol (Fig. 6).

As shown in Fig. 6A, the MTT assay revealed that inoculation with S180 cells resulted in a significant increase in macrophage viability (25%) compared to the control group, indicating heightened metabolic activity. Treatments with VCR, 4-PSQ, or their combination (VCR + 4-PSQ) effectively restored macrophage viability to control levels.

To further evaluate the functional state of these immune cells under tumor-induced inflammatory conditions, cell proliferation was assessed using the SRB assay (Fig. 6B). Contrary to the viability results, S180 inoculation significantly suppressed macrophage proliferation (82%), indicating a potential immunosuppressive or cell cycle-arresting effect of the tumor microenvironment. Both VCR and 4-PSQ, when given alone, were able to counteract this suppression and restore proliferation to nearly baseline levels. However, the combined therapy (VCR + 4-PSQ) did not reverse the inhibitory effect on

proliferation, suggesting a possible interference or antagonistic interaction in the context of tumor-driven immunomodulation.

Oxidative stress analysis

As shown in Fig. 7A, inoculation with S180 cells caused a significant decrease of about 73% in intracellular ROS levels in peritoneal macrophages compared to controls. Neither VCR administration nor 4-PSQ treatment, alone or in combination, significantly affected ROS production.

SOD activity was markedly inhibited following S180 inoculation, showing a 46% decrease compared with the control group (Fig. 7B). Notably, combined treatment with VCR and 4-PSQ restored SOD activity to baseline levels. Regarding the sulfhydryl content, tumor inoculation induced a substantial depletion (~57%) (Fig. 7C). VCR treatment alone and the VCR+4-PSQ combination effectively reversed this depletion, restoring sulfhydryl levels in peritoneal macrophages.

CAT activity, another key antioxidant defense enzyme, was inhibited (72%) in the S180 group compared to controls (Fig. 7D). Both individual and combined treatments restored CAT activity. GST activity, which is involved in xenobiotic detoxification, remained unchanged across all experimental groups, indicating no significant modulation by tumor presence or therapeutic interventions (Fig. 7E).

Nitrite levels, which indicate oxidative and inflammatory processes, increased by 51% after S180 inoculation (Fig. 7F). Treatment with 4-PSQ, either alone or combined with VCR, effectively brought nitrite concentrations in peritoneal macrophages back to normal.

Histopathological Evaluation

Histological analysis of the tarsal region in control animals without tumor inoculation revealed preserved tissue architecture, with no evidence of neoplastic infiltration or muscle damage (Fig. 8; Slides 1–3). In contrast, animals inoculated with

S180 cells exhibited extensive proliferation of pleomorphic tumor cells with prominent nuclei and dispersed chromatin, which invaded the subcutaneous tissue, bone, and skeletal muscle, while preserving the tendon structures (Fig. 8; Slide 4). Furthermore, as observed in Slide 5 (Fig. 8), in mice with sarcoma, a dense neutrophilic inflammatory infiltrate was present among the neoplastic cells, accompanied by the accumulation of cellular debris and frequent mitotic figures. Slide 6 (Fig. 8) also demonstrated, in mice with sarcoma, severe muscle damage (+++) characterized by marked necrosis, with only sparse residual myofibers surrounded by neoplastic cells and inflammatory cells.

Animals with sarcoma that received VCR showed a reduction in the neoplastic area (Fig. 8; Slide 7), although tumor cells continued to infiltrate and degrade bone tissue, leading to evident bone resorption (Fig. 8; Slide 8). VCR administration resulted in less muscle destruction compared to untreated tumor-bearing animals (Fig. 8; Slide 9), and necrosis and inflammation of the myofibers remained severe (+++). These animals exhibited a reduction in neoplastic cell density and subcutaneous invasion (Fig. 8; Slide 10), although bone infiltration persisted (Fig. 8; Slide 11). Muscle tissue damage was less extensive, with fewer necrotic fibers and a milder inflammatory response (Fig. 8; Slide 12). However, muscle damage in this group (S180+4-PSQ) was still classified as moderate (++).

Combined treatment with VCR and 4-PSQ for sarcoma yielded the most favorable histopathological results. Neoplastic cells were confined to specific regions (Fig. 8; Slide 13), and overall tissue damage was significantly lessened. Although some residual tumor infiltration into the bone persisted (Fig. 8; Slide 14), the muscle structure was largely preserved, with only mild necrosis and limited inflammatory infiltration (Fig. 8; Slide 15). Muscle damage in this group (S180+VCR+4-PSQ) was classified as mild (+).

Biochemical Assays

TBARS levels

As shown in Fig. 9A, a significant increase in TBARS levels (45%) was observed

in the cerebral cortex of animals inoculated with S180 tumor cells, as well as in the combination of S180 with VCR (38%), compared to the control group. Treatment with 4-PSQ, either alone or combined with VCR, effectively restored TBARS levels to baseline.

In the spinal cord (Fig. 9B), mice inoculated with S180 tumor cells or receiving VCR alone exhibited significantly elevated TBARS levels (+87% and +71% vs control, respectively). Treatment with 4-PSQ, either alone or combined with VCR, reversed this increase and restored lipid peroxidation to control values. In the hippocampus (Fig. 9C) and cerebellum (Fig. 9D) of S180-inoculated mice, TBARS did not rise significantly, although an upward trend was evident; importantly, 4-PSQ, alone or with VCR, significantly reduced TBARS versus the S180 group, consistent with an antioxidant neuroprotective effect even in regions with subclinical oxidative stress.

Na⁺ K⁺ - ATPase and Mg²⁺ - ATPase activities

As shown in Fig. 10A, enzymatic activity was mainly affected in the cerebral cortex. Inoculation with S180 tumor cells caused a significant increase in Na⁺, K⁺-ATPase activity (106%) compared to the control group. Interestingly, VCR treatment alone was enough to restore this cortical hyperactivity to normal levels when compared to the S180 group. Conversely, treatment with 4-PSQ in the presence of Sarcoma did not reduce the increased enzymatic activity, and there was no additional effect when VCR and 4-PSQ were combined.

In mice inoculated with S180 tumor cells, Na⁺,K⁺-ATPase activity measured in the spinal cord (Fig. 10B) and hippocampus (Fig. 10C) did not change significantly. However, both regions showed a trend toward increased activity. Notably, VCR, administered alone or together with 4-PSQ, significantly reduced hippocampal Na⁺,K⁺-ATPase activity relative to the S180 group. In the cerebellum of S180-bearing mice (Fig. 10D), none of the experimental conditions (tumor inoculation, VCR, 4-PSQ, or their combination) produced significant alterations in Na⁺,K⁺-ATPase activity.

In the cerebral cortex (Fig. 11A), a significant inhibition of Mg^{2+} - ATPase activity was observed only in the group that received both S180 inoculation and VCR treatment, compared to the control. No significant changes were found in the other experimental groups.

In S180-bearing mice, spinal cord Mg^{2+} -ATPase activity (Fig. 11B) tended to be suppressed in the S180 and S180+VCR groups, but changes did not reach statistical significance. By contrast, co-administration of VCR and 4-PSQ in tumor-bearing animals significantly increased Mg^{2+} -ATPase activity versus both S180 and S180+VCR, consistent with compensatory upregulation. In the hippocampus (Fig. 11C) of S180-bearing mice, Mg^{2+} -ATPase activity rose by 27% relative to control; VCR monotherapy significantly suppressed activity compared with both control and tumor groups. Notably, 4-PSQ, administered alone or with VCR, restored hippocampal activity to control levels, indicating modulation of ATPase homeostasis under pathological conditions. In the cerebellum (Fig. 11D) of S180-bearing mice, tumor inoculation produced a non-significant upward trend, whereas VCR significantly inhibited Mg^{2+} -ATPase relative to control and S180. Treatment with 4-PSQ, whether alone or combined with VCR, reversed these alterations, returning values to those observed in controls.

Discussion

This study introduces a novel and translationally relevant model of cancer pain by combining S180-induced nociception with VCR-induced neurotoxicity, thereby recapitulating the mixed pain states experienced by cancer patients. Beyond behavioral outcomes, the work integrates multimodal endpoints—

including histopathology, infrared thermography, biochemical assays of oxidative stress and ATPase function, and immunological profiling of peritoneal macrophages, providing a comprehensive mechanistic framework that links tumor progression, inflammation, and chemotherapy-induced neurotoxicity. The application of thermography represents an innovative, non-invasive approach for monitoring tumor-associated inflammation and therapeutic responses. The detailed characterization of macrophage redox imbalance and the coexistence of M1/M2 subtypes highlights the immune complexity underlying tumor-driven pain. Importantly, the findings establish 4-PSQ not only as an effective analgesic but also as a neuroprotective, antioxidant, and immunomodulatory agent with potential adjuvant antitumor properties, particularly when combined with VCR. Collectively, these advances address a critical gap in preclinical cancer pain research by offering an integrative model that bridges disease- and treatment-related mechanisms, and by positioning 4-PSQ as a promising candidate for the development of multifaceted therapeutic strategies.

The assessment of tumor progression through quantitative analysis of paw dimensions proved to be a reliable and sensitive indicator of local tumor development in the Sarcoma model. Both the mediolateral (width) and dorsoventral (depth) measurements of the inoculated paw progressively increased over the course of the experimental protocol, correlating with the expansion of neoplastic tissue and associated inflammatory processes (Calixto-Campos *et al.*, 2013; Cho *et al.*, 2023; Soyocak *et al.*, 2019). These changes were particularly marked in animals receiving S180 cell inoculation alone, whereas co-treatment with VCR and/or 4-PSQ attenuated paw enlargement, indicating a therapeutic modulation of tumor growth and/or associated edema.

Complementing these findings, terminal evaluation of paw edema through comparative mass analysis between the inoculated and contralateral paw further substantiated the inflammatory and tumoral burden. The marked increase in paw weight observed in the S180 group confirmed substantial edema formation, likely reflecting both tumor mass and peritumoral inflammation. Importantly, this endpoint measurement aligned with the dimensional analyses and was significantly mitigated by all treatment regimens, particularly when VCR and 4-PSQ were administered concurrently, suggesting a synergistic effect in controlling tumor-associated inflammatory swelling. Indeed, our findings are consistent with previous studies that employed S180 cell inoculation for the induction of solid tumors (Fang *et al.*, 2021; Santos *et al.*, 2018). This cell line is well-documented for its high *in vivo* proliferative capacity. In the present study, it successfully promoted robust and progressive tumor development in the hind paw of mice (Fang *et al.*, 2021; Rezende *et al.*, 2021; Santos *et al.*, 2018).

Thermographic analysis provides a non-invasive means of evaluating localized hyperthermia, often reflective of underlying inflammatory or hypermetabolic processes within tissues affected by infection, injury, or neoplastic progression (Masko *et al.*, 2021; Pérez-González *et al.*, 2025; Queiroz; de Cássia Fernandes de Lima, 2023). In the present study, thermographic imaging revealed a marked increase in surface temperature of the left hind paw, the site of S180 cell inoculation, in all tumor-bearing groups, consistent with tumor-induced inflammation and metabolic upregulation. Notably, animals in the S180 + VCR group exhibited the highest recorded temperature at the tumor site, suggesting that VCR potentiated local inflammatory processes. This observation is supported by the well-established proinflammatory properties of VCR, which

include enhanced immune activation and cytokine release, as well as the release of macrophages for phagocytic processes, potentially leading to increased peripheral vasodilation and tissue perfusion (Alenezi, 2023a; Blurette *et al.*, 2021; da Motta *et al.*, 2024). The temperature elevation in this group, which exceeded that observed in the S180 group, reinforces the notion that chemotherapeutic agents, while cytotoxic, may exacerbate inflammation and contribute to peripheral nociceptive sensitization. Interestingly, treatment with 4-PSQ alone or in combination with VCR significantly mitigated the thermal response at the tumor site, suggesting anti-inflammatory and/or antitumoral properties that can modulate local thermogenesis. Notably, the thermal profile of the entire body and contralateral limbs remained relatively unchanged across groups, highlighting the localized nature of the thermographic alterations observed. These findings underscore the utility of infrared thermography as a sensitive, non-invasive technique for detecting tumor-associated inflammation and monitoring therapeutic outcomes in preclinical cancer pain models.

Indeed, thermographic technology has been applied in a wide range of biomedical contexts, including breast cancer screening, burn and wound assessment, facial dermatological disorders, febrile condition monitoring, and evaluation of inflammatory joint diseases such as hand osteoarthritis and rheumatoid arthritis (Kesztyüs *et al.*, 2023). Notably, our study is among the first to employ this approach to visualize temperature changes in solid tumors induced by S180 cells and to demonstrate its sensitivity to chemotherapeutic modulation by VCR, thus opening new avenues for translational research in oncology and pain assessment.

Cancer pain results from a complex interaction among tumor-induced

tissue damage, inflammatory responses, and peripheral or central sensitization, often coexisting with neuropathic mechanisms, especially in the context of chemotherapy regimens such as VCR (Shao *et al.*, 2024; Xu *et al.*, 2023). In our study, behavioral analyses demonstrated that intraplantar inoculation of S180 cells was sufficient to induce persistent mechanical and thermal hyperalgesia, consistent with a model of inflammatory and tumor-related pain. Notably, coadministration of VCR worsened both types of nociception, particularly during the early stages of the protocol, indicating a potentiation of peripheral neuropathy that aligns with the known neurotoxic profile of VCR, involving microtubule disruption and axonal degeneration. These findings suggest a cumulative nociceptive burden resulting from the combined effects of tumor growth and chemotherapeutic toxicity, closely related to the cancer pain experienced by patients with cancer (Deng, 2019; Snijders *et al.*, 2023; Tay *et al.*, 2021b).

It is important to note that a key inflection point in the thermal sensitivity curve was observed on day 11. At this time point, animals subjected to either S180 inoculation or the combination of S180 and VCR (S180 + VCR) showed similar levels of thermal hyperalgesia. However, by day 17, a divergence in pain responses became clear: the S180 group experienced a partial reduction in thermal sensitivity, while the S180 + VCR group exhibited a persistent and even increased hyperalgesic response. This shift likely indicates the development of a chronic pain state driven by the combined effects of tumor growth and VCR-related neurotoxicity. The continued and heightened nociceptive signaling in the S180 + VCR group may suggest maladaptive plasticity, possibly involving peripheral nociceptor sensitization and/or activation of central pain pathways, including glial activation and the release of proinflammatory cytokines within the

spinal cord (Chiba *et al.*, 2022; Shen *et al.*, 2015b). These findings highlight the importance of this model in replicating mixed cancer-chemotherapy pain syndromes and emphasize the critical transition between the subacute and chronic phases of nociceptive regulation.

Notably, 4-PSQ significantly reduced nociceptive behaviors, with effects most pronounced at later time points, in both tumor-bearing mice and those receiving S180+VCR. This temporal profile suggests mechanisms that extend beyond anti-inflammatory actions, aligning with modulation of redox-sensitive signaling and neuromodulatory pathways reported for organochalcogens (de Oliveira *et al.*, 2022a; Ruhee *et al.*, 2020; Vogt *et al.*, 2018a). Consistent with this mechanistic plausibility, 4-PSQ has demonstrated efficacy across chemotherapy-induced neuropathy models, including those induced by oxaliplatin, paclitaxel, and VCR (Paltian *et al.*, 2022a; Reis *et al.*, 2020a, 2020c, 2022). Taken together, these findings position 4-PSQ as a promising candidate to mitigate cancer pain arising from both disease progression and neurotoxic treatment.

The analgesic profile of 4-PSQ is consistent with a neuroprotective mechanism. Prior studies show that 4-PSQ dampens neuroinflammation by lowering pro-inflammatory cytokines and modulates ATPases (Na^+/K^+ -, Ca^{2+} -, Mg^{2+} -ATPases) that govern neuronal excitability, thereby limiting nociceptive transmission along ascending pathways and engaging descending modulatory circuits (Barth *et al.*, 2019a; de Oliveira *et al.*, 2022a; Pinz *et al.*, 2018a; Reis *et al.*, 2020c, 2020a, 2022). In line with this mechanistic plausibility, we observed reversal of thermal and mechanical hypersensitivity, even under chemotherapy-exacerbated conditions, highlighting the relevance of 4-PSQ for mixed cancer pain states. Moreover, this study provides initial evidence that combining 4-PSQ

with VCR can aid tumor control while achieving meaningful analgesia, supporting 4-PSQ as a candidate adjunct for cancer pain management. Further study should refine dosing and scheduling to maximize antineoplastic efficacy while preserving the analgesic benefit.

Peritoneal macrophages were analyzed as indicators of systemic immunoadaptive responses, given their proximity to the intraperitoneal site of VCR administration and their relevance in the context of tumor-induced inflammatory pain. The analysis of peritoneal macrophages revealed functional dysregulation following inoculation with S180 cells. Although cell viability increased (MTT assay), proliferation was suppressed (SRB assay), indicating a metabolically active but non-proliferative profile, typical of tumor-associated macrophages (TAMs) polarized toward an M2-like phenotype, which favors immune modulation over mitosis (Zhu, S. *et al.*, 2021). Considering that the peritoneal cavity typically contains few resident macrophages, the increased cell number likely reflects monocyte recruitment from the bone marrow, consistent with the findings of Motta *et al.* (2024), who observed similar macrophage infiltration in the spinal cords of VCR-treated rats. These data support the notion that tumor burden and chemotherapeutic stress trigger systemic immune mobilization.

VCR, known for its neurotoxic and proinflammatory effects via microtubule disruption (Filippi-Chiela *et al.*, 2022; Starobova; Vetter, 2017a), surprisingly did not intensify the inflammatory phenotype of peritoneal macrophages when co-administered with S180 cells. This may be attributed to tissue-specific pharmacokinetics or the relatively immunologically quiescent nature of the peritoneal environment. Moreover, VCR's cytostatic action could restrict immune

cell expansion without inducing a robust inflammatory response, particularly outside directly affected tissues (Montague-Cardoso; Malcangio, 2021; Rubio *et al.*, 2004). Co-treatment with VCR and 4-PSQ restored both viability and proliferative capacity of macrophages, indicating therapeutic modulation of tumor-induced immune dysfunction. These results highlight a potential immunoregulatory effect of 4-PSQ, particularly relevant in the context of cancer pain and chemotherapy-induced neuroinflammation, where macrophage dynamics play a central role in disease progression and resolution.

Parallel to functional changes, S180 inoculation also disrupted redox balance in peritoneal macrophages, evidenced by decreased ROS, SOD, CAT, and non-protein thiol levels, hallmarks of M2 polarization (Gómez *et al.*, 2020). This redox suppression likely reflects tumor-mediated metabolic reprogramming through interleukin-10 (IL-10) and Transforming growth factor (TGF- β) signaling (Gu *et al.*, 2023; Xue *et al.*, 2020). VCR alone partially reversed this effect, while VCR + 4-PSQ fully restored redox parameters, suggesting a synergistic action on the antioxidant machinery. Interestingly, although ROS levels remained low, nitrite accumulation indicated enhanced nitrosative stress, likely mediated by iNOS activity, reinforcing the idea of a tumor-driven shift in macrophage oxidative pathways. These findings suggest a shift in peritoneal macrophages toward an M1-like profile, characterized by elevated nitrosative stress and impaired redox balance, as indicated by thiol depletion and reduced antioxidant activity (SOD and CAT). Notably, 4-PSQ, alone or with VCR, restored sulfhydryl and nitrite levels, indicating its potential to regulate macrophage redox status and counteract tumor-induced immune dysfunction.

The lack of significant changes in GST activity in peritoneal macrophages

exposed to S180, VCR, and 4-PSQ suggests that phase II detoxification is preserved under these conditions. This may reflect insufficient electrophilic stress to induce GST upregulation or the preferential activation of other antioxidant pathways, such as CAT or SOD. Additionally, GST may not be the primary detoxification route for reactive species generated, or temporal dynamics may have been missed. These results highlight the complexity of macrophage antioxidant responses in the context of tumors and chemotherapy. In summary, the results indicate the coexistence of M1 and M2 macrophage phenotypes, increased nitrosylation associated with inflammation, and inhibited CAT and SOD activities following tumor inoculation. In contrast, combined 4-PSQ and VCR treatment offers a promising strategy to modulate macrophage alterations in this Sarcoma model.

Histopathological analysis is essential for definitively characterizing tumor presence, invasion, tissue changes, and assessing therapeutic effects in this Sarcoma model. In the S180 group, histopathological analysis revealed a highly aggressive tumor phenotype marked by extensive proliferation of neoplastic cells with enlarged nuclei and dispersed chromatin, infiltrating subcutaneous tissue and causing widespread destruction of muscle and bone, sparing only tendons. The presence of abundant mitotic figures and pronounced anisokaryosis highlights the high proliferative capacity and cellular pleomorphism characteristic of malignancy. Additionally, the dense neutrophilic infiltrate and cellular debris reflect a marked inflammatory response secondary to extensive tumor-induced necrosis, which likely plays a dual role in promoting tumor progression and tissue remodeling while representing a host attempt to restrict tumor spread. Indeed, previous studies are in line with what we found, demonstrating neoplastic

proliferation, marked anisokaryosis, neutrophilic infiltration, and pronounced tissue invasion in muscles as characteristics of S180-induced tumors(Kazaryan *et al.*, 2022; Rezende *et al.*, 2021).

Treatment with VCR partially reduced tumor burden, but failed to prevent extensive bone destruction and severe muscle damage, as histopathology revealed persistent osteolytic lesions, marked necrosis, and inflammation, indicating that its cytotoxic effects were insufficient to halt local tissue injury, likely due to VCR-induced inflammatory mechanisms associated with peripheral toxicity. Consistent with previous studies, VCR's efficacy is often limited by incomplete tumor eradication and persistence of tissue damage, especially in bone, reflecting the chemotherapeutic challenges in completely reversing tumor-induced osteolysis(Benjamin *et al.*, 2015; Harris *et al.*, 2016). Furthermore, the sustained muscle necrosis and inflammation observed align with clinical and experimental evidence of VCR-induced tissue toxicity, including neurotoxicity and inflammatory side effects, which may exacerbate local tissue damage despite its antitumor effects (Li *et al.*, 2020a; MaloneyHuss *et al.*, 2020; Zhu, J. *et al.*, 2021).

Animals treated with 4-PSQ showed improved histopathological profiles compared to those treated with VCR alone, characterized by reduced tumor infiltration, moderate muscle preservation, and less inflammation. Despite ongoing bone damage, the attenuation of muscle injury suggests that 4-PSQ may exert protective effects through antioxidant and anti-inflammatory mechanisms that limit oxidative damage and modulate immune responses within the tumor microenvironment.

Remarkably, combination therapy (VCR + 4-PSQ) elicited the most substantial histopathological improvements, with neoplastic cells predominantly

confined to a localized focus, significant reduction of tissue destruction, attenuated bone involvement, and mild muscle necrosis and inflammation. This synergistic effect likely reflects complementary mechanisms whereby VCR exerts direct cytotoxicity while 4-PSQ modulates oxidative stress and inflammatory pathways. The reduced inflammatory infiltrate may correspond to diminished necrotic tumor burden, thereby curtailing neutrophil recruitment and consequent tissue damage. Collectively, these findings substantiate the therapeutic potential of 4-PSQ as an adjuvant in cancer treatment, highlighting the advantage of combined strategies that target both tumor proliferation and the tumor microenvironment to achieve enhanced preservation of tissue integrity and improved antitumor efficacy compared to VCR monotherapy.

Given the extensive tissue injury and inflammation observed histologically during S180 tumor progression and VCR treatment, we next evaluated whether these pathological changes were accompanied by molecular oxidative damage, assessing lipid peroxidation through TBARS quantification in CNS tissues. We found that both Sarcoma and VCR led to a significant increase in TBARS levels in the cerebral cortex and spinal cord of mice. This suggests that the tumor microenvironment is associated with profound metabolic dysfunction, which favors the overproduction of free radicals and subsequent lipid peroxidation. Indeed, dysregulated lipid metabolism has been identified as a key driver in oncogenesis, facilitating malignant transformation and conferring resistance to the cytotoxic effects of oxidative stress and lipid peroxidation (Žarković *et al.*, 2022). Similarly, the impact of VCR may be partly attributed to its ability to induce oxidative stress, as lipid peroxidation has been implicated in the cytotoxic and mitosis-disrupting actions of chemotherapeutic agents (Jaganjac *et al.*, 2020).

However, it is essential to note that the observed elevation of TBARS in the cortex and spinal cord tissues, which are not directly targeted by the tumor, indicates a nonspecific lipid peroxidation process that contributes to neurotoxicity and may underlie the development of peripheral neuropathy.

The cerebral cortex and spinal cord are key structures in pain modulation via the ascending and descending pathways, and elevated TBARS levels in these regions may impair neuronal integrity and enhance hyperalgesia. The cortex contributes to sensory and emotional aspects of pain perception(Sun *et al.*, 2023), while the spinal cord integrates nociceptive input and modulates pain intensity and state transitions(Woolf, 2022). Therefore, oxidative stress in these structures likely contributes to maladaptive pain signaling and altered somatosensory processing in the context of cancer pain.

Treatment with 4-PSQ, alone or in combination with VCR, restored TBARS levels to baseline, indicating strong antioxidant activity against tumor- and drug-induced oxidative damage in the CNS. We hypothesized that its lipophilic nature likely facilitates membrane incorporation, enhancing the protection of lipid bilayers against peroxidation and preserving neuronal integrity. These findings suggest a potential neuroprotective role for 4-PSQ, which may be achieved through the attenuation of reactive species and the stabilization of membrane structures. In hippocampal and cerebellar tissues collected from S180-bearing mice, TBARS levels showed a consistent upward trend that did not reach statistical significance, indicating subclinical oxidative stress. Notably, 4-PSQ treatment significantly reduced TBARS in both regions relative to the S180 group, reinforcing its antioxidant, neuroprotective profile even in the absence of overt oxidative injury.

Na⁺,K⁺-ATPase, a membrane-bound enzyme essential for neuronal excitability, is highly susceptible to lipid peroxidation, which impairs membrane fluidity and ion transport (Bejček *et al.*, 2021; Cassol *et al.*, 2022b; Reis *et al.*, 2022). In cortical tissue collected from S180-bearing mice, tumor inoculation significantly increased Na⁺,K⁺-ATPase activity, likely reflecting a compensatory response to tumor-associated neuroexcitation and/or inflammation; such upregulation, while adaptive, raises ATP demand and may disturb energy homeostasis with consequences for neuronal viability (Zhu *et al.*, 2020). By contrast, VCR markedly inhibited cortical Na⁺,K⁺-ATPase activity, plausibly via oxidative stress or post-translational modification of the β subunit, as reported for another chemotherapeutics (Tummala *et al.*, 2009). Enzymatic inhibition can promote Na⁺ accumulation, compromise Na⁺/Ca²⁺ exchange, and precipitate Ca²⁺ overload, events linked to excitotoxicity and apoptosis in chemotherapy-induced neurotoxicity (Bae; Greenwald; Schwartz, 2021). Notably, 4-PSQ alone maintained Na⁺,K⁺-ATPase activity at elevated levels, mirroring the tumor effect and suggesting adaptive modulation of ion homeostasis under stress conditions. In the hippocampus of S180-bearing, VCR-treated animals, Na⁺,K⁺-ATPase activity was reduced, underscoring regional vulnerability to ion-transport imbalance; in this region, 4-PSQ did not restore enzymatic function, indicating limited efficacy under the present injury context. In spinal cord and cerebellar tissues from S180-bearing mice, Na⁺,K⁺-ATPase activity remained stable at the assessed time point, although observed trends may herald later impairment. Overall, Na⁺,K⁺-ATPase emerges as a region-specific indicator of neurotoxicity in tumor- and chemotherapy-associated settings.

To explore bioenergetic disruption, Mg²⁺-ATPase activity was assessed

across CNS regions. In the cortex, significant inhibition occurred only in the S180+VCR group, indicating that combined tumor and chemotherapeutic stress exceeds compensatory limits, likely due to mitochondrial dysfunction. In contrast, spinal cord Mg^{2+} -ATPase activity was enhanced in tumor-bearing animals treated with VCR+4-PSQ, suggesting a protective role of 4-PSQ via oxidative damage attenuation and energy preservation. In the hippocampus, S180 increased Mg^{2+} -ATPase activity, while VCR reduced it, patterns reversed by 4-PSQ, which also restored activity in the cerebellum. These findings highlight the region-specific vulnerability of Mg^{2+} -ATPase to tumor and drug-induced stress and support the therapeutic potential of 4-PSQ in preserving CNS bioenergetics.

Conclusion

This study explored the therapeutic potential of 4-PSQ in a clinically relevant model of cancer pain induced by S180 cells inoculation and VCR. The following key findings underscore the multifaceted effects of 4-PSQ in modulating tumor progression, pain behavior, neuroinflammation, and oxidative imbalance:

- *Analgesic efficacy in mixed pain states:* 4-PSQ effectively reversed mechanical and thermal hyperalgesia, even under VCR-potentiated conditions, indicating efficacy against both inflammatory and neuropathic components of cancer pain;
- *Modulation of tumor progression and edema:* Treatment with 4-PSQ, alone or in combination with VCR, significantly reduced paw swelling and mass, supporting anti-inflammatory and antitumor effects;
- *Immunomodulatory and antioxidant actions:* 4-PSQ restored redox balance and proliferation in peritoneal macrophages - reversing M2-like polarization; normalized ROS; regulation of the activity of CAT and SOD

enzymes; as well as thiol levels, indicating strong immunoregulatory and antioxidant properties.

- *Neuroprotective preservation of ATPase activity:* The compound preserved Na^+ , K^+ - and Mg^{2+} -ATPase activities in CNS regions affected by tumor burden and VCR, supporting energy homeostasis and neuronal integrity.
- *Thermographic evidence of anti-inflammatory action:* Infrared thermography revealed that 4-PSQ attenuated VCR-induced hyperthermia at the tumor site, confirming its capacity to mitigate localized inflammation.

These findings collectively highlight 4-PSQ as a promising adjuvant strategy in the management of cancer pain syndromes, offering neuroprotective, antioxidant, anti-inflammatory, and analgesic effects in a model of tumor progression combined with chemotherapy-induced neuropathy. Future studies should explore its translational potential in broader oncological contexts.

Acknowledgments and Funding

This study received financial support and scholarships from the following Brazilian agencies: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) (312747/2020-9, 406118/2021-3, 442284/2023-3, 403846/2025-0, 304038/2025-3), Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS) (21/2551-0001943-3, 22/2551-0000389-3, 23/2551-0001861-6; 24/2551-0001948-0). This study was also financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil

(CAPES) - Finance Code 001. This study also received financial assistance from L'ORÉAL-UNESCO-ABC for Women in Science. EAW, DA, FKS, TC, RMS, and MFM are recipients of CNPq fellowship.

Author contributions

KPM and EAW conceived and designed the study. KPM and VMER performed biochemical and behavioral analyses. BSP, TVC, and FKS were responsible for the cell culture of S180 cells. JVZE and MPS were responsible for histological analysis. RT and DA were responsible for the synthesis of the 4-PSQ compound. NSP, NPB, and RMS were responsible for macrophage analysis. JSB, PNP, and MFM were responsible for thermographic analysis. KPM and EAW wrote the manuscript. EAW supervised the study. All authors approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used GPTchat (OpenAI, 2025) to improve readability and language. After using this tool, the authors have reviewed and edited the content as necessary and take full responsibility for the content of the publication.

References

AEBl, H. Catalase in vitro. **Methods in Enzymology**, [S. l.], v. 105, p. 121–126, 1984.

AKSENOV, M. Y.; MARKESBERY, W. R. Changes in thiol content and expression of glutathione redox system genes in the hippocampus and cerebellum in Alzheimer's disease. **Neuroscience Letters**, [s. l.], v. 302, n. 2–3, p. 141–145, 2001.

ALAMRI, F. F. *et al.* Applicability of the grip strength and automated von Frey tactile sensitivity tests in the mouse photothrombotic model of stroke. **Behavioural Brain Research**, [s. l.], v. 336, n. August 2017, p. 250–255, 2018a.

ALAMRI, F. F. *et al.* Applicability of the grip strength and automated von Frey tactile sensitivity tests in the mouse photothrombotic model of stroke. **Behavioural Brain Research**, [s. l.], v. 336, n. August 2017, p. 250–255, 2018b. Disponível em: <http://dx.doi.org/10.1016/j.bbr.2017.09.008>.

ALBENSI, B. C. What Is Nuclear Factor Kappa B (NF- κ B) Doing in and to the Mitochondrion?. **Frontiers in Cell and Developmental Biology**, [s. l.], v. 7, 2019a.

ALBENSI, B. C. What Is Nuclear Factor Kappa B (NF- κ B) Doing in and to the Mitochondrion?. **Frontiers in Cell and Developmental Biology**, [s. l.], v. 7, 2019b. Disponível em: <https://www.frontiersin.org/article/10.3389/fcell.2019.00154/full>.

ALENEZI, S. K. The Ameliorative Effect of Thymoquinone on Vincristine-Induced Peripheral Neuropathy in Mice by Modulating Cellular Oxidative Stress and Cytokine. **Life**, [s. l.], v. 13, n. 1, p. 101, 2022.

ALENEZI, S. K. The Ameliorative Effect of Thymoquinone on Vincristine-Induced Peripheral Neuropathy in Mice by Modulating Cellular Oxidative Stress and Cytokine. **Life**, [s. l.], v. 13, n. 1, 2023a.

ALENEZI, S. K. The Ameliorative Effect of Thymoquinone on Vincristine-Induced Peripheral Neuropathy in Mice by Modulating Cellular Oxidative Stress and Cytokine. **Life**, [s. l.], v. 13, n. 1, 2023b.

ALWHAIBI, A. M. *et al.* Vincristine-Induced Neuropathy in Patients Diagnosed with Solid and Hematological Malignancies: The Role of Dose Rounding. **Journal of Clinical Medicine**, [s. l.], v. 12, n. 17, p. 5662, 2023.

AN, R. *et al.* Methylcobalamin Protects Melanocytes from H₂O₂-Induced Oxidative Stress by Activating the Nrf2/HO-1 Pathway. **Drug Design, Development and Therapy**, [s. l.], v. Volume 15, p. 4837–4848, 2021.

ANAND, K. J. S.; HICKEY, P. R. Pain and Its Effects in the Human Neonate and Fetus. **New England Journal of Medicine**, [s. l.], v. 317, n. 21, p. 1321–1329, 1987.

ANBALAGAN, M. *et al.* Post-translational modifications of nuclear receptors and human disease. **Nuclear receptor signaling**, [s. l.], v. 10, n. Figure 1, 2012.

ARETI, A. *et al.* Oxidative stress and nerve damage: Role in chemotherapy induced peripheral neuropathy. **Redox Biology**, [s. l.], v. 2, n. 1, p. 289–295, 2014.

BAE, E. H.; GREENWALD, M. K.; SCHWARTZ, A. G. Chemotherapy-Induced Peripheral Neuropathy: Mechanisms and Therapeutic Avenues. **Neurotherapeutics**, [s. l.], v. 18, n. 4, p. 2384–2396, 2021.

BAIG, M. A.; PANCHAL, S. S. Streptozotocin-Induced Diabetes Mellitus in Neonatal Rats: An Insight into its Applications to Induce Diabetic Complications. **Current Diabetes Reviews**, [s. l.], v. 16, n. 1, p. 26–39, 2019.

BAKER, D. W. History of The Joint Commission's Pain Standards. **JAMA**, [s. l.], v. 317, n. 11, p. 1117, 2017.

BARTH, A. *et al.* 7-Chloro-4-(Phenylselanyl) Quinoline with Memory Enhancer Action in Aging Rats: Modulation of Neuroplasticity, Acetylcholinesterase Activity, and Cholesterol Levels. **Molecular Neurobiology**, [s. l.], 2019a.

BARTH, A. *et al.* 7-Chloro-4-(Phenylselanyl) Quinoline with Memory Enhancer Action in Aging Rats: Modulation of Neuroplasticity, Acetylcholinesterase Activity, and Cholesterol Levels. **Molecular Neurobiology**, [s. l.], 2019b.

BARTLEY, E. J.; FILLINGIM, R. B. Sex differences in pain: a brief review of clinical and experimental findings. **British Journal of Anaesthesia**, [s. l.], v. 111, n. 1, p. 52–58, 2013.

BEJČEK, J. *et al.* Na⁺/K⁺-ATPase revisited: On its mechanism of action, role in cancer, and activity modulation. **Molecules**, [s. l.], v. 26, n. 7, 2021.

BENJAMIN, R. S. *et al.* Chemotherapy for Bone Sarcomas in Adults: The MD Anderson Experience. **American Society of Clinical Oncology Educational Book**, [s. l.], n. 35, p. e656–e660, 2015.

BENNETT, M. I. *et al.* Prevalence and aetiology of neuropathic pain in cancer patients: A systematic review. **Pain**, [s. l.], v. 153, n. 2, p. 359–365, 2012.

BEYER, C.; KAROLCZAK, M. Estrogenic stimulation of neurite growth in midbrain dopaminergic neurons depends on cAMP/protein kinase A signalling. **Journal of Neuroscience Research**, [s. l.], v. 59, n. 1, p. 107–116, 2000a.

BEYER, C.; KAROLCZAK, M. Estrogenic stimulation of neurite growth in midbrain dopaminergic neurons depends on cAMP/protein kinase A signalling. **Journal of Neuroscience Research**, [s. l.], v. 59, n. 1, p. 107–116, 2000b.

BHATT, S. *et al.* 5-HT₃ Receptor Antagonism: A Potential Therapeutic Approach for the Treatment of Depression and other Disorders. **Current Neuropharmacology**, [s. l.], v. 19, n. 9, p. 1545–1559, 2020.

BILBERG, A. *et al.* High prevalence of widespread pain in women with early rheumatoid arthritis. **Scandinavian Journal of Rheumatology**, [s. l.], v. 47, n. 6, p. 447–454, 2018. Disponível em: <https://doi.org/10.1080/03009742.2018.1447683>.

BLUETTE, C. T. *et al.* Behavioral, Histopathologic, and Molecular Biological Responses of Nanoparticle- and Solution-Based Formulations of Vincristine in Mice. **International Journal of Toxicology**, [s. l.], v. 40, n. 1, p. 40–51, 2021. Disponível em: <http://journals.sagepub.com/doi/10.1177/1091581820968255>.

BRADFORD, M. M. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. **Analytical biochemistry**, [s. l.], v. 72, n. 1–2, p. 248–254, 1976a.

BRADFORD, M. M. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. **Analytical biochemistry**, [s. l.], v. 72, n. 1–2, p. 248–254, 1976b. Disponível em: <https://www.sciencedirect.com/science/article/abs/pii/0003269776905273>.

BREIVIK, H. *et al.* Cancer-related pain: a pan-European survey of prevalence, treatment, and patient attitudes. **Annals of Oncology**, [s. l.], v. 20, n. 8, p. 1420–1433, 2009.

BRIGATTE, P. *et al.* Walker 256 Tumor-Bearing Rats as a Model to Study Cancer Pain. **The Journal of Pain**, [s. l.], v. 8, n. 5, p. 412–421, 2007.

BROWN, A. M.; ROSS, A.; BELSKY, J. A. Vincristine-Induced Autonomic Neuropathy Diagnosed via Quantitative Sudomotor Axon Reflex Sweat Test in an Adolescent Patient With Acute Leukemia. **Pediatric Blood & Cancer**, [s. l.], 2025.

BROZOVIĆ, G. Cancer Pain and Therapy. **Acta Clinica Croatica**, [s. l.], 2022.

BUJALSKA, M.; GUMUŁKA, S. W. Effect of cyclooxygenase and nitric oxide synthase inhibitors on vincristine induced hyperalgesia in rats. **Pharmacological Reports**, [s. l.], v. 60, n. 5, p. 735–741, 2008.

BURT, R. *et al.* Activated stromal cells transfer mitochondria to rescue acute lymphoblastic leukemia cells from oxidative stress. **Blood**, [s. l.], v. 134, n. 17, p. 1415–1429, 2019.

BUSCH, C. J.; BINDER, C. J. Malondialdehyde epitopes as mediators of sterile inflammation. **Biochimica et Biophysica Acta - Molecular and Cell Biology of Lipids**, [s. l.], v. 1862, n. 4, p. 398–406, 2017. Disponível em: <http://dx.doi.org/10.1016/j.bbalip.2016.06.016>.

CALIXTO-CAMPOS, C. *et al.* The Ehrlich Tumor Induces Pain-Like Behavior in Mice: A Novel Model of Cancer Pain for Pathophysiological Studies and Pharmacological Screening. **BioMed Research International**, [s. l.], v. 2013, p. 1–12, 2013.

CANTA, A.; POZZI, E.; CAROZZI, V. A. Mitochondrial dysfunction in chemotherapy-induced peripheral neuropathy (CIPN). **Toxics**, [s. l.], v. 3, n. 2, p. 198–223, 2015a.

CANTA, A.; POZZI, E.; CAROZZI, V. A. Mitochondrial dysfunction in chemotherapy-induced peripheral neuropathy (CIPN). **Toxics**, [s. l.], v. 3, n. 2, p. 198–223, 2015b.

CARACENI, A.; SHKODRA, M. Cancer Pain Assessment and Classification. **Cancers**, [s. l.], v. 11, n. 4, p. 510, 2019.

CASSOL, G. *et al.* A role of Na⁺, K⁺ -ATPase in spatial memory deficits and inflammatory/oxidative stress after recurrent concussion in adolescent rats. **Brain Research Bulletin**, [s. l.], v. 180, p. 1–11, 2022a.

CASSOL, G. *et al.* A role of Na⁺, K⁺ -ATPase in spatial memory deficits and inflammatory/oxidative stress after recurrent concussion in adolescent rats. **Brain Research Bulletin**, [s. l.], v. 180, p. 1–11, 2022b. Disponível em: <https://linkinghub.elsevier.com/retrieve/pii/S0361923021003543>.

CAVIEDES, A. *et al.* BDNF/NF-κB Signaling in the Neurobiology of Depression. **Current Pharmaceutical Design**, [s. l.], v. 23, n. 21, 2017a.

CAVIEDES, A. *et al.* BDNF/NF-κB Signaling in the Neurobiology of Depression. **Current Pharmaceutical Design**, [s. l.], v. 23, n. 21, 2017b. Disponível em: <http://www.eurekaselect.com/149163/article>.

CHANCAY, M. G.; GUENDSECHADZE, S. N.; BLANCO, I. Types of pain and their psychosocial impact in women with rheumatoid arthritis. **Women's Midlife Health**, [s. l.], v. 5, n. 1, p. 1–9, 2019.

CHANTAL, T. *et al.* ACTION OF VINCA ALKALOIDES ON CALCIUM MOVEMENTS THROUGH MITOCHONDRIAL MEMBRANE. **Pharmacological Research Communications**, [s. l.], v. 18, n. 6, p. 519–528, 1986.

CHEN, C. *et al.* Body weight, frailty, and chronic pain in older adults: A cross-sectional study. **BMC Geriatrics**, [s. l.], v. 19, n. 1, p. 1–10, 2019.

CHEN, X. *et al.* Current understanding of the molecular mechanisms of chemotherapy-induced peripheral neuropathy. **Frontiers in Molecular Neuroscience**, [s. l.], v. 17, 2024.

CHEN, S. P. *et al.* Involvement of hippocampal acetylcholinergic receptors in electroacupuncture analgesia in neuropathic pain rats. **Behavioral and Brain Functions**, [s. l.], v. 12, n. 1, p. 1–10, 2016.

CHEN, Q. M. Nrf2 for protection against oxidant generation and mitochondrial damage in cardiac injury. **Free Radical Biology and Medicine**, [s. l.], v. 179, p. 133–143, 2022.

CHEN, X.-J.; WANG, L.; SONG, X.-Y. Mitoquinone alleviates vincristine-induced neuropathic pain through inhibiting oxidative stress and apoptosis via the improvement of mitochondrial dysfunction. **Biomedicine & Pharmacotherapy**, [s. l.], v. 125, p. 110003, 2020.

CHENG, H. *et al.* Case report: Wallerian degeneration: The innate-immune response to adult-onset Still's disease peripheral nerve injury. **Frontiers in Neurology**, [s. l.], v. 13, 2022.

CHEON, J. H. *et al.* P-gp Inhibition by XL019, a JAK2 Inhibitor, Increases Apoptosis of Vincristine-treated Resistant KBV20C Cells with Increased p21 and pH2AX Expression. **Anticancer Research**, [s. l.], v. 37, n. 12, 2017a.

CHEON, J. H. *et al.* P-gp Inhibition by XL019, a JAK2 Inhibitor, Increases Apoptosis of Vincristine-treated Resistant KBV20C Cells with Increased p21 and pH2AX Expression. **Anticancer Research**, [s. l.], v. 37, n. 12, 2017b. Disponível em: <http://ar.iiarjournals.org/content/37/12/6761.abstract>.

CHIBA, T. *et al.* Vincristine increased spinal cord substance P levels in a peripheral neuropathy rat model. **Drug and Chemical Toxicology**, [s. l.], v. 45, n. 1, p. 393–397, 2022. Disponível em: <https://www.tandfonline.com/doi/full/10.1080/01480545.2019.1706547>.

CHIECHIO, S. *et al.* l-Acetylcarnitine Induces Analgesia by Selectively Up-Regulating mGlu2 Metabotropic Glutamate Receptors. **Molecular Pharmacology**, [s. l.], v. 61, n. 5, p. 989–996, 2002.

CHO, S.-H. *et al.* Anti-inflammatory activity of Echinosophora koreensis nakai root extract in lipopolysaccharides-stimulated RAW 264.7 cells and carrageenan-induced mouse paw edema model. **Journal of Ethnopharmacology**, [s. l.], v. 302, p. 115940, 2023.

CLARK, A. K.; MALCANGIO, M. Microglial signalling mechanisms: Cathepsin S and Fractalkine. **Experimental Neurology**, [s. l.], v. 234, n. 2, p. 283–292, 2012.

COBB, C. A.; COLE, M. P. Oxidative and nitrate stress in neurodegeneration. **Neurobiology of Disease**, [s. l.], v. 84, p. 4–21, 2015. Disponível em: <http://dx.doi.org/10.1016/j.nbd.2015.04.020>.

COLUZZI, F. *et al.* Pain management in childhood leukemia: Diagnosis and available analgesic treatments. **Cancers**, [s. l.], v. 12, n. 12, p. 1–13, 2020.

COLVIN, L. A. Chemotherapy-induced peripheral neuropathy: where are we now?. **Pain**, [s. l.], v. 160, n. 1, p. S1–S10, 2019.

COOK, K. M. *et al.* Experience of early-life pain in premature infants is associated with atypical cerebellar development and later neurodevelopmental deficits. **BMC Medicine**, [s. l.], v. 21, n. 1, p. 435, 2023.

COSTA, Y. M. *et al.* Reliability of the nociceptive blink reflex evoked by electrical stimulation of the trigeminal nerve in humans. **Clinical Oral Investigations**, [s. l.], v. 21, n. 8, p. 2453–2463, 2017.

COX, B. C. *et al.* Transport of multiple nicotinic acetylcholine receptors in the rat optic nerve: High densities of receptors containing $\alpha 6$ and $\beta 3$ subunits. **Journal of Neurochemistry**, [s. l.], v. 105, n. 5, p. 1924–1938, 2008.

CUREALL FRAMEWORK: WHO GLOBAL INITIATIVE FOR CHILDHOOD CANCER INCREASING ACCESS, ADVANCING QUALITY, SAVING LIVES. . [S. l.: s. n.], [s. d.].

DA MOTTA, K. P. *et al.* Insights into Vincristine-Induced Peripheral Neuropathy in Aged Rats: Wallerian Degeneration, Oxidative Damage, and Alterations in ATPase Enzymes. **ACS Chemical Neuroscience**, [s. l.], v. 15, n. 21, p. 3954–3969, 2024.

DA MOTTA, K. P. *et al.* The Antinociceptive Responses of MTDZ to Paclitaxel – Induced Peripheral Neuropathy and Acute Nociception in Mice : Behavioral , Pharmacological , and Biochemical Approaches. **Pharmaceuticals**, [s. l.], v. 16, n. 9, p. 1217, 2023.

DA ROCHA, V. M. E. *et al.* Structure-Activity Relationship of 7-Chloro-4-(Phenylselanyl) Quinoline: Novel Antinociceptive and Anti-Inflammatory Effects in Mice. **Chemistry & Biodiversity**, [s. l.], v. 22, n. 3, 2025.

DAGNINO, A. P. A.; CAMPOS, M. M. Chronic Pain in the Elderly: Mechanisms and Perspectives. **Frontiers in Human Neuroscience**, [s. l.], v. 16, p. 1–11, 2022.

DANG, X. *et al.* Alantolactone suppresses inflammation, apoptosis and oxidative stress in cigarette smoke-induced human bronchial epithelial cells through activation of Nrf2/HO-1 and inhibition of the NF- κ B pathways. **Respiratory Research**, [s. l.], v. 21, n. 1, p. 95, 2020.

DAVIS, R. L. *et al.* Effects of mechanistically distinct NF- κ B inhibitors on glial inducible nitric-oxide synthase expression. **Nitric Oxide**, [s. l.], v. 12, n. 4, p. 200–209, 2005.

DE FREITAS COUTO, S. *et al.* 7-chloro-4-(phenylselanyl) quinoline prevents dopamine depletion in a *Drosophila melanogaster* model of Parkinson's-like disease. **Journal of Trace Elements in Medicine and Biology**, [s. l.], v. 54, p. 232–243, 2019a. Disponível em: <https://linkinghub.elsevier.com/retrieve/pii/S0946672X1830405X>.

DE FREITAS COUTO, S. *et al.* 7-chloro-4-(phenylselanyl) quinoline prevents dopamine depletion in a *Drosophila melanogaster* model of Parkinson's-like disease. **Journal of Trace Elements in Medicine and Biology**, [s. l.], v. 54, p. 232–243, 2019b.

DE OLIVEIRA, R. L. *et al.* Prospecting for a quinoline containing selenium for comorbidities depression and memory impairment induced by restriction stress in mice. **Psychopharmacology**, [s. l.], v. 239, n. 1, p. 59–81, 2022a. Disponível em: <https://doi.org/10.1007/s00213-021-06039-8>.

DE OLIVEIRA, R. L. *et al.* Prospecting for a quinoline containing selenium for comorbidities depression and memory impairment induced by restriction stress in mice. **Psychopharmacology**, [s. l.], v. 239, n. 1, p. 59–81, 2022b.

DEL RIO, D.; STEWART, A. J.; PELLEGRINI, N. A review of recent studies on malondialdehyde as toxic molecule and biological marker of oxidative stress. **Nutrition, Metabolism and Cardiovascular Diseases**, [s. l.], v. 15, n. 4, p. 316–328, 2005.

DENG, G. Integrative Medicine Therapies for Pain Management in Cancer Patients. **The Cancer Journal**, [s. l.], v. 25, n. 5, p. 343–348, 2019.

DESFORGES, A. D. *et al.* Treatment and diagnosis of chemotherapy-induced peripheral neuropathy: An update. **Biomedicine & Pharmacotherapy**, [s. l.], v. 147, p. 112671, 2022.

DIOUF, B. *et al.* Association of an inherited genetic variant with vincristine-related peripheral neuropathy in children with acute lymphoblastic leukemia Critical revision of the manuscript for important intellectual content: Barthelemy Diouf; HHS Public Access. **Jama**, [s. l.], v. 313, n. 8, p. 815–823, 2015.

DOBRETISOV, M. Neuronal function and alpha3 isoform of the Na/K-ATPase. **Frontiers in Bioscience**, [s. l.], v. 10, n. 1–3, p. 2373, 2005a.

DOBRETISOV, M. Neuronal function and alpha3 isoform of the Na/K-ATPase. **Frontiers in Bioscience**, [s. l.], v. 10, n. 1–3, p. 2373, 2005b. Disponível em: <https://imrpess.com/journal/FBL/10/3/10.2741/1704>.

DOS SANTOS, L. M. *et al.* Methionine and methionine sulfoxide treatment induces M1/classical macrophage polarization and modulates oxidative stress and purinergic signaling parameters. **Molecular and Cellular Biochemistry**, [s. l.], v. 424, n. 1–2, p. 69–78, 2017.

DUARTE, L. F. B. *et al.* A simple method for the synthesis of 4-arylselanyl-7-chloroquinolines used as in vitro acetylcholinesterase inhibitors and in vivo memory improvement. **Tetrahedron Letters**, [s. l.], v. 58, n. 33, p. 3319–3322, 2017a.

DUARTE, L. F. B. *et al.* Organoselenium compounds from purines: Synthesis of 6-arylselanylpurines with antioxidant and anticholinesterase activities and memory improvement effect. **Bioorganic & Medicinal Chemistry**, [s. l.], v. 25, n. 24, p. 6718–6723, 2017b.

DUPUIS, L. L. *et al.* Anxiety, pain, and nausea during the treatment of standard-risk childhood acute lymphoblastic leukemia: A prospective, longitudinal study

from the Children's Oncology Group. **Cancer**, [s. l.], v. 122, n. 7, p. 1116–1125, 2016.

DZIECHCIAŻ, M.; BALICKA-ADAMIK, L.; FILIP, R. The problem of pain in old age. **Annals of agricultural and environmental medicine : AAEM**, [s. l.], v. . 1, n. 1, p. 35–38, 2013.

EDINOFF, A. N. *et al.* Selective Serotonin Reuptake Inhibitors and Adverse Effects: A Narrative Review. **Neurology International**, [s. l.], v. 13, n. 3, p. 387–401, 2021.

EDWARDS, R. R. *et al.* The role of psychosocial processes in the development and maintenance of chronic pain disorders. **Pain**, [s. l.], v. 176, n. 1, p. 70–92, 2017.

EIDE, S.; FENG, Z. P. Doxorubicin chemotherapy-induced “chemo-brain”: Meta-analysis. **European Journal of Pharmacology**, [s. l.], v. 881, n. July 2019, p. 173078, 2020.

EL HACHEM, G. *et al.* Advances in pain management for older patients with cancer. **ecancermedicalscience**, [s. l.], v. 13, 2019.

ELDUFANI, J.; BLAISE, G. The role of acetylcholinesterase inhibitors such as neostigmine and rivastigmine on chronic pain and cognitive function in aging: A review of recent clinical applications. **Alzheimer's and Dementia: Translational Research and Clinical Interventions**, [s. l.], v. 5, p. 175–183, 2019.

ELLMAN, G. L. Tissue Sulfhydryl Groups. **Archives of biochemistry and biophysics**, [s. l.], v. 82, n. 1, p. 70–77, 1959.

ELTOKHY, A. K.; TOEMA, O.; EL-DEEB, O. S. The Correlation Between PINK-1/Parkin Mediated Mitophagy, Endoplasmic Reticulum Stress and Total Polyamines in Pediatric Bronchial Asthma: An Integrated Network of Pathways. **Molecular Biology Reports**, [s. l.], v. 49, n. 1, p. 227–235, 2022.

EVENEPOEL, M. *et al.* Pain Prevalence During Cancer Treatment: A Systematic Review and Meta-Analysis. **Journal of Pain and Symptom Management**, [s. l.], v. 63, n. 3, p. e317–e335, 2022.

FANE, M.; WEERARATNA, A. T. How the ageing microenvironment influences tumour progression. **Nature Reviews Cancer**, [s. l.], v. 20, n. 2, p. 89–106, 2020.

FANG, J. *et al.* Expression Dynamics of Heme Oxygenase-1 in Tumor Cells and the Host Contributes to the Progression of Tumors. **Journal of Personalized Medicine**, [s. l.], v. 11, n. 12, p. 1340, 2021.

FILIPPI-CHIELA, E. C. *et al.* Vincristine promotes differential levels of apoptosis, mitotic catastrophe, and senescence depending on the genetic background of glioblastoma cells. **Toxicology in Vitro**, [s. l.], v. 85, p. 105472, 2022.

FISKE, B. C. H.; SUBBAROW, Y. The colorimetric determination of phosphorus. **The Journal of Biological Chemistry**, [s. l.], v. 66, n. september, p. 375–400, 1925a.

FISKE, B. C. H.; SUBBAROW, Y. The colorimetric determination of phosphorus. **The Journal of Biological Chemistry**, [s. l.], v. 66, n. september, p. 375–400, 1925b.

FITZMAURICE, C. *et al.* Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study Global Burden . **JAMA Oncology**, [s. l.], v. 3, n. 4, p. 524–548, 2017.

FLATTERS, S. J. L.; DOUGHERTY, P. M.; COLVIN, L. A. Clinical and preclinical perspectives on Chemotherapy-Induced Peripheral Neuropathy (CIPN): A narrative review. **British Journal of Anaesthesia**, [s. l.], v. 119, n. 4, p. 737–749, 2017.

FRANÇOIS, A. *et al.* The Low-Threshold Calcium Channel Cav3.2 Determines Low-Threshold Mechanoreceptor Function. **Cell Reports**, [s. l.], v. 10, n. 3, p. 370–382, 2015.

GAUTHIER, I.; TARR, M. J. Visual Object Recognition: Do We (Finally) Know More Now Than We Did?. **Annual Review of Vision Science**, [s. l.], v. 2, n. 1, p. 377–396, 2016.

GEŃGOTEK, A.; SKRZYDLEWSKA, E. Biological effect of protein modifications by lipid peroxidation products. **Chemistry and Physics of Lipids**, [s. l.], v. 221, n. February, p. 46–52, 2019.

GEŃGOTEK, A.; SKRZYDLEWSKA, E. Lipid peroxidation products' role in autophagy regulation. **Free Radical Biology and Medicine**, [s. l.], v. 212, p. 375–383, 2024.

GEISLER, S. Vincristine- and bortezomib-induced neuropathies – from bedside to bench and back. **Experimental Neurology**, [s. l.], v. 336, p. 113519, 2021a.

GEISLER, S. Vincristine- and bortezomib-induced neuropathies – from bedside to bench and back. **Experimental Neurology**, [s. l.], v. 336, p. 113519, 2021b. Disponível em: <https://doi.org/10.1016/j.expneurol.2020.113519>.

GEORGE, E. B.; GLASS, J. D.; GRIFFIN, J. W. Axotomy-induced axonal degeneration is mediated by calcium influx through ion-specific channels. **Journal of Neuroscience**, [s. l.], v. 15, n. 10, p. 6445–6452, 1995.

GILCHRIST, L. S.; MARAIS, L.; TANNER, L. Comparison of two chemotherapy-induced peripheral neuropathy measurement approaches in children. **Supportive Care in Cancer**, [s. l.], v. 22, n. 2, p. 359–366, 2014.

GILCHRIST, L.; TANNER, L. Gait Patterns in Children With Cancer and Vincristine Neuropathy. **Pediatric Physical Therapy**, [s. l.], v. 28, n. 1, p. 16–22, 2016.

GLOBAL CANCER BURDEN GROWING, AMIDST MOUNTING NEED FOR SERVICES. **Saudi medical journal**, [s. l.], v. 45, n. 3, p. 326–327, 2024.

GOESLING, J.; LIN, L. A.; CLAUW, D. J. Psychiatry and Pain Management: at the Intersection of Chronic Pain and Mental Health. **Current Psychiatry Reports**, [s. l.], v. 20, n. 2, 2018.

GOLCHIN, L. *et al.* Pistachio supplementation attenuates motor and cognition impairments induced by cisplatin or vincristine in rats. **Advanced Biomedical Research**, [s. l.], v. 4, n. 1, p. 92, 2015.

GOMBER, S.; DEWAN, P.; CHHONKER, D. Vincristine induced neurotoxicity in cancer patients. **Indian Journal of Pediatrics**, [s. l.], v. 77, n. 1, p. 97–100, 2010a.

GOMBER, S.; DEWAN, P.; CHHONKER, D. Vincristine induced neurotoxicity in cancer patients. **Indian Journal of Pediatrics**, [s. l.], v. 77, n. 1, p. 97–100, 2010b.

GÓMEZ, V. *et al.* Breast cancer–associated macrophages promote tumorigenesis by suppressing succinate dehydrogenase in tumor cells. **Science Signaling**, [s. l.], v. 13, n. 652, 2020.

GOUVEIA, D. N. *et al.* α -Terpineol reduces cancer pain via modulation of oxidative stress and inhibition of iNOS. **Biomedicine & Pharmacotherapy**, [s. l.], v. 105, p. 652–661, 2018.

GRANT, C. H. *et al.* Multimorbidity and analgesic-related harms: a systematic review. **British Journal of Anaesthesia**, [s. l.], v. 134, n. 6, p. 1717–1745, 2025.

GROTEN, C. J.; MACVICAR, B. A. Mitochondrial Ca^{2+} uptake by the MCU facilitates pyramidal neuron excitability and metabolism during action potential firing. **Communications Biology**, [s. l.], v. 5, n. 1, p. 900, 2022.

GU, C. *et al.* Cancer Cells Promote Immune Regulatory Function of Macrophages by Upregulating Scavenger Receptor MARCO Expression. **The Journal of Immunology**, [s. l.], v. 211, n. 1, p. 57–70, 2023.

GUHA, L.; SINGH, N.; KUMAR, H. Different Ways to Die: Cell Death Pathways and Their Association With Spinal Cord Injury. **Neurospine**, [s. l.], v. 20, n. 2, p. 430–448, 2023a.

GUHA, L.; SINGH, N.; KUMAR, H. Different Ways to Die: Cell Death Pathways and Their Association With Spinal Cord Injury. **Neurospine**, [s. l.], v. 20, n. 2, p. 430–448, 2023b.

HABIF, M. *et al.* Early Long-Term Memory Impairment and Changes in the Expression of Synaptic Plasticity-Associated Genes, in the McGill-R-Thy1-APP Rat Model of Alzheimer's-Like Brain Amyloidosis. **Frontiers in Aging Neuroscience**, [s. l.], v. 12, 2021. Disponível em: <https://www.frontiersin.org/articles/10.3389/fnagi.2020.585873/full>.

HABIG, W. H.; JAKOBY, M. J. P.; B., W. J. Glutathione S-Transferases: The first enzymatic step in mercapturic acid formation. **THE JOURNAL OF BIOLOGICAL CHEMISTRY**, [s. l.], v. 249, n. 22, p. 7130–7139, 1974.

HARRIS, J. C. *et al.* Sustained delivery of vincristine inside an orthotopic mouse sarcoma model decreases tumor growth. **Journal of Pediatric Surgery**, [s. l.], v. 51, n. 12, p. 2058–2062, 2016.

HASHMI, J. A.; DAVIS, K. D. Women experience greater heat pain adaptation and habituation than men. **Pain**, [s. l.], v. 145, n. 3, p. 350–357, 2009a.

HASHMI, J. A.; DAVIS, K. D. Women experience greater heat pain adaptation and habituation than men. **Pain**, [s. l.], v. 145, n. 3, p. 350–357, 2009b. Disponível em: <http://dx.doi.org/10.1016/j.pain.2009.07.002>.

HATHWAY, G. J. *et al.* Cancer Chemotherapy in Early Life Significantly Alters the Maturation of Pain Processing. **Neuroscience**, [s. l.], v. 387, p. 214–229, 2018.

HE, X.; SUN, J.; HUANG, X. Expression of caspase-3, Bax and Bcl-2 in hippocampus of rats with diabetes and subarachnoid hemorrhage. **Experimental and Therapeutic Medicine**, [s. l.], 2017.

HODAPP, J. W.; ALI, S.; DRENDEL, A. L. Bringing It All Together: A Review of the Challenges in Measuring Children's Satisfaction as a Key Component of Acute Pain Management. **Children**, [s. l.], v. 7, n. 11, p. 243, 2020.

HOLLIDAY, L. S. Vacuolar H⁺-ATPases (V-ATPases) as therapeutic targets: a brief review and recent developments. **Biotarget**, [s. l.], v. 1, n. 7, p. 18–18, 2017.

HONE, A. J.; MCINTOSH, J. M. **Nicotinic Acetylcholine Receptors in Neuropathic and Inflammatory Pain**. [S. l.: s. n.], 2018-. ISSN 1751553X.v. 592

HOOGEN, N. J. van den *et al.* Neonatal Plasticity of the Nociceptive System: Mechanisms, Effects, and Treatment of Repetitive Painful Procedures During NICU Admittance. **Current Pharmaceutical Design**, [s. l.], v. 23, n. 38, p. 5902–5910, 2018.

HORIE, K.; MA, J.; UMEZAWA, K. Inhibition of Canonical NF-κB Nuclear Localization by (–)-DHMEQ via Impairment of DNA Binding. **Oncology Research Featuring Preclinical and Clinical Cancer Therapeutics**, [s. l.], v. 22, n. 2, p. 105–115, 2015.

HOU, Y. *et al.* Ageing as a risk factor for neurodegenerative disease. **Nature**

Reviews Neurology, [s. l.], v. 15, n. 10, p. 565–581, 2019.

HUANG, Y. L. *et al.* Chronic pain and use of analgesics in the elderly: A nationwide population-based study. **Archives of Medical Science**, [s. l.], v. 16, n. 2, p. 627–634, 2020.

ISAKSEN, T. J.; LYKKE-HARTMANN, K. Insights into the Pathology of the $\alpha 2$ -Na⁺/K⁺-ATPase in Neurological Disorders; Lessons from Animal Models. **Frontiers in Physiology**, [s. l.], v. 7, 2016a.

ISAKSEN, T. J.; LYKKE-HARTMANN, K. Insights into the Pathology of the $\alpha 2$ -Na⁺/K⁺-ATPase in Neurological Disorders; Lessons from Animal Models. **Frontiers in Physiology**, [s. l.], v. 7, 2016b. Disponível em: <http://journal.frontiersin.org/Article/10.3389/fphys.2016.00161/abstract>.

JAGANJAC, M. *et al.* The relevance of pathophysiological alterations in redox signaling of 4-hydroxynonenal for pharmacological therapies of major stress-associated diseases. **Free Radical Biology and Medicine**, [s. l.], v. 157, p. 128–153, 2020.

JIANG, K.; SHI, Jinshan; SHI, Jing. Morin Alleviates Vincristine-Induced Neuropathic Pain via Nerve protective Effect and Inhibition of NF- κ B Pathway in Rats. **Cellular and Molecular Neurobiology**, [s. l.], v. 39, n. 6, p. 799–808, 2019a.

JIANG, K.; SHI, Jinshan; SHI, Jing. Morin Alleviates Vincristine-Induced Neuropathic Pain via Nerve protective Effect and Inhibition of NF- κ B Pathway in Rats. **Cellular and Molecular Neurobiology**, [s. l.], v. 39, n. 6, p. 799–808, 2019b. Disponível em: <https://doi.org/10.1007/s10571-019-00679-3>.

JIN, T.; LENG, B. Cynaropicrin Averts the Oxidative Stress and Neuroinflammation in Ischemic/Reperfusion Injury Through the Modulation of NF- κ B. **Applied Biochemistry and Biotechnology**, [s. l.], v. 195, n. 9, p. 5424–5438, 2023.

JOSEPH, E. K.; LEVINE, J. D. Mitochondrial electron transport in models of neuropathic and inflammatory pain. **Pain**, [s. l.], v. 121, n. 1–2, p. 105–114, 2006.

KAI, K. *et al.* Species and Sex Differences in Susceptibility to Olfactory Lesions Among the Mouse, Rat and Monkey Following an Intravenous Injection of Vincristine Sulphate. **Toxicologic Pathology**, [s. l.], v. 34, n. 3, p. 223–231, 2006.

KAKATKAR, S.; NARAYAN, A.; BALKRISHNAN, R. Prescription analgesic overuse in older adults: Can we mitigate this growing problem?. **AGING MEDICINE**, [s. l.], v. 5, n. 4, p. 294–296, 2022.

KALTSCHMIDT, B.; KALTSCHMIDT, C. NF-KappaB in Long-Term Memory and Structural Plasticity in the Adult Mammalian Brain. **Frontiers in Molecular Neuroscience**, [s. l.], v. 8, 2015.

KANG, L. *et al.* Oxaliplatin-induced peripheral neuropathy: clinical features, mechanisms, prevention and treatment. **Journal of Neurology**, [s. l.], n. 0123456789, 2020. Disponível em: <https://doi.org/10.1007/s00415-020-09942-w>.

KANZAKI, H. *et al.* Disabling the Nuclear Translocalization of RelA/NF- κ B by a Small Molecule Inhibits Triple-Negative Breast Cancer Growth. **Breast Cancer: Targets and Therapy**, [s. l.], v. Volume 13, p. 419–430, 2021.

KASAI, S. *et al.* Regulation of Nrf2 by Mitochondrial Reactive Oxygen Species in Physiology and Pathology. **Biomolecules**, [s. l.], v. 10, n. 2, p. 320, 2020.

KATSUYAMA, S. *et al.* Antinociceptive Effects of the Serotonin and Noradrenaline Reuptake Inhibitors Milnacipran and Duloxetine on Vincristine-Induced Neuropathic Pain Model in Mice. **ISRN Pain**, [s. l.], v. 2014, p. 1–7, 2014.

KAZARYAN, S. *et al.* Oxidative stress and histopathological changes in several organs of mice injected with biogenic silver nanoparticles. **Artificial Cells, Nanomedicine, and Biotechnology**, [s. l.], v. 50, n. 1, p. 331–342, 2022.

KESZTYÜS, D. *et al.* Use of Infrared Thermography in Medical Diagnosis, Screening, and Disease Monitoring: A Scoping Review. **Medicina**, [s. l.], v. 59, n. 12, p. 2139, 2023.

KHALILZADEH, M. *et al.* Aripiprazole prevents from development of vincristine-induced neuropathic nociception by limiting neural NOS overexpression and NF- κ B hyperactivation. **Cancer Chemotherapy and Pharmacology**, [s. l.], v. 86, n. 3, p. 393–404, 2020a.

KHALILZADEH, M. *et al.* Aripiprazole prevents from development of vincristine-induced neuropathic nociception by limiting neural NOS overexpression and NF- κ B hyperactivation. **Cancer Chemotherapy and Pharmacology**, [s. l.], v. 86, n. 3, p. 393–404, 2020b. Disponível em: <https://doi.org/10.1007/s00280-020-04127-8>.

KHIDR, H. Y. *et al.* Formoterol attenuated mitochondrial dysfunction in rotenone-induced Parkinson's disease in a rat model: Role of PINK-1/PARKIN and PI3K/Akt/CREB/BDNF/TrKB axis. **International Immunopharmacology**, [s. l.], v. 125, p. 111207, 2023.

KIGUCHI, N. *et al.* The critical role of invading peripheral macrophage-derived interleukin-6 in vincristine-induced mechanical allodynia in mice. **European Journal of Pharmacology**, [s. l.], v. 592, n. 1–3, p. 87–92, 2008.

KIM, S. J. *et al.* Antitumor Effects of Selenium. **International Journal of Molecular Sciences**, [s. l.], v. 22, n. 21, p. 11844, 2021.

KIM, Y. S. *et al.* Assessment of pain in the elderly: A literature review. **National Medical Journal of India**, [s. l.], v. 30, n. 4, p. 203–207, 2017a.

KIM, Y. S. *et al.* Assessment of pain in the elderly: A literature review. **National Medical Journal of India**, [s. l.], v. 30, n. 4, p. 203–207, 2017b.

KIM, S. H. *et al.* Regulation of P21-Activated Kinase-4 by Progesterone and Tumor Necrosis Factor- α in Human Endometrium and Its Increased Expression in Advanced-Stage Endometriosis. **The Journal of Clinical Endocrinology & Metabolism**, [s. l.], v. 98, n. 2, p. E238–E248, 2013a.

KIM, S. H. *et al.* Regulation of P21-Activated Kinase-4 by Progesterone and Tumor Necrosis Factor- α in Human Endometrium and Its Increased Expression in Advanced-Stage Endometriosis. **The Journal of Clinical Endocrinology & Metabolism**, [s. l.], v. 98, n. 2, p. E238–E248, 2013b. Disponível em: <https://academic.oup.com/jcem/article-lookup/doi/10.1210/jc.2012-2969>.

KIM, J.; SHARMA, R. P. Calcium-mediated activation of c-Jun NH2-terminal kinase (JNK) and apoptosis in response to cadmium in murine macrophages. **Toxicological Sciences**, [s. l.], v. 81, n. 2, p. 518–527, 2004.

KINOSHITA, P. F. *et al.* The influence of Na⁺, K⁺-ATPase on glutamate signaling in neurodegenerative diseases and senescence. **Frontiers in Physiology**, [s. l.], v. 7, n. JUN, p. 1–19, 2016.

KINTOSSOU, A. K. *et al.* Early Life Nutrition Factors and Risk of Acute Leukemia in Children: Systematic Review and Meta-Analysis. **Nutrients**, [s. l.], v. 15, n. 17, p. 3775, 2023.

KOHNO, T. *et al.* Peripheral nerve injury alters excitatory synaptic transmission in lamina II of the rat dorsal horn. **Journal of Physiology**, [s. l.], v. 548, n. 1, p. 131–138, 2003.

KOSTIĆ, M.; MARJANOVIĆ, J.; DIVAC, V. Organoselenium transition metal complexes as promising candidates in medicine area. **JBIC Journal of Biological Inorganic Chemistry**, [s. l.], v. 29, n. 6, p. 555–571, 2024.

KREMER, M. *et al.* How to study anxiety and depression in rodent models of chronic pain?. **European Journal of Neuroscience**, [s. l.], v. 53, n. 1, p. 236–270, 2021.

KUPPUSAMY, P. *et al.* Targeting metabolic pathways alleviates bortezomib-induced neuropathic pain without compromising anticancer efficacy in a sex-specific manner. **Frontiers in Pain Research**, [s. l.], v. 5, 2024.

LAFORGIA, M. *et al.* Peripheral Neuropathy under Oncologic Therapies: A Literature Review on Pathogenetic Mechanisms. **International Journal of Molecular Sciences**, [s. l.], v. 22, n. 4, p. 1980, 2021.

LAURITZEN, M. *et al.* Clinical Relevance of Cortical Spreading Depression in Neurological Disorders: Migraine, Malignant Stroke, Subarachnoid and Intracranial Hemorrhage, and Traumatic Brain Injury. **Journal of Cerebral Blood**

Flow & Metabolism, [s. l.], v. 31, n. 1, p. 17–35, 2011a.

LAURITZEN, M. *et al.* Clinical Relevance of Cortical Spreading Depression in Neurological Disorders: Migraine, Malignant Stroke, Subarachnoid and Intracranial Hemorrhage, and Traumatic Brain Injury. **Journal of Cerebral Blood Flow & Metabolism**, [s. l.], v. 31, n. 1, p. 17–35, 2011b. Disponível em: <http://journals.sagepub.com/doi/10.1038/jcbfm.2010.191>.

LAW, A. Y. S. *et al.* Histone deacetylase inhibitor-induced cellular apoptosis involves stanniocalcin-1 activation. **Experimental Cell Research**, [s. l.], v. 314, n. 16, p. 2975–2984, 2008.

LEE, S. J. *et al.* Fetal Pain. **JAMA**, [s. l.], v. 294, n. 8, p. 947, 2005.

LEE, J. Y. *et al.* The Antiallodynic Effect of Nefopam on Vincristine-Induced Neuropathy in Mice. **Journal of Pain Research**, [s. l.], v. Volume 13, p. 323–329, 2020. Disponível em: <https://www.dovepress.com/the-antiallodynic-effect-of-nefopam-on-vincristine-induced-neuropathy-peer-reviewed-article-JPR>.

LEE, B. Y.; HUR, E. M. A role of microtubules in oligodendrocyte differentiation. **International Journal of Molecular Sciences**, [s. l.], v. 21, n. 3, 2020.

LEGAKIS, L. P.; BIGBEE, J. W.; NEGUS, S. S. Lack of paclitaxel effects on intracranial Self-Stimulation in male and female rats: Comparison to mechanical sensitivity. **Behavioural Pharmacology**, [s. l.], v. 29, p. 290–298, 2018.

LEMOS, B. B. *et al.* ROLE OF 7-CHLORO-4- (PHENYLSELANYL) QUINOLINE IN THE TREATMENT. **Canadian physiology and pharmacology**, [s. l.], v. 99(4), n. 378–388, p. 1–50, 2021a.

LEMOS, B. B. *et al.* ROLE OF 7-CHLORO-4- (PHENYLSELANYL) QUINOLINE IN THE TREATMENT. **Canadian physiology and pharmacology**, [s. l.], v. 99(4), n. 378–388, p. 1–50, 2021b.

LI, H. *et al.* Adipocyte Fatty Acid-Binding Protein Promotes Palmitate-Induced Mitochondrial Dysfunction and Apoptosis in Macrophages. **Frontiers in Immunology**, [s. l.], v. 9, 2018.

LI, G. zhou *et al.* CaMKII and CaV3.2 T-type calcium channel mediate Connexin-43-dependent inflammation by activating astrocytes in vincristine-induced neuropathic pain. **Cell Biology and Toxicology**, [s. l.], p. 679–702, 2021a.

LI, G. zhou *et al.* CaMKII and CaV3.2 T-type calcium channel mediate Connexin-43-dependent inflammation by activating astrocytes in vincristine-induced neuropathic pain. **Cell Biology and Toxicology**, [s. l.], p. 679–702, 2021b.

LI, T. *et al.* Characterising vincristine-induced peripheral neuropathy in adults: symptom development and long-term persistent outcomes. **Supportive Care in Cancer**, [s. l.], v. 32, n. 5, p. 278, 2024.

LI, Y. *et al.* Dorsal root ganglion neurons become hyperexcitable and increase expression of voltage-gated T-type calcium channels (Cav3.2) in paclitaxel-induced peripheral neuropathy. **Pain**, [s. l.], v. 158, n. 3, p. 417–429, 2017.

LI, W. *et al.* Ibrutinib alleviates LPS-induced neuroinflammation and synaptic defects in a mouse model of depression. **Brain, Behavior, and Immunity**, [s. l.], v. 92, p. 10–24, 2021.

LI, G. zhou *et al.* Vincristine-induced peripheral neuropathy: A mini-review. **NeuroToxicology**, [s. l.], v. 81, p. 161–171, 2020a.

LI, G. zhou *et al.* Vincristine-induced peripheral neuropathy: A mini-review. **NeuroToxicology**, [s. l.], v. 81, p. 161–171, 2020b.

LIU, J. *et al.* Glutamatergic Neurons in the Amygdala Are Involved in Paclitaxel-Induced Pain and Anxiety. **Frontiers in Psychiatry**, [s. l.], v. 13, n. April, p. 1–11, 2022.

LIU, J. *et al.* Na/K-ATPase signaling and salt sensitivity: The role of oxidative stress. **Antioxidants**, [s. l.], v. 6, n. 1, p. 12–14, 2017a.

LIU, J. *et al.* Na/K-ATPase signaling and salt sensitivity: The role of oxidative stress. **Antioxidants**, [s. l.], v. 6, n. 1, p. 12–14, 2017b.

LIU, J.; LILLY, M. N.; SHAPIRO, J. I. Targeting Na/K-ATPase Signaling: A New Approach to Control Oxidative Stress. **Current Pharmaceutical Design**, [s. l.], v. 24, n. 3, p. 359–364, 2018a.

LIU, J.; LILLY, M. N.; SHAPIRO, J. I. Targeting Na/K-ATPase Signaling: A New Approach to Control Oxidative Stress. **Current Pharmaceutical Design**, [s. l.], v. 24, n. 3, p. 359–364, 2018b. Disponível em: <https://www.eurekaselect.com/158913/article>.

LIVAK, K. J.; SCHMITTGEN, T. D. Analysis of Relative Gene Expression Data Using Real-Time Quantitative PCR and the 2- $\Delta\Delta$ CT Method. **Methods**, [s. l.], v. 25, n. 4, p. 402–408, 2001a.

LIVAK, K. J.; SCHMITTGEN, T. D. Analysis of relative gene expression data using real-time quantitative PCR and the 2- $\Delta\Delta$ CT method. **Methods**, [s. l.], v. 25, n. 4, p. 402–408, 2001b.

LOWRY, Oliver H. *et al.* PROTEIN MEASUREMENT WITH THE FOLIN PHENOL REAGENT. **Journal of Biological Chemistry**, [s. l.], v. 193, n. 1, p. 265–275, 1951.

LUHMANN, H. J.; FUKUDA, A. Can we understand human brain development from experimental studies in rodents?. **Pediatrics International**, [s. l.], v. 62, n. 10, p. 1139–1144, 2020.

MACDONALD, A. D.; WOOLFE, G. Analgesic action of pethidine derivatives and

related compounds. **British journal of pharmacology and chemotherapy**, [s. l.], v. 1, p. 4–14, 1946.

MADSEN, M. L. *et al.* Aspects of vincristine-induced neuropathy in hematologic malignancies: a systematic review. **Cancer Chemotherapy and Pharmacology**, [s. l.], v. 84, n. 3, p. 471–485, 2019. Disponível em: <https://doi.org/10.1007/s00280-019-03884-5>.

MAGEE, J. C.; GRIENBERGER, C. Synaptic Plasticity Forms and Functions. **Annual Review of Neuroscience**, [s. l.], v. 43, n. 1, p. 95–117, 2020a.

MAGEE, J. C.; GRIENBERGER, C. Synaptic Plasticity Forms and Functions. **Annual Review of Neuroscience**, [s. l.], v. 43, n. 1, p. 95–117, 2020b. Disponível em: <https://www.annualreviews.org/doi/10.1146/annurev-neuro-090919-022842>.

MALDONADO, L. A. G. *et al.* Influence of tumor cell-derived TGF- β on macrophage phenotype and macrophage-mediated tumor cell invasion. **The International Journal of Biochemistry & Cell Biology**, [s. l.], v. 153, p. 106330, 2022.

MALONEYHUSS, M. A. *et al.* Efficacy and toxicity of mustargen, vincristine, procarbazine and prednisone (MOPP) for the treatment of relapsed or resistant lymphoma in cats. **Journal of Feline Medicine and Surgery**, [s. l.], v. 22, n. 4, p. 299–304, 2020.

MARKOVIC, T. *et al.* Pain induces adaptations in ventral tegmental area dopamine neurons to drive anhedonia-like behavior. **Nature Neuroscience**, [s. l.], v. 24, n. 11, p. 1601–1613, 2021.

MASKO, M. *et al.* A novel approach to thermographic images analysis of equine thoracolumbar region: the effect of effort and rider's body weight on structural image complexity. **BMC Veterinary Research**, [s. l.], v. 17, n. 1, p. 99, 2021.

MCCALLUM, J. B. *et al.* Loss of T-type calcium current in sensory neurons of rats with neuropathic pain. **Anesthesiology**, [s. l.], v. 98, n. 1, p. 209–216, 2003.

MCILWAIN, K. L. *et al.* The use of behavioral test batteries: Effects of training history. **Physiology & Behavior**, [s. l.], v. 73, n. 5, p. 705–717, 2001.

MCKELVEY, R. *et al.* Neuropathic pain is constitutively suppressed in early life by anti-inflammatory neuroimmune regulation. **Journal of Neuroscience**, [s. l.], v. 35, n. 2, p. 457–466, 2015.

MEFFERT, M. K. *et al.* NF- κ B functions in synaptic signaling and behavior. **Nature Neuroscience**, [s. l.], v. 6, n. 10, p. 1072–1078, 2003.

MELÉNDEZ, D. M. *et al.* Spatial memory deficits after vincristine-induced lesions to the dorsal hippocampus. **PLoS ONE**, [s. l.], v. 15, n. 4, p. 1–16, 2020.

MESTDAGH, F.; STEYAERT, A.; LAVAND'HOMME, P. Cancer Pain Management: A Narrative Review of Current Concepts, Strategies, and Techniques. **Current Oncology**, [s. l.], v. 30, n. 7, p. 6838–6858, 2023.

MICLESCU, A. A. *et al.* Association between systemic inflammation and experimental pain sensitivity in subjects with pain and painless neuropathy after traumatic nerve injuries. **Scandinavian Journal of Pain**, [s. l.], v. 7, 2022.

MINJ, E.; UPADHAYAY, S.; MEHAN, S. Nrf2/HO-1 Signaling Activator Acetyl-11-keto-beta Boswellic Acid (AKBA)-Mediated Neuroprotection in Methyl Mercury-Induced Experimental Model of ALS. **Neurochemical Research**, [s. l.], v. 46, n. 11, p. 2867–2884, 2021.

MISRA, H. P.; FRIDOVICH, I. The role of superoxide anion in the autoxidation of epinephrine and a simple assay for superoxide dismutase. **Journal of Biological Chemistry**, [s. l.], v. 247, n. 10, p. 3170–3175, 1972.

MOJARAD-JABALI, S. *et al.* Comparison of three synthetic transferrin mimetic small peptides to promote the blood–brain barrier penetration of vincristine liposomes for improved glioma targeted therapy. **International Journal of Pharmaceutics**, [s. l.], v. 613, p. 121395, 2022.

MOK, C. C.; LOK, E. Y. C.; CHEUNG, E. F. C. Concurrent psychiatric disorders are associated with significantly poorer quality of life in patients with rheumatoid arthritis. **Scandinavian Journal of Rheumatology**, [s. l.], v. 41, n. 4, p. 253–259, 2012.

MONTAGUE, K. *et al.* A novel interaction between CX 3 CR 1 and CCR 2 signalling in monocytes constitutes an underlying mechanism for persistent vincristine-induced pain. **Journal of Neuroinflammation**, [s. l.], v. 15, n. 1, p. 1–15, 2018.

MONTAGUE-CARDOSO, K.; MALCANGIO, M. Changes in blood–spinal cord barrier permeability and neuroimmune interactions in the underlying mechanisms of chronic pain. **Pain Reports**, [s. l.], v. 6, n. 1, p. 1–7, 2021.

MORA, E. *et al.* Vincristine-induced peripheral neuropathy in pediatric cancer patients. **American Journal of Cancer Research**, [s. l.], v. 6, n. 11, p. 2416–2430, 2016.

MORTAZAVI, H. Balance training as a promising intervention for reducing the risk of fall in elderly patients with chemotherapy-induced peripheral neuropathy. **Journal of Cancer Research and Therapeutics**, [s. l.], v. 15, n. 5, p. 1192, 2019.

MOSCHETTI, G. *et al.* Prokineticin 2 promotes and sustains neuroinflammation in vincristine treated mice: Focus on pain and emotional like behavior. **Brain, Behavior, and Immunity**, [s. l.], v. 82, n. September, p. 422–431, 2019a.

MOSCHETTI, G. *et al.* Prokineticin 2 promotes and sustains neuroinflammation in vincristine treated mice: Focus on pain and emotional like behavior. **Brain**,

Behavior, and Immunity, [s. l.], v. 82, n. September, p. 422–431, 2019b.

MOSELEY, A. E. *et al.* Deficiency in Na,K-ATPase α isoform genes alters spatial learning, motor activity, and anxiety in mice. **Journal of Neuroscience**, [s. l.], v. 27, n. 3, p. 616–626, 2007.

MOTTA, K. P. da *et al.* **7-Chloro-4- (phenylselanyl) quinoline reduces renal oxidative stress induced by oxaliplatin in mice**. [S. l.: s. n.], 2021a.

MOTTA, K. P. da *et al.* 7-Chloro-4- (phenylselanyl) quinoline reduces renal oxidative stress induced by oxaliplatin in mice. **Canadian physiology and pharmacology**, [s. l.], p. 1–37, 2021b.

MOTTA, K. P. da *et al.* 7-Chloro-4- (phenylselanyl) quinoline reduces renal oxidative stress induced by oxaliplatin in mice. **Canadian physiology and pharmacology**, [s. l.], p. 1–37, 2021c.

MOTTA, K. P. da *et al.* Target enzymes in oxaliplatin-induced peripheral neuropathy in Swiss mice: A new acetylcholinesterase inhibitor as therapeutic strategy. **Chemico-Biological Interactions**, [s. l.], v. 352, n. November 2021, p. 109772, 2022. Disponível em: <https://doi.org/10.1016/j.cbi.2021.109772>.

MOWLAVI, A. *et al.* Increased cutaneous nerve fibers in female specimens. **Plastic and Reconstructive Surgery**, [s. l.], v. 116, n. 5, p. 1407–1410, 2005.

MUSSBACHER, M. *et al.* NF- κ B in monocytes and macrophages – an inflammatory master regulator in multitasked immune cells. **Frontiers in Immunology**, [s. l.], v. 14, 2023a.

MUSSBACHER, M. *et al.* NF- κ B in monocytes and macrophages – an inflammatory master regulator in multitasked immune cells. **Frontiers in Immunology**, [s. l.], v. 14, 2023b. Disponível em: <https://www.frontiersin.org/articles/10.3389/fimmu.2023.1134661/full>.

NAGAI, J.; GOSHIMA, Y.; OHSHIMA, T. CRMP4 mediates MAG-induced inhibition of axonal outgrowth and protection against Vincristine-induced axonal degeneration. **Neuroscience Letters**, [s. l.], v. 519, n. 1, p. 56–61, 2012a. Disponível em: <http://dx.doi.org/10.1016/j.neulet.2012.05.020>.

NAGAI, J.; GOSHIMA, Y.; OHSHIMA, T. CRMP4 mediates MAG-induced inhibition of axonal outgrowth and protection against Vincristine-induced axonal degeneration. **Neuroscience Letters**, [s. l.], v. 519, n. 1, p. 56–61, 2012b.

NGO, V.; DUENNWALD, M. L. Nrf2 and Oxidative Stress: A General Overview of Mechanisms and Implications in Human Disease. **Antioxidants**, [s. l.], v. 11, n. 12, p. 2345, 2022.

NOGUEIRA, C. W.; ROCHA, J. B. T. Toxicology and pharmacology of selenium: Emphasis on synthetic organoselenium compounds. **Archives of Toxicology**, [s. l.], v. 85, n. 11, p. 1313–1359, 2011.

NOGUEIRA, C. W.; ZENI, G.; ROCHA, J. B. T. Organoselenium and organotellurium compounds: Toxicology and pharmacology. **Chemical Reviews**, [s. l.], v. 104, n. 12, p. 6255–6285, 2004.

NOVELLE, M. G.; CAMACHO-MORALES, A.; MARTÍNEZ DE MORENTIN, P. B. Editorial: Role of estrogens as key regulators of energy homeostasis. **Frontiers in Endocrinology**, [s. l.], v. 14, 2023.

OHKAWA, H.; OHISHI, N.; YAGI, K. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. **Analytical Biochemistry**, [s. l.], v. 95, n. 2, p. 351–358, 1979.

OLD, E. A. *et al.* Monocytes expressing CX3CR1 orchestrate the development of vincristine-induced pain. **Journal of Clinical Investigation**, [s. l.], v. 124, n. 5, p. 2023–2036, 2014a.

OLD, E. A. *et al.* Monocytes expressing CX3CR1 orchestrate the development of vincristine-induced pain. **Journal of Clinical Investigation**, [s. l.], v. 124, n. 5, p. 2023–2036, 2014b.

O'ROURKE, S. A.; SHANLEY, L. C.; DUNNE, A. The Nrf2-HO-1 system and inflammaging. **Frontiers in Immunology**, [s. l.], v. 15, 2024.

PAICE, J. A. *et al.* Management of Chronic Pain in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. **Journal of Clinical Oncology**, [s. l.], v. 34, n. 27, p. 3325–3345, 2016.

PALTIAN, J. J. *et al.* 7-chloro-4-(phenylselanyl) quinoline incorporation into polymeric nanocapsules improves its pharmacological action: Physicochemical, toxicological, and behavioral studies. **International Journal of Pharmaceutics**, [s. l.], v. 673, p. 125370, 2025.

PALTIAN, J. J. *et al.* 7-Chloro-4-(Phenylselanyl) Quinoline Is a Novel Multitarget Therapy to Combat Peripheral Neuropathy and Comorbidities Induced by Paclitaxel in Mice. **Molecular Neurobiology**, [s. l.], n. 0123456789, 2022a. Disponível em: <https://doi.org/10.1007/s12035-022-02991-4>.

PALTIAN, J. J. *et al.* 7-Chloro-4-(Phenylselanyl) Quinoline Is a Novel Multitarget Therapy to Combat Peripheral Neuropathy and Comorbidities Induced by Paclitaxel in Mice. **Molecular Neurobiology**, [s. l.], n. 0123456789, 2022b.

PALTIAN, J. J. *et al.* The anxiolytic effect of a promising quinoline containing selenium with the contribution of the serotonergic and GABAergic pathways: Modulation of parameters associated with anxiety in mice. **Behavioural Brain Research**, [s. l.], v. 393, n. June, p. 112797, 2020a. Disponível em: <https://doi.org/10.1016/j.bbr.2020.112797>.

PALTIAN, J. J. *et al.* The anxiolytic effect of a promising quinoline containing selenium with the contribution of the serotonergic and GABAergic pathways:

Modulation of parameters associated with anxiety in mice. **Behavioural Brain Research**, [s. l.], v. 393, n. June, p. 112797, 2020b.

PATIL, M. J. *et al.* Ginger Constituent 6-Shogaol Attenuates Vincristine-Induced Activation of Mouse Gastroesophageal Vagal Afferent C-Fibers. **Molecules**, [s. l.], v. 27, n. 21, 2022.

PAUWELS, B. *et al.* Comparison of the sulforhodamine B assay and the clonogenic assay for in vitro chemoradiation studies. **Cancer Chemotherapy and Pharmacology**, [s. l.], v. 51, n. 3, p. 221–226, 2003.

PEDRA, N. S. *et al.* Impact of gallic acid on tumor suppression: Modulation of redox homeostasis and purinergic response in in vitro and a preclinical glioblastoma model. **The Journal of Nutritional Biochemistry**, [s. l.], v. 110, p. 109156, 2022.

PELLOW, S. *et al.* Validation of open : closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. **Journal of Neuroscience Methods**, [s. l.], v. 14, n. 3, p. 149–167, 1985.

PÉREZ-GONZÁLEZ, M. Z. *et al.* Anti-inflammatory, antioxidant, and acute toxicity of Brugmansia arborea extracts from wild plants and shoots obtained by indirect organogenesis. A thermographic assay to anti-inflammatory evaluation. **Biomedicine & Pharmacotherapy**, [s. l.], v. 186, p. 117972, 2025.

PIETROBON, D.; MOSKOWITZ, M. A. Pathophysiology of Migraine. **Annual Review of Physiology**, [s. l.], v. 75, n. 1, p. 365–391, 2013a.

PIETROBON, D.; MOSKOWITZ, M. A. Pathophysiology of Migraine. **Annual Review of Physiology**, [s. l.], v. 75, n. 1, p. 365–391, 2013b. Disponível em: <https://www.annualreviews.org/doi/10.1146/annurev-physiol-030212-183717>.

PINZ, M. *et al.* 4-Phenylselenyl-7-chloroquinoline, a new quinoline derivative containing selenium, has potential antinociceptive and anti-inflammatory actions. **European Journal of Pharmacology**, [s. l.], v. 780, p. 122–128, 2016a. Disponível em: <http://dx.doi.org/10.1016/j.ejphar.2016.03.039>.

PINZ, M. *et al.* 4-Phenylselenyl-7-chloroquinoline, a new quinoline derivative containing selenium, has potential antinociceptive and anti-inflammatory actions. **European Journal of Pharmacology**, [s. l.], v. 780, p. 122–128, 2016b.

PINZ, M. P. *et al.* Current advances of pharmacological properties of 7-chloro-4-(phenylselenyl) quinoline: Prevention of cognitive deficit and anxiety in Alzheimer's disease model. **Biomedicine and Pharmacotherapy**, [s. l.], v. 105, n. June, p. 1006–1014, 2018a. Disponível em: <https://doi.org/10.1016/j.biopha.2018.06.049>.

PINZ, M. P. *et al.* Current advances of pharmacological properties of 7-chloro-4-(phenylselenyl) quinoline: Prevention of cognitive deficit and anxiety in Alzheimer's disease model. **Biomedicine and Pharmacotherapy**, [s. l.], v. 105,

n. June, p. 1006–1014, 2018b.

PURSER, M. J.; JOHNSTON, D. L.; MCMILLAN, H. J. Chemotherapy-induced Peripheral Neuropathy Among Paediatric Oncology Patients. **Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques**, [s. l.], v. 41, n. 4, p. 442–447, 2014.

QUEIROZ, M. P. *et al.* Effect of Conjugated Linoleic Acid on Memory and Reflex Maturation in Rats Treated During Early Life. **Frontiers in Neuroscience**, [s. l.], v. 13, 2019.

QUEIROZ, K. F. F. da C.; DE CÁSSIA FERNANDES DE LIMA, R. Smart screening system for breast cancer: the use of thermographic images, evolutionary algorithms, and oversampling. **Biomedical Physics & Engineering Express**, [s. l.], v. 9, n. 5, p. 055027, 2023.

QUINES, C. B. *et al.* Involvement of the serotonergic system in the anxiolytic-like effect of 2-phenylethynyl butyltellurium in mice. **Behavioural Brain Research**, [s. l.], v. 277, p. 221–227, 2015.

QUINN, R. Comparing rat's to human's age: How old is my rat in people years? **Nutrition**, [s. l.], v. 21, n. 6, p. 775–777, 2005.

QUITON, R. L.; GREENSPAN, J. D. Sex differences in endogenous pain modulation by distracting and painful conditioning stimulation. **Pain**, [s. l.], p. 132–149, 2007.

RAASING, L. R. M. *et al.* Current View of Diagnosing Small Fiber Neuropathy. **Journal of Neuromuscular Diseases**, [s. l.], v. 8, n. 2, p. 185–207, 2021.

REIS, A. S. *et al.* 4-phenylselenyl-7-chloroquinoline, a novel multitarget compound with anxiolytic activity: Contribution of the glutamatergic system. **Journal of Psychiatric Research**, [s. l.], v. 84, p. 191–199, 2017a.

REIS, A. S. *et al.* 4-phenylselenyl-7-chloroquinoline, a novel multitarget compound with anxiolytic activity: Contribution of the glutamatergic system. **Journal of Psychiatric Research**, [s. l.], v. 84, p. 191–199, 2017b.

REIS, A. S. *et al.* 4-phenylselenyl-7-chloroquinoline, a novel multitarget compound with anxiolytic activity: Contribution of the glutamatergic system. **Journal of Psychiatric Research**, [s. l.], v. 84, p. 191–199, 2017c. Disponível em: <https://linkinghub.elsevier.com/retrieve/pii/S0022395616304976>.

REIS, A. S. *et al.* Advances in the Understanding of Oxaliplatin-Induced Peripheral Neuropathy in Mice: 7-Chloro-4-(Phenylselenyl) Quinoline as a Promising Therapeutic Agent. **Molecular Neurobiology**, [s. l.], v. 57, n. 12, p. 5219–5234, 2020a.

REIS, A. S. *et al.* Advances in the Understanding of Oxaliplatin-Induced Peripheral Neuropathy in Mice: 7-Chloro-4-(Phenylselenyl) Quinoline as a

Promising Therapeutic Agent. **Molecular Neurobiology**, [s. l.], v. 57, n. 12, p. 5219–5234, 2020b.

REIS, A. S. *et al.* Interface of Aging and Acute Peripheral Neuropathy Induced by Oxaliplatin in Mice: Target-Directed Approaches for Na⁺, K⁺—ATPase, Oxidative Stress, and 7-Chloro-4-(phenylselanyl) quinoline Therapy. **Molecular Neurobiology**, [s. l.], v. 59, n. 3, p. 1766–1780, 2022. Disponível em: <https://doi.org/10.1007/s12035-021-02659-5>.

REIS, A. S. *et al.* Pharmacological modulation of Na⁺, K⁺-ATPase as a potential target for OXA-induced neurotoxicity: Correlation between anxiety and cognitive decline and beneficial effects of 7-chloro-4-(phenylselanyl) quinoline. **Brain Research Bulletin**, [s. l.], v. 162, n. June, p. 282–290, 2020c.

REIS, A. S. *et al.* Pharmacological modulation of Na⁺, K⁺-ATPase as a potential target for OXA-induced neurotoxicity: Correlation between anxiety and cognitive decline and beneficial effects of 7-chloro-4-(phenylselanyl) quinoline. **Brain Research Bulletin**, [s. l.], v. 162, n. June, p. 282–290, 2020d.

REIS, A. S. *et al.* Platinum Deposition in the Central Nervous System: A Novel Insight into Oxaliplatin-induced Peripheral Neuropathy in Young and Old Mice. **Molecular Neurobiology**, [s. l.], v. 62, n. 3, p. 3712–3729, 2025.

REZENDE, A. A. *et al.* Anti-Tumor Efficiency of Perillylalcohol/ β -Cyclodextrin Inclusion Complexes in a Sarcoma S180-Induced Mice Model. **Pharmaceutics**, [s. l.], v. 13, n. 2, p. 245, 2021.

RODRIGUES, K. C. *et al.* The neurotherapeutic role of a selenium-functionalized quinoline in hypothalamic obese rats. **Psychopharmacology**, [s. l.], v. 238, n. 7, p. 1937–1951, 2021a.

RODRIGUES, K. C. *et al.* The neurotherapeutic role of a selenium-functionalized quinoline in hypothalamic obese rats. **Psychopharmacology**, [s. l.], v. 238, n. 7, p. 1937–1951, 2021b.

ROHN, T. T.; HINDS, T. R.; VINCENZI, F. F. Ion transport ATPases as targets for free radical damage. **Biochemical Pharmacology**, [s. l.], v. 46, n. 3, p. 525–534, 1993.

RUAN, Y. *et al.* An effective and concise device for detecting cold allodynia in mice. **Scientific Reports**, [s. l.], v. 8, n. 1, 2018.

RUBIO, M. *et al.* The immunosuppressive effect of vincristine on allostimulatory potential of human dendritic cells interferes with their function and survival. **International Journal of Oncology**, [s. l.], 2004.

RUDNITSKAYA, E. A. *et al.* Features of Postnatal Hippocampal Development in a Rat Model of Sporadic Alzheimer's Disease. **Frontiers in Neuroscience**, [s. l.], v. 14, 2020.

RUHEE, R. T. *et al.* Organosulfur Compounds: A Review of Their Anti-inflammatory Effects in Human Health. **Frontiers in Nutrition**, [s. l.], v. 7, 2020.

SAGALAJEV, B. *et al.* Bidirectional amygdaloid control of neuropathic hypersensitivity mediated by descending serotonergic pathways acting on spinal 5-HT₃ and 5-HT_{1A} receptors. **Behavioural Brain Research**, [s. l.], v. 282, p. 14–24, 2015.

SAHRANAVARD, S. *et al.* Hydroethanolic extract of *Lavandula angustifolia* ameliorates vincristine-induced peripheral neuropathy in rats. **Research in Pharmaceutical Sciences**, [s. l.], v. 17, n. 3, p. 265, 2022. Disponível em: <https://journals.lww.com/10.4103/1735-5362.343080>.

SAŁAT, K.; FILIPEK, B. Antinociceptive activity of transient receptor potential channel TRPV1, TRPA1, and TRPM8 antagonists in neurogenic and neuropathic pain models in mice. **Journal of Zhejiang University-SCIENCE B**, [s. l.], v. 16, n. 3, p. 167–178, 2015.

SAMPATHKUMAR, V. *et al.* Integration of signals from different cortical areas in higher order thalamic neurons. **Proceedings of the National Academy of Sciences**, [s. l.], v. 118, n. 30, 2021.

SANTOS, G. J. L. *et al.* *Himatanthus drasticus* (Apocynaceae) latex reduces oxidative stress and modulates CD4⁺, CD8⁺, FoxP3⁺ and HSP-60⁺ expressions in Sarcoma 180-bearing mice. **Journal of Ethnopharmacology**, [s. l.], v. 220, p. 159–168, 2018.

SAVEGNAGO, L. *et al.* Synthesis and antioxidant properties of novel quinoline-chalcogenium compounds. **Tetrahedron Letters**, [s. l.], v. 54, n. 1, p. 40–44, 2013a.

SAVEGNAGO, L. *et al.* Synthesis and antioxidant properties of novel quinoline-chalcogenium compounds. **Tetrahedron Letters**, [s. l.], v. 54, n. 1, p. 40–44, 2013b. Disponível em: <http://dx.doi.org/10.1016/j.tetlet.2012.10.067>.

SCHAPPACHER, K. A. *et al.* Neonatal vincristine administration modulates intrinsic neuronal excitability in the rat dorsal root ganglion and spinal dorsal horn during adolescence. **Pain**, [s. l.], v. 160, n. 3, p. 645–657, 2019a.

SCHAPPACHER, K. A. *et al.* Neonatal vincristine administration modulates intrinsic neuronal excitability in the rat dorsal root ganglion and spinal dorsal horn during adolescence. **Pain**, [s. l.], v. 160, n. 3, p. 645–657, 2019b.

SCHAPPACHER, K. A. *et al.* Neonatal vincristine administration modulates intrinsic neuronal excitability in the rat dorsal root ganglion and spinal dorsal horn during adolescence. **Pain**, [s. l.], v. 160, n. 3, p. 645–657, 2019c.

SCHAPPACHER, K. A.; STYCZYNSKI, L.; BACCEI, M. L. **Early life vincristine exposure evokes mechanical pain hypersensitivity in the developing rat.** [S. l.: s. n.], 2017-. ISSN 18726623.v. 158

SEKERES, M. J.; WINOCUR, G.; MOSCOVITCH, M. The hippocampus and related neocortical structures in memory transformation. **Neuroscience Letters**, [s. l.], v. 680, p. 39–53, 2018.

SEMPLE, B. D. *et al.* Brain development in rodents and humans: Identifying benchmarks of maturation and vulnerability to injury across species. **Progress in Neurobiology**, [s. l.], v. 106–107, p. 1–16, 2013.

SENGUPTA, S. *et al.* Adverse Neonatal Outcomes Associated With Early-Term Birth. **JAMA Pediatrics**, [s. l.], v. 167, n. 11, p. 1053, 2013.

SHABANI, M. *et al.* Profound destructive effects of adolescent exposure to Vincristine accompanied with some sex differences in motor and memory performance. **Canadian Journal of Physiology and Pharmacology**, [s. l.], v. 90, n. 4, p. 379–386, 2012a.

SHABANI, M. *et al.* Profound destructive effects of adolescent exposure to Vincristine accompanied with some sex differences in motor and memory performance. **Canadian Journal of Physiology and Pharmacology**, [s. l.], v. 90, n. 4, p. 379–386, 2012b.

SHAO, Y. *et al.* Morin Regulates M1/M2 Microglial Polarization via NF- κ B p65 to Alleviate Vincristine-Induced Neuropathic Pain. **Drug Design, Development and Therapy**, [s. l.], v. Volume 18, p. 3143–3156, 2024.

SHAYESTEH, S. *et al.* Dapsone improves the vincristine-induced neuropathic nociception by modulating neuroinflammation and oxidative stress. **DARU, Journal of Pharmaceutical Sciences**, [s. l.], v. 30, n. 2, p. 303–310, 2022a.

SHAYESTEH, S. *et al.* Dapsone improves the vincristine-induced neuropathic nociception by modulating neuroinflammation and oxidative stress. **DARU, Journal of Pharmaceutical Sciences**, [s. l.], v. 30, n. 2, p. 303–310, 2022b. Disponível em: <https://doi.org/10.1007/s40199-022-00448-6>.

SHEN, Y. *et al.* Exogenous induction of HO-1 alleviates vincristine-induced neuropathic pain by reducing spinal glial activation in mice. **Neurobiology of Disease**, [s. l.], v. 79, p. 100–110, 2015a.

SHEN, Y. *et al.* Exogenous induction of HO-1 alleviates vincristine-induced neuropathic pain by reducing spinal glial activation in mice. **Neurobiology of Disease**, [s. l.], v. 79, p. 100–110, 2015b. Disponível em: <http://dx.doi.org/10.1016/j.nbd.2015.04.012>.

SHINWARI, Z. *et al.* Vincristine and lomustine induce apoptosis and p21WAF1 up-regulation in medulloblastoma and normal human epithelial and fibroblast cells. **Journal of Neuro-Oncology**, [s. l.], v. 87, n. 2, p. 123–132, 2008.

SILVA, A. V. Associations between clinical signs and pathological findings in toxicity testing. **ALTEX**, [s. l.], 2020.

SILVA, V. D. G. *et al.* Further analysis of acute antinociceptive and anti-inflammatory actions of 4-phenylselenyl-7-chloroquinoline in mice. **Fundamental and Clinical Pharmacology**, [s. l.], v. 31, n. 5, p. 513–525, 2017a.

SILVA, V. D. G. *et al.* Further analysis of acute antinociceptive and anti-inflammatory actions of 4-phenylselenyl-7-chloroquinoline in mice. **Fundamental and Clinical Pharmacology**, [s. l.], v. 31, n. 5, p. 513–525, 2017b.

SIMÃO, D. A. da S. *et al.* Chemotherapy-induced peripheral neuropathy: review for clinical practice. **Revista Dor**, [s. l.], v. 16, n. 3, p. 215–220, 2015.

ŞİMŞEK, Ş.; OYMAK SOYSAL, A. N.; KAŞ ÖZDEMİR, A. Association between Pain Intensity, Pain Belief, and Coping Strategies in Older Adults. **Experimental Aging Research**, [s. l.], v. 49, n. 3, p. 244–251, 2023a. Disponível em: <https://doi.org/10.1080/0361073X.2022.2101304>.

ŞİMŞEK, Ş.; OYMAK SOYSAL, A. N.; KAŞ ÖZDEMİR, A. Association between Pain Intensity, Pain Belief, and Coping Strategies in Older Adults. **Experimental Aging Research**, [s. l.], v. 49, n. 3, p. 244–251, 2023b.

SINGH, G. *et al.* Bergapten Ameliorates Vincristine-Induced Peripheral Neuropathy by Inhibition of Inflammatory Cytokines and NFκB Signaling. research-article. **ACS Chemical Neuroscience**, [s. l.], v. 10, n. 6, p. 3008–3017, 2019a.

SINGH, G. *et al.* Bergapten Ameliorates Vincristine-Induced Peripheral Neuropathy by Inhibition of Inflammatory Cytokines and NFκB Signaling. research-article. **ACS Chemical Neuroscience**, [s. l.], v. 10, n. 6, p. 3008–3017, 2019b.

SMART, J. L.; DOBBING, J. Vulnerability of developing brain. II. Effects of early nutritional deprivation on reflex ontogeny and development of behaviour in the rat. **Brain Research**, [s. l.], v. 28, n. 1, p. 85–95, 1971.

SMITH, E. M. L. *et al.* Predictors of duloxetine response in patients with oxaliplatin-induced painful chemotherapy-induced peripheral neuropathy (CIPN): a secondary analysis of randomised controlled trial – CALGB/alliance 170601. **European Journal of Cancer Care**, [s. l.], v. 26, n. 2, 2017.

SNIJDERS, R. *et al.* Update on Prevalence of Pain in Patients with Cancer 2022: A Systematic Literature Review and Meta-Analysis. **Cancers**, [s. l.], v. 15, n. 3, p. 591, 2023.

SONG, B. *et al.* Inhibitory phosphorylation of GSK-3 by CaMKII couples depolarization to neuronal survival. **Journal of Biological Chemistry**, [s. l.], v. 285, n. 52, p. 41122–41134, 2010.

SORIANO, D. *et al.* Chemotherapy-induced neuropathy and pain in pediatric oncology patients: impact of combination therapies. **European Journal of**

Pediatrics, [s. l.], v. 183, n. 9, p. 3749–3756, 2024.

SOYOCAK, A. *et al.* Tannic acid exhibits anti-inflammatory effects on formalin-induced paw edema model of inflammation in rats. **Human & Experimental Toxicology**, [s. l.], v. 38, n. 11, p. 1296–1301, 2019.

STANGHERLIN, E. C.; ROCHA, J. B. T.; NOGUEIRA, C. W. Diphenyl ditelluride impairs short-term memory and alters neurochemical parameters in young rats. **Pharmacology Biochemistry and Behavior**, [s. l.], v. 91, n. 3, p. 430–435, 2009.

STAROBOVA, H. *et al.* Minocycline prevents the development of mechanical allodynia in mouse models of vincristine-induced peripheral neuropathy. **Frontiers in Neuroscience**, [s. l.], v. 13, n. JUN, p. 1–10, 2019.

STAROBOVA, H.; VETTER, I. Pathophysiology of chemotherapy-induced peripheral neuropathy. **Frontiers in Molecular Neuroscience**, [s. l.], v. 10, n. May, p. 1–21, 2017a.

STAROBOVA, H.; VETTER, I. Pathophysiology of chemotherapy-induced peripheral neuropathy. **Frontiers in Molecular Neuroscience**, [s. l.], v. 10, n. May, p. 1–21, 2017b.

STEEL, A. *et al.* A network linking scene perception and spatial memory systems in posterior cerebral cortex. **Nature Communications**, [s. l.], v. 12, n. 1, p. 2632, 2021.

STERU, L. *et al.* The tail suspension test: A new method for screening antidepressants in mice. **Psychopharmacology**, [s. l.], v. 85, n. 3, p. 367–370, 1985.

STYCZYNSKI, L. M.; SCHAPPACHER, K. A.; BACCEI, M. L. Early life vincristine fails to prime developing pain pathways. **Neuroscience Letters**, [s. l.], v. 720, n. January, p. 134764, 2020. Disponível em: <https://doi.org/10.1016/j.neulet.2020.134764>.

SU, H. *et al.* Regulation of the Nrf2/HO-1 axis by mesenchymal stem cells-derived extracellular vesicles: implications for disease treatment. **Frontiers in Cell and Developmental Biology**, [s. l.], v. 12, 2024.

SU, Y.-C. *et al.* Survivors of Non-Hodgkin's Lymphoma: A Comparative Study on Patients With Vincristine-Induced Neuropathy and Their Quality of Life. **Journal of Nursing Research**, [s. l.], v. 33, n. 3, p. e393, 2025.

SUN, J. *et al.* Hemoprotein Bach1 regulates enhancer availability of heme oxygenase-1 gene. **The EMBO Journal**, [s. l.], v. 21, n. 19, p. 5216–5224, 2002.

SUN, G. *et al.* Temporal pain processing in the primary somatosensory cortex and anterior cingulate cortex. **Molecular Brain**, [s. l.], v. 16, n. 1, p. 3, 2023.

SUNG, J. Y. *et al.* Sensory axonal dysfunction in cervical radiculopathy. **Journal of Neurology, Neurosurgery and Psychiatry**, [s. l.], v. 86, n. 6, p. 640–645, 2015a.

SUNG, J. Y. *et al.* Sensory axonal dysfunction in cervical radiculopathy. **Journal of Neurology, Neurosurgery and Psychiatry**, [s. l.], v. 86, n. 6, p. 640–645, 2015b.

SWARM, R. A. *et al.* Adult Cancer Pain. **Journal of the National Comprehensive Cancer Network**, [s. l.], v. 11, n. 8, p. 992–1022, 2013.

SY, A. *et al.* Heterozygosity for CMT Type 4 Predicts a Severe Vincristine-induced Polyneuropathy Phenotype: A Case Report and Review of Literature. **Journal of Pediatric Hematology/Oncology**, [s. l.], v. 41, n. 1, p. E41–E43, 2019a.

SY, A. *et al.* Heterozygosity for CMT Type 4 Predicts a Severe Vincristine-induced Polyneuropathy Phenotype: A Case Report and Review of Literature. **Journal of Pediatric Hematology/Oncology**, [s. l.], v. 41, n. 1, p. E41–E43, 2019b.

TAKEDA, M.; TAKAHASHI, M.; MATSUMOTO, S. Suppression of neurokinin-1 receptor in trigeminal ganglia attenuates central sensitization following inflammation. **Journal of the Peripheral Nervous System**, [s. l.], v. 17, n. 2, p. 169–181, 2012.

TANTAWY, S. I. *et al.* Targeting MCL-1 protein to treat cancer: opportunities and challenges. **Frontiers in Oncology**, [s. l.], v. 13, 2023.

TAVES, S. *et al.* Microglia and Spinal Cord Synaptic Plasticity in Persistent Pain. **Neural Plasticity**, [s. l.], v. 2013, p. 1–10, 2013. Disponível em: <http://www.hindawi.com/journals/np/2013/753656/>.

TAY, N. *et al.* Chemotherapy-induced peripheral neuropathy in children and adolescent cancer patients. **Frontiers in Molecular Biosciences**, [s. l.], v. 9, 2022.

TAY, S. Y. *et al.* Pediatric Oncology Patients With Vincristine-Induced Recurrent Laryngeal Nerve Palsy: Two Case Reports and a Brief Review of Literature. **Ear, Nose and Throat Journal**, [s. l.], v. 100, n. 10, p. NP459–NP463, 2021a.

TAY, S. Y. *et al.* Pediatric Oncology Patients With Vincristine-Induced Recurrent Laryngeal Nerve Palsy: Two Case Reports and a Brief Review of Literature. **Ear, Nose and Throat Journal**, [s. l.], v. 100, n. 10, p. NP459–NP463, 2021b.

TIMMINS, H. C. *et al.* The impact of obesity on neuropathy outcomes for paclitaxel- and oxaliplatin-treated cancer survivors. **Journal of Cancer Survivorship**, [s. l.], v. 16, n. 2, p. 223–232, 2022.

TINNIRELLO, A.; MAZZOLENI, S.; SANTI, C. Chronic Pain in the Elderly:

Mechanisms and Perspectives. **Biomolecules**, [s. l.], v. 11, n. March, p. 1256, 2021.

TOWER, J.; POMATTO, L. C. D.; DAVIES, K. J. A. Sex differences in the response to oxidative and proteolytic stress. **Redox Biology**, [s. l.], v. 31, p. 101488, 2020.

TREEDE, R. D. The International Association for the Study of Pain definition of pain: As valid in 2018 as in 1979, but in need of regularly updated footnotes. **Pain Reports**, [s. l.], v. 3, n. 2, p. 1–3, 2018.

TREVISAN, G. *et al.* Antinociceptive Effects of 14-Membered Cyclopeptide Alkaloids. **Journal of natural products**, [s. l.], v. 72, p. 608–612, 2009.

TRIARICO, S. *et al.* Vincristine-induced peripheral neuropathy (Vipn) in pediatric tumors: Mechanisms, risk factors, strategies of prevention and treatment. **International Journal of Molecular Sciences**, [s. l.], v. 22, n. 8, 2021a.

TRIARICO, S. *et al.* Vincristine-induced peripheral neuropathy (Vipn) in pediatric tumors: Mechanisms, risk factors, strategies of prevention and treatment. **International Journal of Molecular Sciences**, [s. l.], v. 22, n. 8, 2021b.

TRIARICO, S. *et al.* Vincristine-Induced Peripheral Neuropathy (VIPN) in Pediatric Tumors: Mechanisms, Risk Factors, Strategies of Prevention and Treatment. **International Journal of Molecular Sciences**, [s. l.], v. 22, n. 8, p. 4112, 2021c.

TUCKER, M. H.; TIWARI, P.; CARTER, B. S. The physiology, assessment, and treatment of neonatal pain. **Seminars in Fetal and Neonatal Medicine**, [s. l.], v. 28, n. 4, p. 101465, 2023.

TUMMALA, R. *et al.* Expression of Na,K-ATPase- β 1 subunit increases uptake and sensitizes carcinoma cells to oxaliplatin. **Cancer Chemistry and Pharmacology**, [s. l.], v. 64, n. 6, p. 1187–1194, 2009.

TUNJUNGSARI, D. A.; GUNAWAN, P. I.; UGRASENA, I. D. G. RISK FACTORS OF VINCRISTINE-INDUCED PERIPHERAL NEUROPATHY IN ACUTE LYMPHOBLASTIC LEUKAEMIA CHILDREN. **The Journal of Medical Investigation**, [s. l.], v. 68, n. 3.4, p. 232–237, 2021.

TURCU-STIOLICA, A. *et al.* Diagnostic Accuracy of Machine-Learning Models on Predicting Chemo-Brain in Breast Cancer Survivors Previously Treated with Chemotherapy: A Meta-Analysis. **International Journal of Environmental Research and Public Health**, [s. l.], v. 19, n. 24, p. 16832, 2022.

UITTENBOOGAARD, A. *et al.* Pharmacogenomics of Vincristine-Induced Peripheral Neuropathy in Children with Cancer: A Systematic Review and Meta-Analysis. **Cancers**, [s. l.], v. 14, n. 3, p. 612, 2022.

UMANA, I. C. *et al.* Nicotinic modulation of descending pain control circuitry.

[S. l.: s. n.], 2017-. ISSN 18726623.v. 158

VAN DE VELDE, M. E. *et al.* The association between vincristine-induced peripheral neuropathy and health-related quality of life in children with cancer. **Cancer Medicine**, [s. l.], v. 10, n. 22, p. 8172–8181, 2021.

VAN DE VELDE, M. E. *et al.* Vincristine-induced peripheral neuropathy in children with cancer: A systematic review. **Critical Reviews in Oncology/Hematology**, [s. l.], v. 114, p. 114–130, 2017a. Disponível em: <https://doi.org/10.1016/j.critrevonc.2017.04.004>.

VAN DE VELDE, M. E. *et al.* Vincristine-induced peripheral neuropathy in children with cancer: A systematic review. **Critical Reviews in Oncology/Hematology**, [s. l.], v. 114, p. 114–130, 2017b.

VAN DEN BEUKEN-VAN EVERDINGEN, M. H. J. *et al.* Prevalence of pain in patients with cancer: a systematic review of the past 40 years. **Annals of Oncology**, [s. l.], v. 18, n. 9, p. 1437–1449, 2007.

VEGA-AVELAIRA, D.; MOSS, A.; FITZGERALD, M. Age-related changes in the spinal cord microglial and astrocytic response profile to nerve injury. **Brain, Behavior, and Immunity**, [s. l.], v. 21, n. 5, p. 617–623, 2007.

VOGT, A. G. *et al.* Organoselenium group is critical for antioxidant activity of 7-chloro-4-phenylselenyl-quinoline. **Chemico-Biological Interactions**, [s. l.], v. 282, p. 7–12, 2018a. Disponível em: <https://doi.org/10.1016/j.cbi.2018.01.003>.

VOGT, A. G. *et al.* Organoselenium group is critical for antioxidant activity of 7-chloro-4-phenylselenyl-quinoline. **Chemico-Biological Interactions**, [s. l.], v. 282, p. 7–12, 2018b.

VOSS, G. T. *et al.* Therapeutic and technological potential of 7-chloro-4-phenylselenyl quinoline for the treatment of atopic dermatitis-like skin lesions in mice. **Materials Science and Engineering C**, [s. l.], v. 84, n. August 2017, p. 90–98, 2017a. Disponível em: <https://doi.org/10.1016/j.msec.2017.11.026>.

VOSS, G. T. *et al.* Therapeutic and technological potential of 7-chloro-4-phenylselenyl quinoline for the treatment of atopic dermatitis-like skin lesions in mice. **Materials Science and Engineering C**, [s. l.], v. 84, n. August 2017, p. 90–98, 2017b.

WALKER, J. L. *et al.* Gait-stance duration as a measure of injury and recovery in the rat sciatic nerve model. **Journal of Neuroscience Methods**, [s. l.], v. 52, n. 1, p. 47–52, 1994.

WALSH, R. N.; CUMMINS, R. A. The open-field test: A critical review. **Psychological Bulletin**, [s. l.], v. 83, n. 3, p. 482–504, 1976.

WANG, F. *et al.* Influence of blood-brain barrier efflux pumps on the distribution of vincristine in brain and brain tumors. **Neuro-Oncology**, [s. l.], v. 12, n. 10, p.

1043–1049, 2010.

WANG, X. *et al.* Observation of Acetylcholinesterase in Stress-Induced Depression Phenotypes by Two-Photon Fluorescence Imaging in the Mouse Brain. **Journal of the American Chemical Society**, [s. l.], v. 141, n. 5, p. 2061–2068, 2019.

WANG, M. S. *et al.* Pathogenesis of axonal degeneration: Parallels between Wallerian degeneration and vincristine neuropathy. **Journal of Neuropathology and Experimental Neurology**, [s. l.], v. 59, n. 7, p. 599–606, 2000a.

WANG, M. S. *et al.* Pathogenesis of axonal degeneration: Parallels between Wallerian degeneration and vincristine neuropathy. **Journal of Neuropathology and Experimental Neurology**, [s. l.], v. 59, n. 7, p. 599–606, 2000b.

WANG, J. H. *et al.* Relationship between prescribed opioids, pain management satisfaction, and pain intensity in oncology outpatients. **Supportive Care in Cancer**, [s. l.], v. 30, n. 4, p. 3233–3240, 2022. Disponível em: <https://doi.org/10.1007/s00520-021-06722-8>.

WANG, L.; AHN, Y. J.; ASMIS, R. Sexual dimorphism in glutathione metabolism and glutathione-dependent responses. **Redox Biology**, [s. l.], v. 31, p. 101410, 2020.

WEEKS, J. C.; LEVINE, R. B. Steroid hormone effects on neurons subserving behavior. **Current Opinion in Neurobiology**, [s. l.], v. 5, n. 6, p. 809–815, 1995.

WHITE, D. *et al.* Targeting translation: A review of preclinical animal models in the development of treatments for chemotherapy-induced peripheral neuropathy. **Journal of the Peripheral Nervous System**, [s. l.], v. 28, n. 2, p. 179–190, 2023.

WIESKOPF, J. S. *et al.* The nicotinic $\alpha 6$ subunit gene determines variability in chronic pain sensitivity via cross-inhibition of P2X2/3 receptors. **Science Translational Medicine**, [s. l.], v. 7, n. 287, 2015.

WILHELM, E. A. *et al.* Antioxidant effect of quinoline derivatives containing or not selenium: Relationship with antinociceptive action quinolines are antioxidant and antinociceptive. **Anais da Academia Brasileira de Ciencias**, [s. l.], v. 89, n. 1, p. 457–467, 2017.

WILLIAMS, M. D.; LASCELLES, B. D. X. Early Neonatal Pain—A Review of Clinical and Experimental Implications on Painful Conditions Later in Life. **Frontiers in Pediatrics**, [s. l.], v. 8, 2020a.

WILLIAMS, M. D.; LASCELLES, B. D. X. Early Neonatal Pain—A Review of Clinical and Experimental Implications on Painful Conditions Later in Life. **Frontiers in Pediatrics**, [s. l.], v. 8, 2020b.

WOLF, E. *et al.* Innate Conformational Dynamics Drive Binding Specificity in Anti-Apoptotic Proteins Mcl-1 and Bcl-2. **Biochemistry**, [s. l.], v. 62, n. 11, p. 1619–

1630, 2023.

WOOLF, C. J. Pain modulation in the spinal cord. **Frontiers in Pain Research**, [s. l.], v. 3, 2022.

WOOLFE, G.; MACDONALD, A. D. The Evaluation of the analgesic action of pethidine hydrochloride (demerol). **Journal of Pharmacology and Experimental Therapeutics**, [s. l.], v. 80, n. 3, p. 300–307, 1944.

WORLD HEALTH ORGANIZATION (WHO). **Global cancer burden growing, amidst mounting need for services**. [S. l.: s. n.], 2024. Disponível em: : <https://www.who.int/news/item/01-02-2024-global-cancer-burden-growing--amidstmounting-need-for-services>. Acesso em: 14 jul. 2025.

XIAOHONG, G. *et al.* [Effects of glucocorticoid receptor agonists on hyperalgesia of rats with neuropathic pain and its mechanisms]. **Chinese Journal of Applied Physiology**, [s. l.], v. 38, n. 5, p. 470–474, 2022.

XU, T. *et al.* Epigenetic upregulation of CXCL12 expression mediates antitubulin chemotherapeutics-induced neuropathic pain. **Pain**, [s. l.], v. 158, n. 4, p. 637–648, 2017a.

XU, T. *et al.* Epigenetic upregulation of CXCL12 expression mediates antitubulin chemotherapeutics-induced neuropathic pain. **Pain**, [s. l.], v. 158, n. 4, p. 637–648, 2017b.

XU, J. *et al.* Longer versus Shorter Schedules of Vincristine, Irinotecan, and Temozolomide (VIT) for Relapsed or Refractory Ewing Sarcoma: A Randomized Controlled Phase 2 Trial. **Clinical Cancer Research**, [s. l.], v. 29, n. 6, p. 1040–1046, 2023.

XUE, V. W. *et al.* Transforming Growth Factor- β : A Multifunctional Regulator of Cancer Immunity. **Cancers**, [s. l.], v. 12, n. 11, p. 3099, 2020.

YOHN, C. N.; GERGUES, M. M.; SAMUELS, B. A. The role of 5-HT receptors in depression Tim Bliss. **Molecular Brain**, [s. l.], v. 10, n. 1, p. 1–12, 2017.

YOON, S. Y.; OH, J. Neuropathic cancer pain: Prevalence, pathophysiology, and management. **Korean Journal of Internal Medicine**, [s. l.], v. 33, n. 6, p. 1058–1069, 2018.

ZAJĄCZKOWSKA, R. *et al.* Mechanisms of Chemotherapy-Induced Peripheral Neuropathy. **International Journal of Molecular Sciences**, [s. l.], v. 20, n. 6, p. 1451, 2019.

ŽARKOVIĆ, N. *et al.* Spontaneous Regression of Cancer: Revealing Granulocytes and Oxidative Stress as the Crucial Double-edge Sword. **Frontiers in Bioscience-Landmark**, [s. l.], v. 27, n. 4, 2022.

ZHAN, X.; LI, J.; ZHOU, T. Targeting Nrf2-Mediated Oxidative Stress Response

Signaling Pathways as New Therapeutic Strategy for Pituitary Adenomas. **Frontiers in Pharmacology**, [s. l.], v. 12, 2021.

ZHANG, H. Cancer Pain Management—New Therapies. **Current Oncology Reports**, [s. l.], v. 24, n. 2, p. 223–226, 2022.

ZHANG, S. Chemotherapy-induced peripheral neuropathy and rehabilitation: A review. **Seminars in Oncology**, [s. l.], v. 48, n. 3, p. 193–207, 2021.

ZHAO, J. Y. *et al.* DNA methyltransferase DNMT3a contributes to neuropathic pain by repressing Kcna2 in primary afferent neurons. **Nature Communications**, [s. l.], v. 8, n. May 2016, p. 1–15, 2017.

ZHAO, B. *et al.* Supplementation of lycopene attenuates oxidative stress induced neuroinflammation and cognitive impairment via Nrf2/NF- κ B transcriptional pathway. **Food and Chemical Toxicology**, [s. l.], v. 109, p. 505–516, 2017a.

ZHAO, B. *et al.* Supplementation of lycopene attenuates oxidative stress induced neuroinflammation and cognitive impairment via Nrf2/NF- κ B transcriptional pathway. **Food and Chemical Toxicology**, [s. l.], v. 109, p. 505–516, 2017b. Disponível em: <https://doi.org/10.1016/j.fct.2017.09.050>.

ZHENG, S. *et al.* TNF- α Impairs Pericyte-Mediated Cerebral Microcirculation via the NF- κ B/iNOS Axis after Experimental Traumatic Brain Injury. **Journal of Neurotrauma**, [s. l.], v. 40, n. 3–4, p. 349–364, 2023a.

ZHENG, S. *et al.* TNF- α Impairs Pericyte-Mediated Cerebral Microcirculation via the NF- κ B/iNOS Axis after Experimental Traumatic Brain Injury. **Journal of Neurotrauma**, [s. l.], v. 40, n. 3–4, p. 349–364, 2023b. Disponível em: <https://www.liebertpub.com/doi/10.1089/neu.2022.0016>.

ZHU, Y. *et al.* Inhibition of PINK1 senses ROS signaling to facilitate neuroblastoma cell pyroptosis. **Autophagy**, [s. l.], p. 1–20, 2025.

ZHU, M. *et al.* Na⁺/K⁺-ATPase-dependent autophagy protects brain against ischemic injury. **Signal Transduction and Targeted Therapy**, [s. l.], v. 5, n. 1, p. 55, 2020.

ZHU, S. *et al.* Roles of tumor-associated macrophages in tumor progression: implications on therapeutic strategies. **Experimental Hematology & Oncology**, [s. l.], v. 10, n. 1, p. 60, 2021.

ZHU, J. *et al.* The neuroprotective effect of oxytocin on vincristine-induced neurotoxicity in mice. **Toxicology Letters**, [s. l.], v. 340, p. 67–76, 2021. Disponível em: <https://linkinghub.elsevier.com/retrieve/pii/S0378427421000096>.

Figure captions

Fig. 1 - Chemical structure of 7-chloro-4-(phenylselanyl) quinoline (4-PSQ).

Fig. 2 - Experimental design scheme. Evaluation of the therapeutic potential of 7-chloro-4-(phenylselanyl)quinoline (4-PSQ) against cancer pain in Sarcoma (S180 cells) and/or vincristine (VCR)-induced peripheral neuropathy. Male mice were randomly assigned to five experimental groups: (I) Control, (II) S180, (III) S180 + VCR, (IV) S180 + 4-PSQ, and (V) S180 + VCR + 4-PSQ. On day 0, baseline nociceptive thresholds were assessed. On day 1, groups II–V received an intraplantar (i.pl.) injection of 25 μ L of a suspension containing 10^6 S180 tumor cells into the left instep, whereas group I received 25 μ L of phosphate buffered saline (PBS) (vehicle, i.pl.). From days 2 to 6, groups III and V were treated with VCR (0.1 mg/kg, intraperitoneally), whereas the remaining groups received 0.9% saline (vehicle, 10 mg/mL, intraperitoneally). From days 8 to 17, animals received daily oral administration of 4-PSQ (1 mg/kg). Nociceptive assessments (mechanical and thermal hyperalgesia) were performed on days 0, 7, 11, and 17. Tumor progression was monitored by measuring paw volume every two days. On day 18, thermographic imaging was conducted, followed by euthanasia. Tumor-inoculated paws were harvested for histopathological analysis. Central nervous system tissues (cortex, spinal cord, cerebellum, and hippocampus) were dissected for biochemical assays, and peritoneal exudate was collected for evaluation of macrophage phenotypes.

Fig. 3 - Evaluation of the therapeutic potential of 7-chloro-4-(phenylselanyl)quinoline (4-PSQ) and vincristine (VCR) against tumor progression of Sarcoma (S180 cells) in a cancer pain model. Left hind paw width (A) and depth (B) were assessed every two days throughout the experimental protocol. Tumor-associated paw edema was evaluated as the difference between the weight of the tumor-bearing paw and the contralateral control paw

(Δ = control paw weight – tumor paw weight) (C). Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 7 animals per group. (*) $P < 0.05$, (**) $P < 0.01$, (***) $P < 0.001$, and (****) $P < 0.0001$ denote significance levels when compared with the control group. (#) $P < 0.05$, (##) $P < 0.01$, (###) $P < 0.001$, and (####) $P < 0.0001$ denote significance levels compared with S180 group. (+) $P < 0.05$, (++) $P < 0.01$, and (++++) $P < 0.0001$ denote significance levels compared with S180 + VCR group. The symbols ($\leq$) denote that the p-value is equal to or higher than the significance. One-way ANOVA followed by Tukey's test was used.

Fig. 4 - Thermographic images employed to measure tumor temperature ($^{\circ}\text{C}$).

Fig. 5 - Evaluation of the therapeutic potential of 7-chloro-4-(phenylselanyl)quinoline (4-PSQ) against mechanical and thermal hyperalgesia in a model of cancer pain induced by Sarcoma (S180 cells) and vincristine (VCR). Evaluation of mechanical hyperalgesia (A) and evaluation of thermal hyperalgesia to heat (B). Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 7 animals per group. (*) $P < 0.05$, (**) $P < 0.01$, (***) $P < 0.001$ and (****) $P < 0.0001$ denote significance levels when compared with the control group. (#) $P < 0.05$, (##) $P < 0.01$ and (####) $P < 0.0001$ denote significance levels when compared with the S180 group. (+) $P < 0.05$, (++) $P < 0.01$, (+++) $P < 0.001$ and (++++) $P < 0.0001$ denote significance levels compared with S180 + VCR group. One-way ANOVA followed by Tukey's test was used.

Fig. 6 - Evaluation of 7-chloro-4-(phenylselanyl)quinoline (4-PSQ), Sarcoma (S180 cells), and vincristine (VCR) on the cytotoxicity of macrophages from peritoneal cavity fluids. Analysis of cell viability (A) and cell proliferation (B). Each column represents the mean $\pm$ standard error of the mean (S.E.M.) of 5 -

6 animals per group. (*) $P < 0.05$ and (**) $P < 0.01$ denote significance levels when compared with the control group. (##) $P < 0.01$ and (###) $P < 0.001$ denote significance levels when compared with the S180 group. One-way ANOVA followed by Tukey's test was used.

Fig. 7 - Evaluation of 7-chloro-4-(phenylselanyl)quinoline (4-PSQ), Sarcoma (S180 cells), and vincristine (VCR) on oxidative damage of peritoneal cavity fluid macrophages. Analysis of reactive oxygen species (ROS) (A); superoxide dismutase (SOD) activity (B); sulfhydryl content (C); catalase (CAT) activity (D); glutathione S-transferase (GST) activity (E); and nitrite levels (F). Each column represents the mean $\pm$ standard error of the mean (S.E.M.) of 5 - 6 animals per group. (*) $P < 0.05$ and (**) $P < 0.01$ denote significance levels when compared with the control group. (#) $P < 0.05$ and (##) $P < 0.01$ denote significance levels when compared with the S180 group. One-way ANOVA followed by Tukey's test was used.

Fig. 8 - Histopathology of the tarsal (paw) region after S180 inoculation (i.pl.) and treatment with 7-chloro-4-(phenylselanyl)quinoline (4-PSQ; 1 mg/kg, p.o.) and/or vincristine (VCR; 0.1 mg/kg, i.p.). Hematoxylin–eosin (H&E). Labels: **B** = bone; **T** = tendon; * = necrotic debris; **arrows** indicate features described. **Slides 1–3** (controls, no sarcoma): preserved architecture of T and B ($\times 40$); intact connective tissue with well-preserved T/B ($\times 100$); normal skeletal muscle and B without neoplastic infiltration ($\times 200$). **Slides 4–6** (S180, untreated): extensive neoplastic proliferation infiltrating subcutis and encircling B ($\times 40$); abundant * within tumor mass ($\times 100$); widespread skeletal muscle destruction with residual fibers (arrow) amid dense neoplastic infiltration ($\times 200$). **Slides 7–9** (S180+VCR): marked reduction in tumor burden with preserved B and T ($\times 40$); focal bone degradation with neoplastic invasion of bone matrix and discrete bone fragments (arrow), B indicated ($\times 200$); partial preservation of

muscle architecture (arrow) and attenuated invasion vs. untreated, B shown ($\times 100$).

Slides 10–12 (S180+4-PSQ): substantial decrease in tumor cell density and lesion area vs. untreated and VCR groups, B/T evident ($\times 40$); neoplastic infiltration into bone persists, though less severe than with VCR monotherapy; bone undergoing resorption (arrow), B indicated ($\times 200$); decreased tumor infiltration and preserved muscle fibers (arrow) with less destruction than VCR, B shown ($\times 100$). **Slides 13–15** (S180+VCR + 4-PSQ): spatially confined tumor regions (between arrows) with improved local control vs. other arms; preserved B/T ($\times 40$); focal bone invasion persists but is markedly attenuated; tumor cells invading bone (arrow), B indicated ($\times 200$); residual neoplastic infiltration interspersed with skeletal muscle and inflammatory infiltrates (arrow), lower than in VCR or vehicle groups ($\times 100$).

Fig. 9 - Evaluation of 7-chloro-4-(phenylselanyl)quinoline (4-PSQ), Sarcoma (S180 cells), and vincristine (VCR) in the thiobarbituric acid reactive species (TBARS) assay. Lipid peroxidation analysis by TBARS in the cerebral cortex (A), spinal cord (B), hippocampus (C), and cerebellum (D) of mice. Each column represents the mean $\pm$ standard error of the mean (S.E.M) of 6 - 7 animals per group. (*) $P < 0.05$ and (**) $P < 0.01$ denote significance levels when compared with the control group. (#) $P < 0.05$ and (##) $P < 0.01$ denote significance levels compared with S180 group. (+) $P < 0.05$ and (++) $P < 0.01$ denote significance levels compared with S180 + VCR group. One-way ANOVA followed by Tukey's test was used.

Fig. 10 - Evaluation of 7-chloro-4-(phenylselanyl)quinoline (4-PSQ), Sarcoma (S180 cells) and vincristine (VCR) on Na^+ , K^+ - ATPase activity. Enzymatic analysis of Na^+ , K^+ - ATPase in the cerebral cortex (A), spinal cord (B), hippocampus (C) and cerebellum (D). Each column represents the mean $\pm$ standard error of the mean (S.E.M.) of 6 - 7 animals per group. (*) $P < 0.05$

denotes significance levels when compared with the control group. (#) $P < 0.05$ and (##) $P < 0.01$ denote significance levels when compared with the S180 group. (++) $P < 0.01$ denotes significance levels when compared with the S180 + VCR group. One-way ANOVA followed by Tukey's test was used.

Fig. 11 - Evaluation of 7-chloro-4-(phenylselanyl)quinoline (4-PSQ), Sarcoma (S180 cells), and vincristine (VCR) on Mg^{2+} - ATPase activity. Enzymatic analysis of Mg^{2+} - ATPase in the cerebral cortex (A), spinal cord (B), hippocampus (C), and cerebellum (D). Each column represents the mean $\pm$ standard error of the mean (S.E.M.) of 6 - 7 animals per group. (**) $P < 0.01$ denotes significance levels when compared with the control group. (##) $P < 0.01$ and (####) $P < 0.0001$ denote significance levels when compared with the S180 group. (++) $P < 0.01$ denotes significance levels when compared with the S180 + VCR group. One-way ANOVA followed by Tukey's test was used.

Figures

Fig. 1

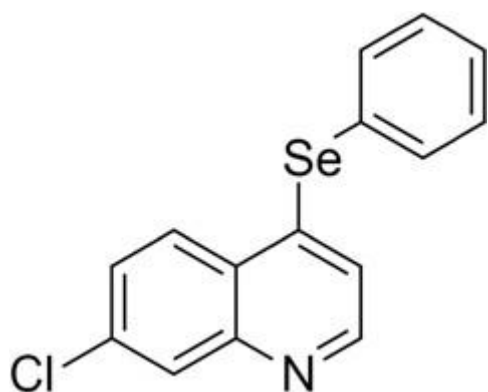


Fig. 2

Experimental Design

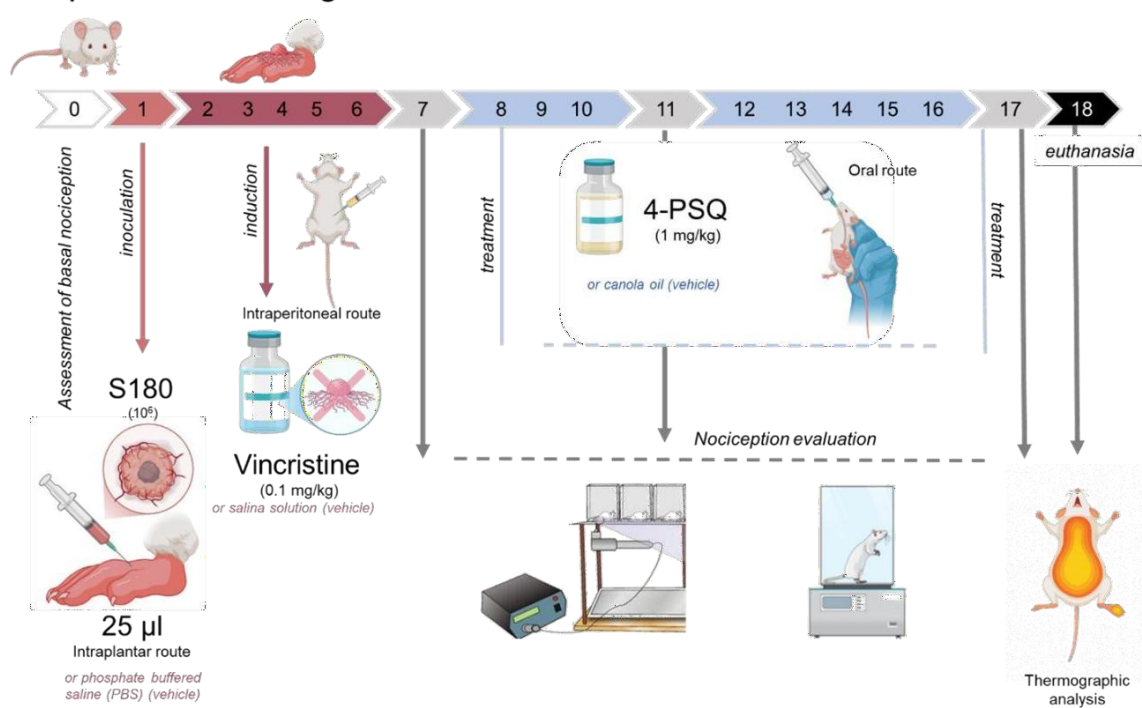


Fig. 3

Tumor progression

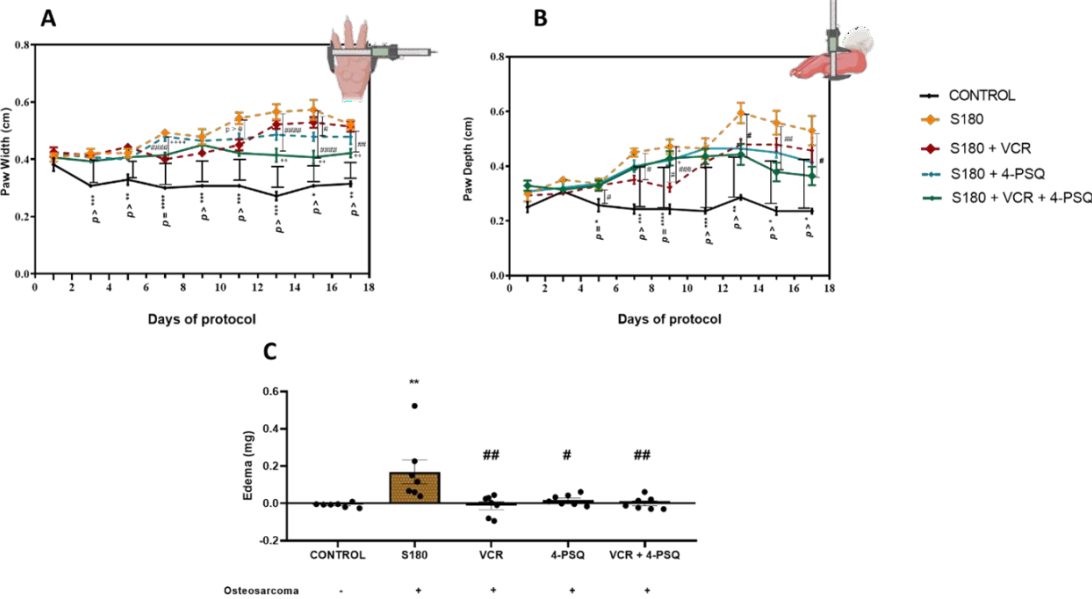


Fig. 4

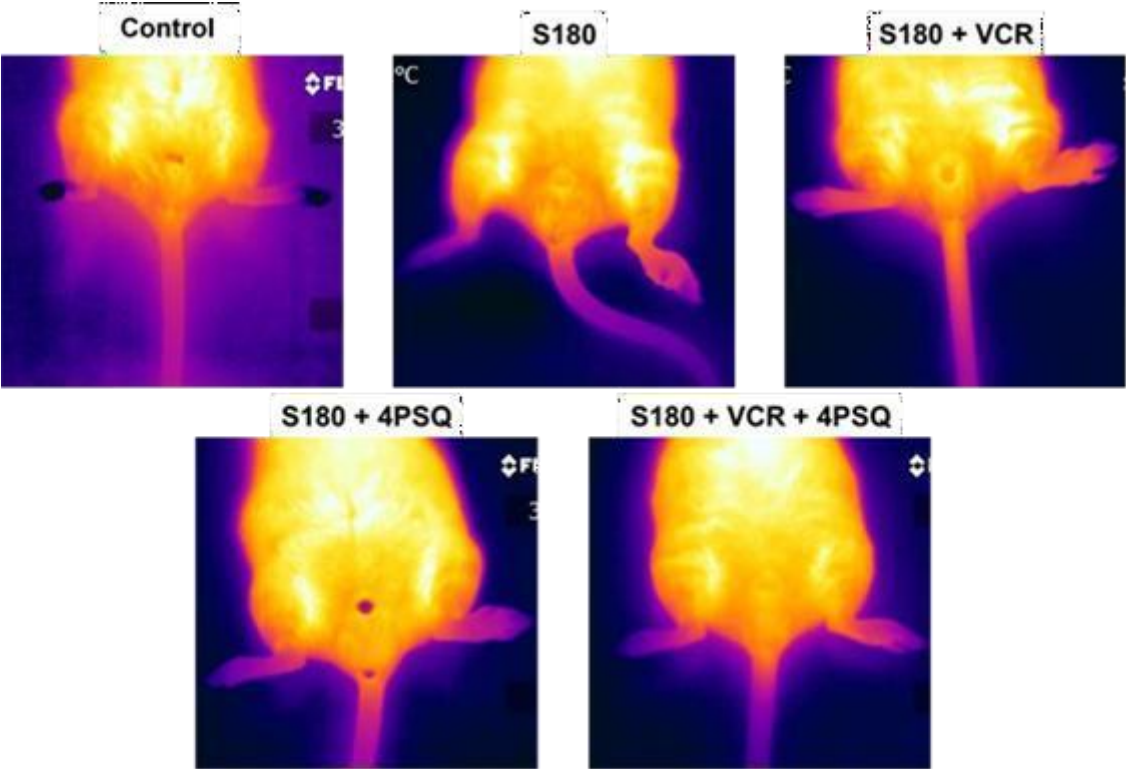


Fig. 5

Oncological nociception

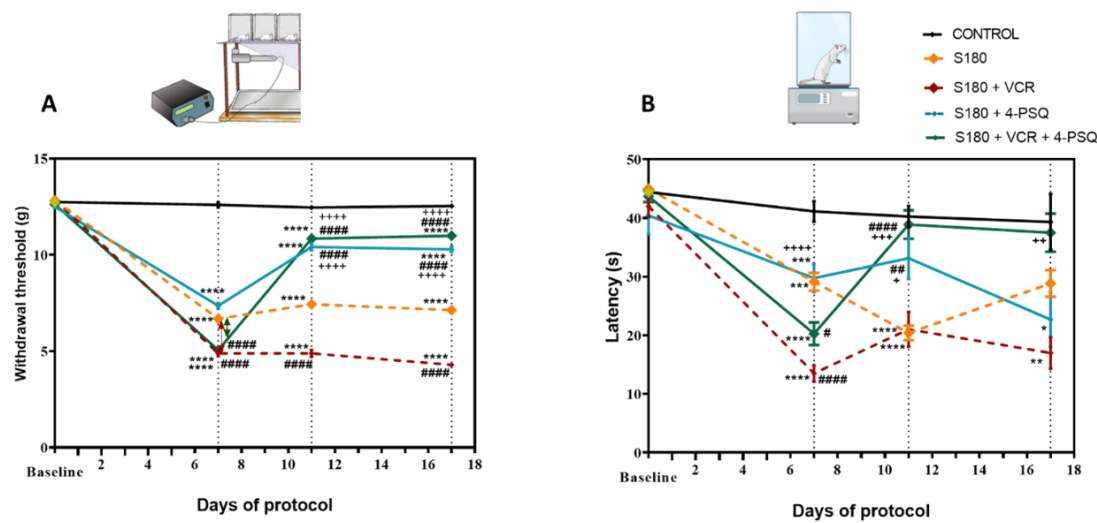


Fig. 6

Citotoxicity

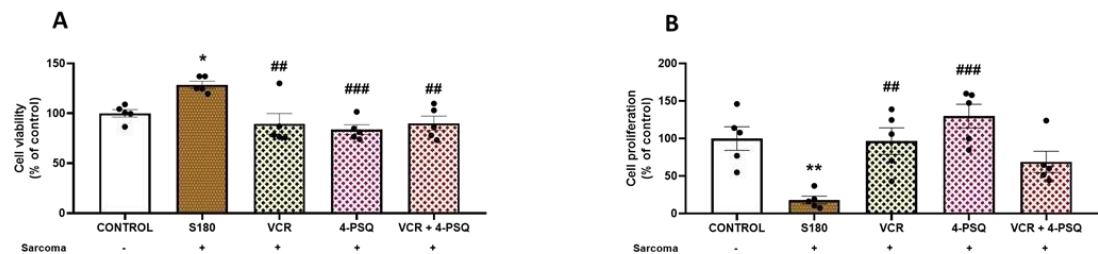


Fig. 7

Oxidative damage - analysis in macrophages

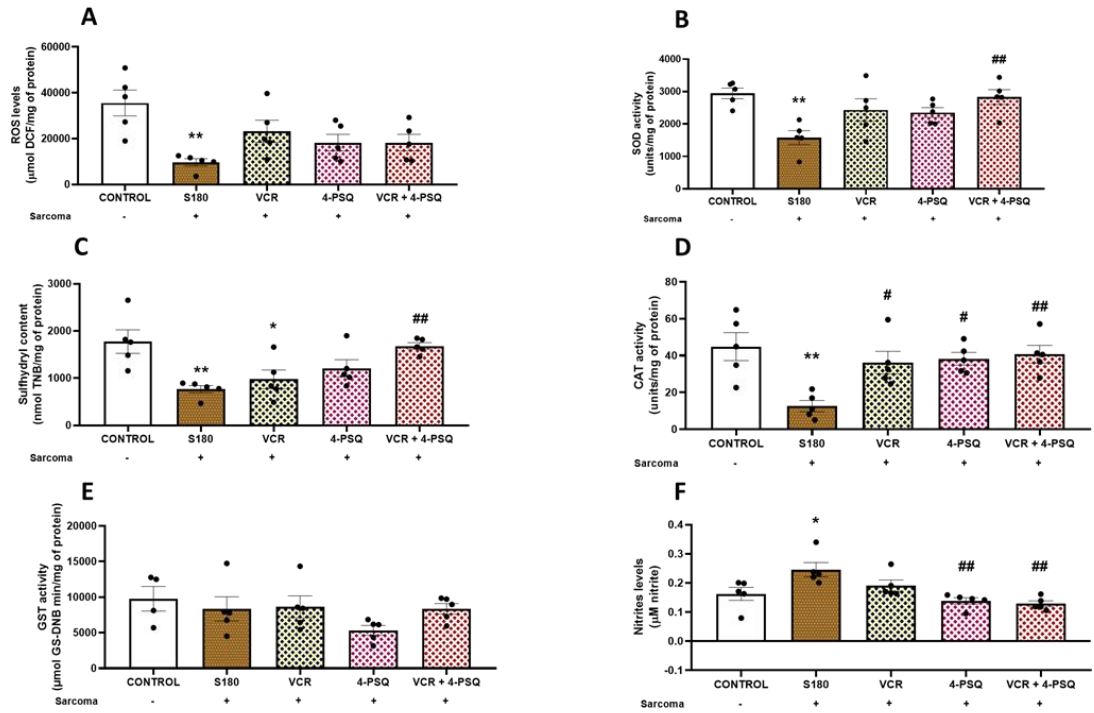


Fig. 8

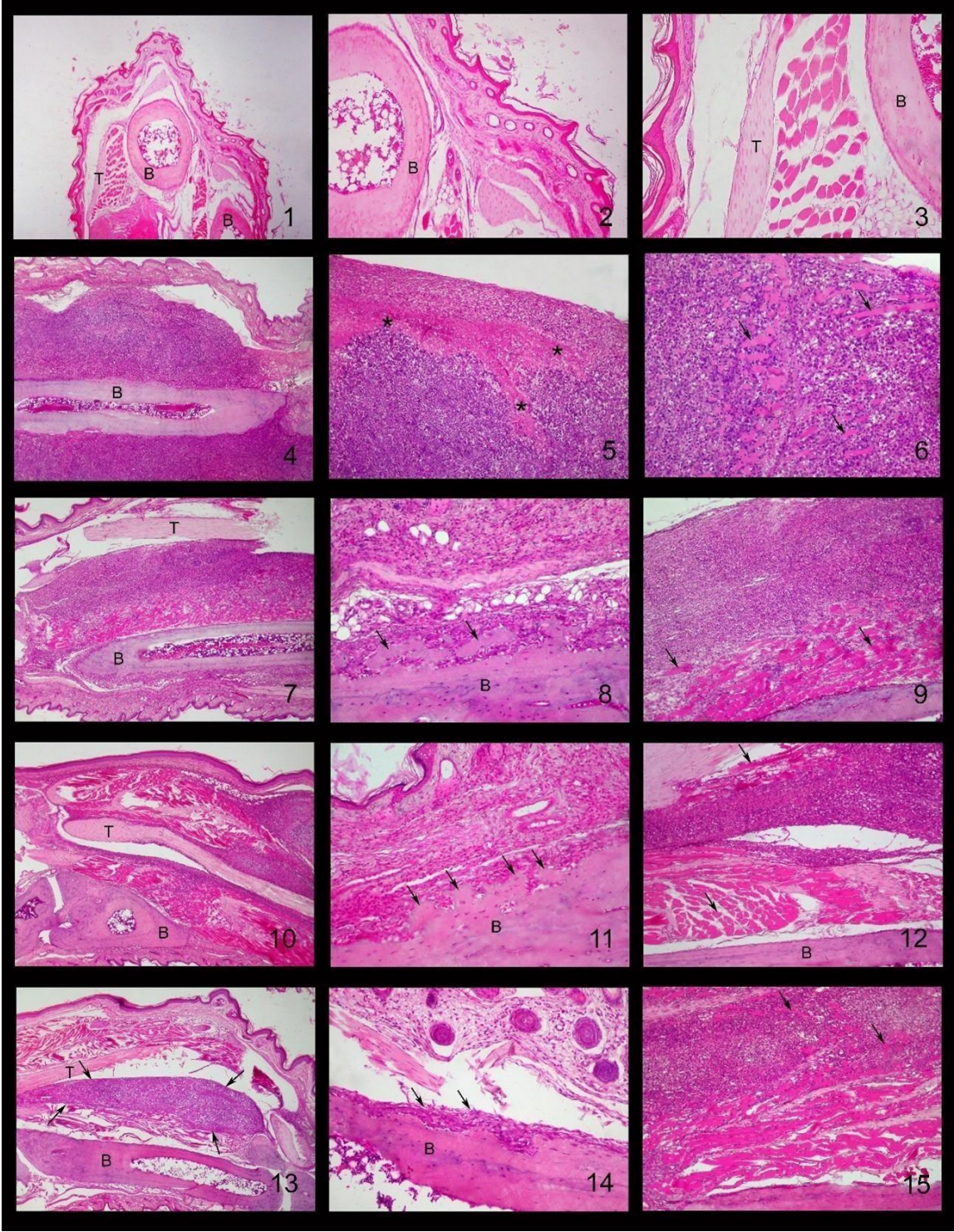


Fig. 9

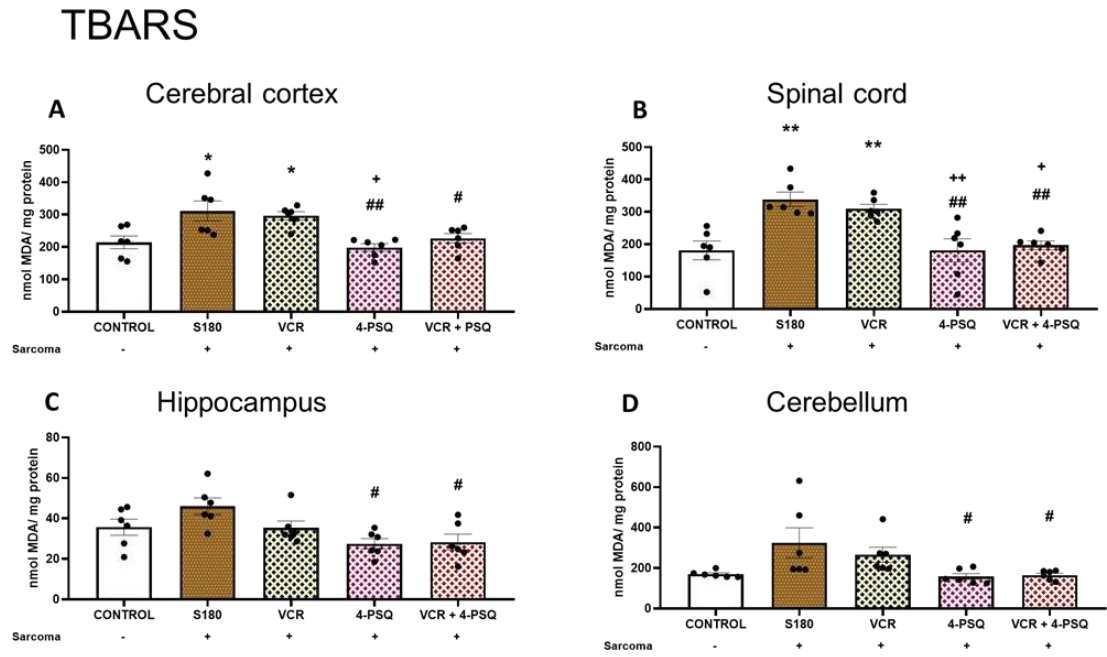


Fig. 10

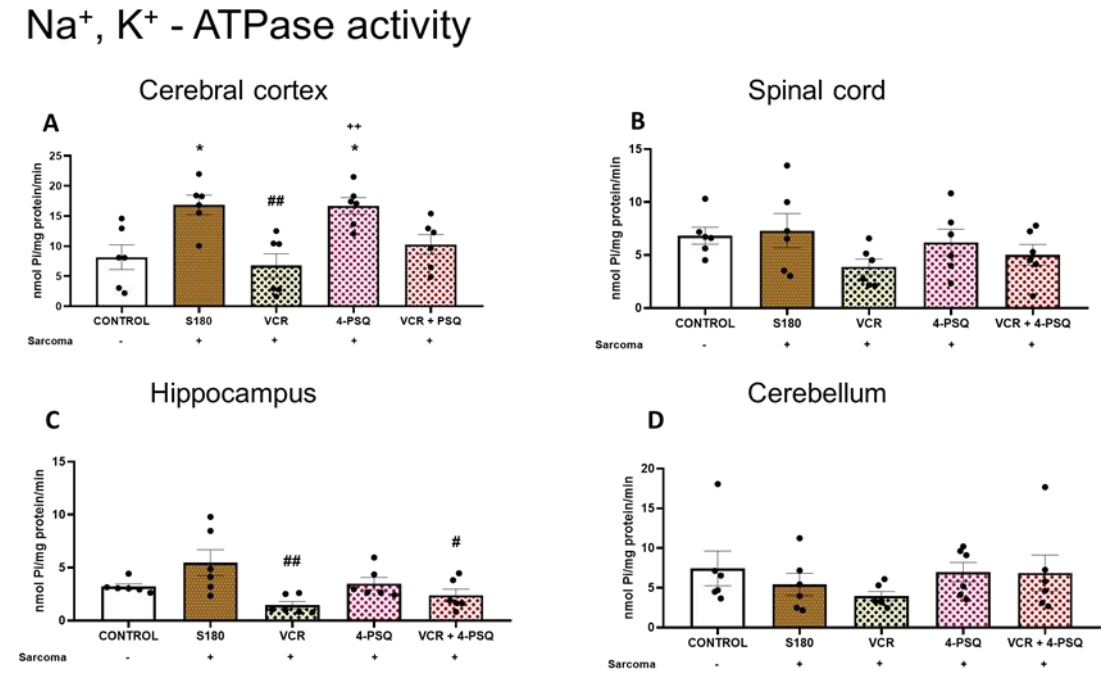
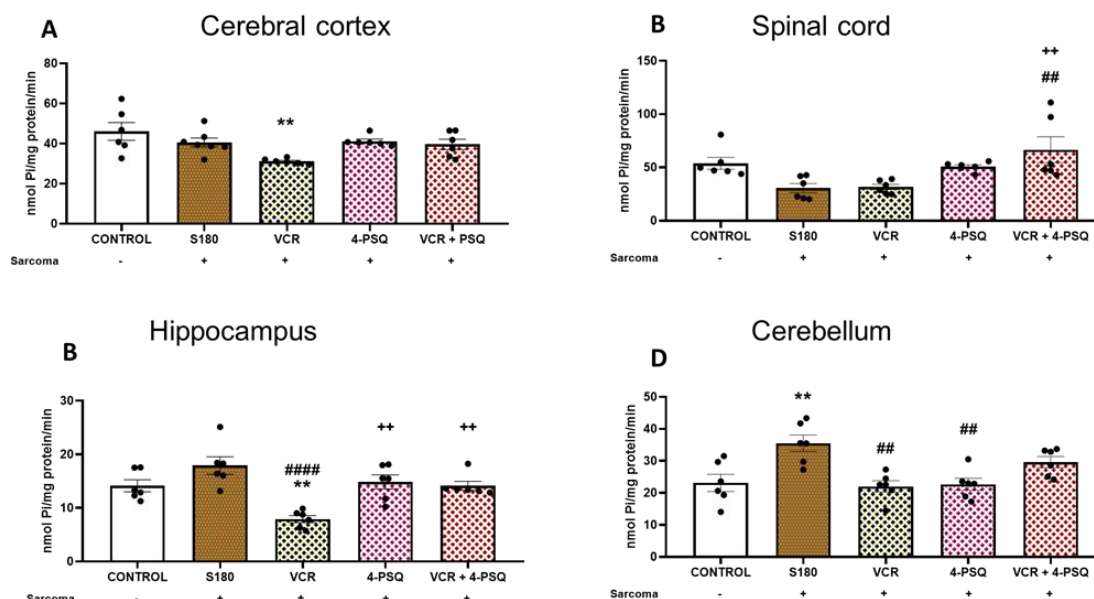


Fig. 11

Mg²⁺ - ATPase activity



Highlights

- Novel model integrates tumor progression with chemotherapy-induced neurotoxicity.
- Infrared thermography serves as a non-invasive biomarker of tumor inflammation.
- 4-PSQ provides analgesic, antioxidant, neuroprotective, and immunomodulatory actions.
- Combined VCR and 4-PSQ enhances antitumor efficacy and reduces chemotherapy toxicity.
- 4-PSQ emerges as a promising adjuvant for multifaceted cancer pain management.

4.6. Capítulo 6 – Resultados Adicionais

Resultados obtidos durante o período de doutorado sanduíche em parceria com a *Universidad Miguel Hernández De Elche*

Avaliação do efeito do composto 7-cloro-4-(fenilselanil) quinolina (4-PSQ) sob os canais de Receptor de Potencial Transitório (TRPs) – TRPA1, TRPM8 e TRPV1.

Durante o período do doutorado sanduíche, realizado no exterior, foram desenvolvidas atividades experimentais que complementaram e ampliaram a abordagem metodológica inicialmente proposta no Brasil. Essa etapa possibilitou a imersão em novas técnicas e abordagens, como cultivo celular, ensaios de cálcio (*calcium imaging*), imunohistoquímica e *patch clamp*. A inserção nesse ambiente científico internacional favoreceu a consolidação de colaborações, a troca de experiências com outros pesquisadores e o contato com diferentes perspectivas sobre a temática investigada.

Os resultados obtidos nesse estágio embora sejam preliminares, favoreceram o conhecimento e aperfeiçoamento de novas técnicas bem como para a compreensão dos mecanismos associados a análise do potencial terapêutico do composto 4-PSQ. Dessa forma, os achados parciais apresentados a seguir não apenas reforçam a relevância da pesquisa em andamento, mas também representam um avanço no escopo investigativo delineado para esta tese.

A análise realizada forneceu insights prévios da atividade do 4-PSQ sob canais TRPs (TRPA1, TRPM8 e TRPV1) transfectados em células renais embrionárias humanas -293 (HEK-293). Em suma, observou-se uma possibilidade do 4-PSQ atuar como um agonista dos canais TRPA1, entretanto mais ensaios experimentais se fazem necessários para validação desta hipótese.

Investigação dos efeitos do 7-cloro-4-(fenilselanil) quinolina (4-PSQ) sobre os canais TRPA1, TRPM8 e TRPV1 por meio de *calcium imaging* em células HEK- 293 transfectadas.

A análise da possível atividade do 4-PSQ sob os seguintes canais se deu por meio da análise *in vitro* em células HEK-293 que foram previamente transfectadas com os receptores TRPs de interesse. Para verificações que possíveis atividades do 4-PSQ nas células HEK-293 foram testadas por meio da técnica de registro de cálcio (*calcium imaging*).

Metodologia

Cultivo Celular

As células foram cultivadas a 37 °C em meio Eagle modificado por Dulbecco (DMEM) contendo soro fetal bovino (SFB) e 1% de penicilina/estreptomicina em atmosfera de 5% de CO₂. As células foram semeadas em placas de 24 poços a 2 × 10 células /poço e, 24 h após o plaqueamento, foram transfectadas com diferentes DNAs plasmidiais utilizando Lipofectamine™ 2000 (Thermo Fisher Scientific); foram utilizados 1 µg de DNA total e 2 µl de Lipofectamine™ por poço, respectivamente. Para a transfecção, a Lipofectamine™ foi misturada ao DNA em 100 µl de OptiMem (Thermo Fisher Scientific). As células foram tripsinizadas e replantadas em lamínulas redondas revestidas com poli-L-lisina (6 mm de diâmetro) a 80.000 células/lamínula, 24 a 48 horas após a transfecção. Células fluorescentes de proteína (+) foram selecionadas para registros de cálcio. Os diferentes DNAs plasmidiais utilizados e suas fontes são descritos na Tabela 1.

Tabela 1. Características e fontes de plasmídeos de DNA.

Plasmídeo de DNA	Características
mTRPM8-EYFP	1,19 ug/ul (Kan)
	29/07/2024
	preparo para 1 µg
EYFP/TRPV1	1615 ng/ul
	preparo para 1 µg

	1040 ng/ul
hTRPA1/tGFP	preparo para 1 µg
	8348 ng/ul
t- hTRPA1-GFP	16/02/2021 MTP9211
	preparo para 1 µg

Isolamento e cultura de neurônios do gânglio da raiz dorsal de camundongos

Neurônios do gânglio da raiz dorsal (DRG) de camundongos foram dissociados conforme descrito por Caires et al. (2015). Resumidamente, camundongos machos C57BL/6 foram anestesiados com isoflurano e sacrificados por deslocamento cervical. A medula espinhal foi removida e 25 a 30 DRGs foram extraídos e lavados em solução salina tamponada de Hank's fria (Invitrogen). Os gânglios foram incubados em 900 U/ml de collagenase (Sigma tipo XI) e 5,46 U/ml de dispase (Invitrogen) por 45 minutos a 37°C em 5% de CO₂. Em seguida, foram trituradas delicadamente com pipeta de vidro polido à chama em meio de cultura isento de cálcio, solução salina tamponada de Hank (Invitrogen) + 1% de MEM-Vit (Invitrogen) + 10% de SFB (Invitrogen) + 100 mg/ml de penicilina/estreptomicina (Invitrogen), e a suspensão resultante foi centrifugada. O pellet obtido foi ressuspenso em meio de cultura com a seguinte composição: MEM (Invitrogen) + 1% de MEM-Vit (Invitrogen) + 10% de SFB (Invitrogen) + 100 mg/ml de penicilina/estreptomicina (Invitrogen). As células foram semeadas em lamínulas de vidro redondas tratadas com 0,01% de poli-L-lisina (Sigma) e mantidas a 37°C e 5% de CO₂.

Registro de cálcio intracelular (*calcium imaging*)

A detecção das variações de cálcio intracelular foi realizada utilizando o corante ratiométrico Fura-2 AM, conforme metodologia previamente estabelecida por Marcotti et al. (2023). Células HEK-293 transfectadas ou neurônios DRG dissociados foram incubados com Fura-2 AM (5 μ M, 30 min, 37 °C) em solução tampão (HBSS suplementado com 10 mM HEPES). Após lavagem, as células foram mantidas em câmara de perfusão sob fluxo contínuo de solução extracelular. Fura-2 foi excitado usando uma lâmpada de arco de xenônio (Sutter Instruments) em comprimentos de onda de 340 e 380 nm, alternando entre ambos com uma roda de filtro controlada por computador (Lambda 10-2; Sutter Instruments), e a fluorescência emitida foi filtrada por passagem longa a 510 nm. As imagens foram adquiridas usando uma câmera ORCA ER CCD (Hamamatsu Photonics KK) a uma frequência de 0,33 Hz e analisadas com o software Metafluor (Molecular Devices). O sinal foi expresso como razão F340/F380 (*ratio*), proporcional à concentração de Ca^{2+} intracelular. Os estímulos farmacológicos foram aplicados por sistema de perfusão controlado, garantindo trocas rápidas de soluções (1–2 s).

Resultados parciais e Discussão

Atividade do 4-PSQ sob os canais TRPV1

A modulação do canal TRPV1 desempenha um papel crucial na dor neuropática, uma vez que sua ativação química, principalmente por agonistas como a capsaicina, assim como por estímulos térmicos sensíveis a calor (acima de $\sim 42^\circ\text{C}$), provoca influxo de cálcio em neurônios sensoriais, contribuindo para

a hiperexcitabilidade neuronal característica dessa condição. Por esse motivo, TRPV1 constitui um alvo promissor para agentes com efeito antinociceptivo, como o 4-PSQ. Nesse contexto, avaliamos os efeitos do 4-PSQ na ativação de TRPV1 (Figura 1) utilizando ensaios de calcium imaging, com o objetivo de investigar seu potencial modulador desse canal na dor neuropática. Observamos que o 4-PSQ não atuou como agonista dos receptores TRPV1, um achado relevante, considerando que estímulos agonísticos nesse receptor podem desencadear nocicepção, sugerindo que o 4-PSQ poderia exercer efeito antinociceptivo sem provocar ativação indesejada de TRPV1.

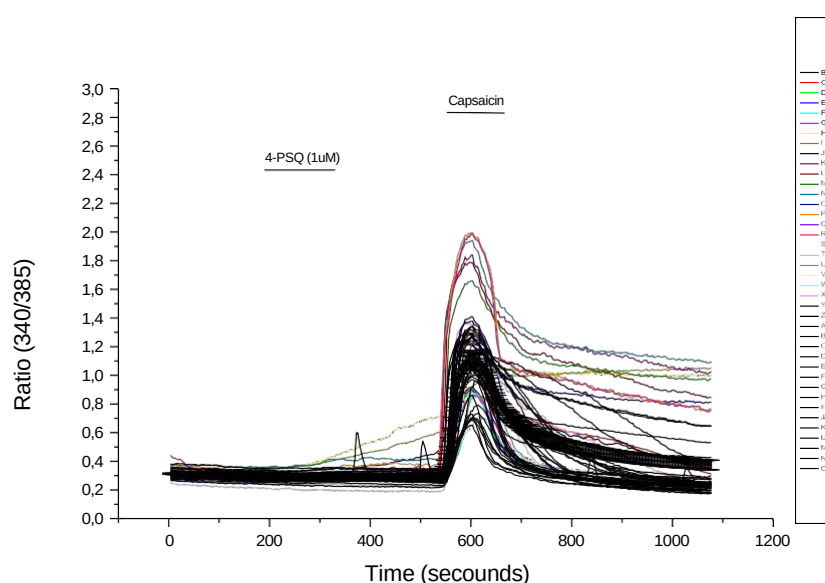


Figura 1 – Respostas de cálcio intracelular induzidas por 7-cloro-4-fenilselanil quinolina (4-PSQ) e capsaicina em células renais embrionárias humanas (HEK-293). O potencial efeito agonista de 4-PSQ sobre os canais TRPV1 transfectados em HEK-293 foi avaliado por meio de experimentos de *calcium imaging*. As células foram estimuladas sequencialmente com 4-PSQ (1 μ M) seguido de capsaicina (100 nM), conforme indicado pelas barras horizontais. Os traçados representam respostas individuais obtidas com o indicador fluorescente Fura-2 AM. O eixo y mostra a razão de fluorescência (340/380 nm), que reflete alterações na concentração intracelular de cálcio, enquanto o eixo x corresponde

ao tempo experimental (segundos).

Paralelamente, observamos a possibilidade do 4-PSQ atuar como um agente bloqueador do canal TRPV1. Para isso, foram levantadas 3 hipóteses: I) 4-PSQ poderia fechar/bloquear o canal TRPV1 e impedir a ativação posterior por meio da capsaicina; II) 4-PSQ poderia fechar/bloquear o canal TRPV1 mesmo após pré-abertura por meio da capsaicina; e III) Previa incubação de 45min com 4-PSQ poderia impossibilitar ativação do canal TRPV1 pelo agonista TRPV1. Segundo os resultados prévios observados na Figura 2, não averiguamos modulações significativas pelo 4-PSQ que tenham sido de fato, potencialmente capazes de bloquear e/ou inibir efeito de ativação do canal antes ou após estímulo do agonista capsaicina.

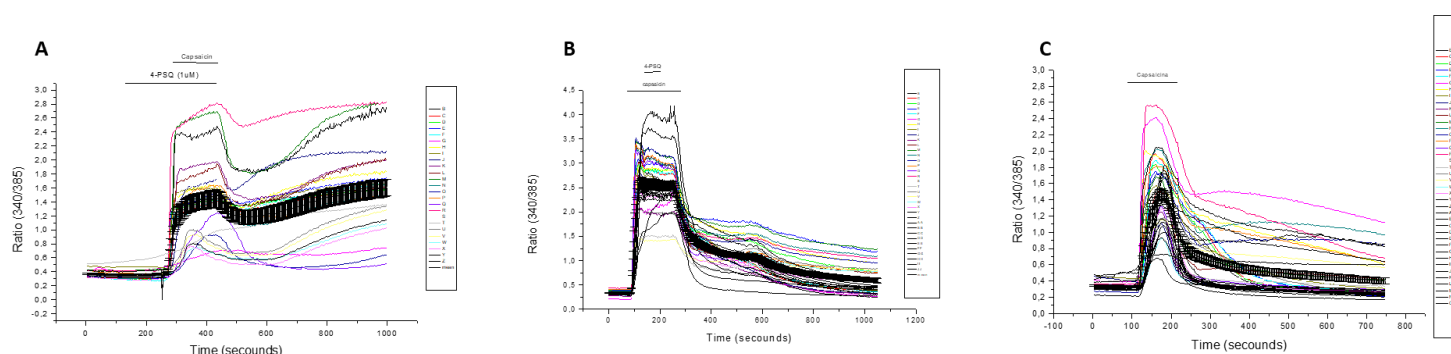


Figura 2 – Respostas de cálcio intracelular induzidas por 7-cloro-4-fenilselanil quinolina (4-PSQ) e capsaicina em células renais embrionárias humanas (HEK-293). (A) Células HEK-293 transfectadas com TRPA1 foram avaliadas quanto ao possível bloqueio da resposta induzida por capsaicina após exposição inicial a 4-PSQ (1 μM). (B) Análise do efeito de 4-PSQ após estímulo prévio com capsaicina (100 nM), seguido de nova aplicação de capsaicina. (C) Incubação de 4-PSQ por 45 minutos em células HEK-293 transfectadas com TRPA1, seguida de estimulação com agonista capsaicina durante o ensaio de calcium imaging. Os traçados representam experimentos de fluorescência com Fura-2 AM, onde cada linha corresponde à resposta de uma célula individual. O eixo y mostra a razão de fluorescência (340/380 nm), indicativa das variações na concentração intracelular de cálcio, enquanto o eixo x indica o tempo do experimento (segundos).

Atividade do 4-PSQ sob os canais TRPM8

O canal TRPM8 é um receptor sensível ao frio, ativado por baixas temperaturas e por agonistas químicos como o mentol ou WS12. Sua ativação tem sido associada à modulação da percepção de dor, especialmente em condições de dor neuropática, enquanto a sua inibição pode contribuir para efeitos antinociceptivos ao reduzir a excitabilidade neuronal induzida por estímulos nocivos. Dessa forma, a avaliação do efeito do 4-PSQ sobre o TRPM8 é de grande relevância, pois a atividade desse composto como agonista ou antagonista deste canal pode esclarecer seu potencial modulador de respostas dolorosas.

Inicialmente, conforme demonstrado pela Figura 3, o 4-PSQ não atuou como um agonista do receptor TRPM8. A inatividade como agonista do 4-PSQ sob o canal TRPM8 é um achado que pode demonstrar que o composto sintético não apresenta capacidade de ativar cascatas de excitabilidade que elevam a dor por meio do canal TRPM8.

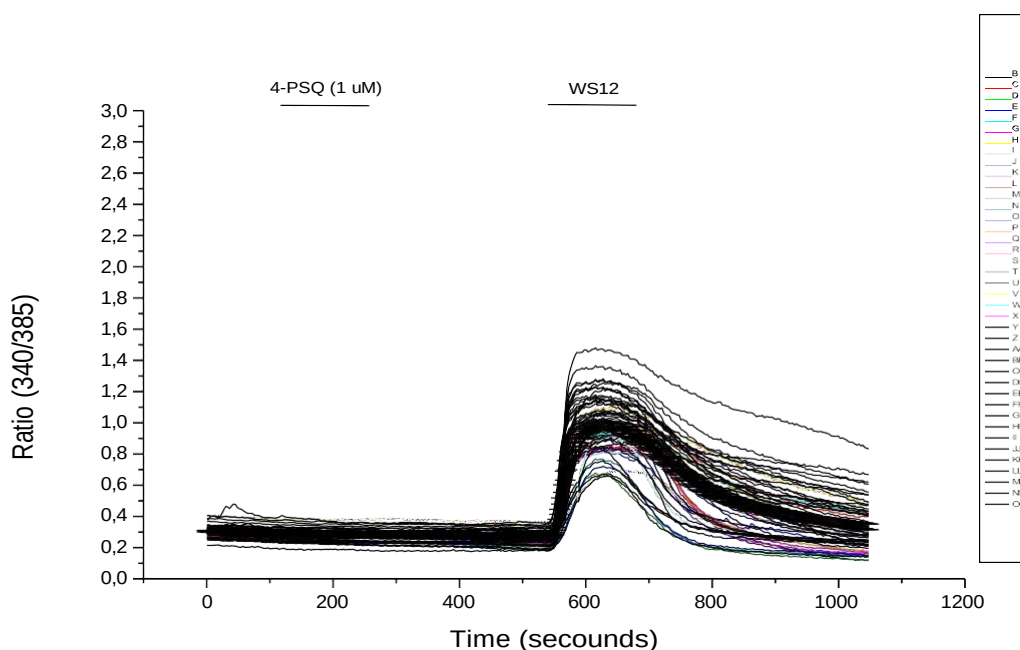


Figura 3 – Respostas de cálcio intracelular induzidas por 7-cloro-4-fenilselanil quinolina (4-PSQ) e WS12 em células renais embrionárias humanas (HEK-293). O potencial efeito agonista de 4-PSQ sobre os canais TRPM8 transfectados em HEK-293 foi avaliado por meio de experimentos de *calcium imaging*. As células foram estimuladas sequencialmente com 4-PSQ (1 μ M) seguido de WS12 (10 μ M), conforme indicado pelas barras horizontais. Os traçados representam respostas individuais obtidas com o indicador fluorescente Fura-2 AM. O eixo y mostra a razão de fluorescência (340/380 nm), que reflete alterações na concentração intracelular de cálcio, enquanto o eixo x corresponde ao tempo experimental (segundos).

Sequencialmente, verificamos conforme demonstrado na Figura 4, que o 4-PSQ não atuou como antagonista dos canais TRPM8. Conforme comentado anteriormente, 3 hipóteses foram levantadas para avaliação do potencial efeito do 4-PSQ sob os canais TRPM8: I) 4-PSQ poderia fechar/bloquear o canal TRPM8 e impedir a ativação posterior por meio da WS12; II) 4-PSQ poderia fechar/bloquear o canal TRPM8 mesmo após pré-abertura por meio da WS12; e III) Preactivação de 45min com 4-PSQ poderia impossibilitar ativação do canal TRPM8 pelo agonista WS12. A Figura 4A, 4B e 4C respondem

respectivamente as hipóteses I, II e III. A Figura 4, indica que possivelmente o 4-PSQ não apresenta potencial efeito inibitório do canal TRPM8. Nossos dados prévios demonstram que o 4-PSQ não foi capaz de bloquear a abertura do canal por WS12, ou mesmo fechá-lo após a ativação do canal pelo WS12, e ainda mesmo após 45min de incubação não verificamos um bloqueio significativo 4-PSQ sob TRPM8.

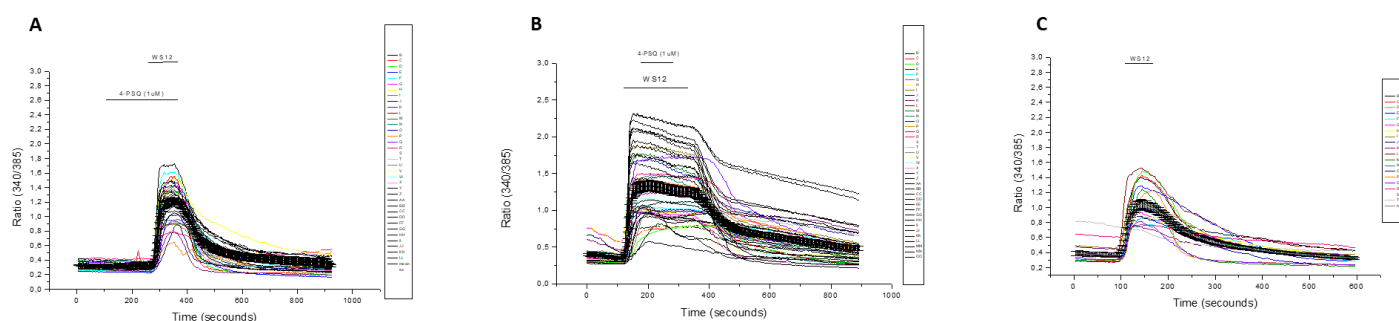


Figura 4 – Respostas de cálcio intracelular induzidas por 7-cloro-4-fenilselanil quinolina (4-PSQ) e WS12 em células renais embrionárias humanas (HEK-293). (A) Células HEK-293 transfectadas com TRPM8 foram avaliadas quanto ao possível bloqueio da resposta induzida por capsaicina após exposição inicial a 4-PSQ (1 μ M). (B) Análise do efeito de 4-PSQ após estímulo prévio com WS12 (10 μ M), seguido de nova aplicação de WS12. (C) Incubação de 4-PSQ por 45 minutos em células HEK-293 transfectadas com TRPM8, seguida de estimulação com agonista WS12 durante o ensaio de *calcium imaging*. Os traçados representam experimentos de fluorescência com Fura-2 AM, onde cada linha corresponde à resposta de uma célula individual. O eixo y mostra a razão de fluorescência (340/380 nm), indicativa das variações na concentração intracelular de cálcio, enquanto o eixo x indica o tempo do experimento (segundos).

Atividade do 4-PSQ sob os canais TRPA1

O canal TRPA1 é um receptor sensível a estímulos químicos irritantes, frio intenso e inflamação, sendo amplamente implicado na percepção de dor e na hipersensibilidade característica de condições como a dor neuropática. A

modulação deste canal, seja por ativação ou inibição, pode influenciar significativamente a excitabilidade neuronal e a transmissão de sinais nociceptivos. Nesse contexto, investigar os efeitos do 4-PSQ sobre o TRPA1 é relevante para avaliar seu potencial como agente antinociceptivo, uma vez que sua ação sobre este canal pode contribuir para a redução da dor neuropática sem provocar ativação nociva dos neurônios sensoriais.

Conforme observamos na Figura 5A-5B, verificamos algumas inconsistências na atividade do 4-PSQ sob o canal TRPA1. Na Figura 5A, o 4-PSQ aparentemente não levou a ativação dos canais TRPA1, enquanto que na Figura 5B observamos uma ativação significativa do 4-PSQ sob o mesmo canal. É importante salientar que estes resultados são prévios uma vez que se fazem necessárias repetições consistentes (que simulem a mesma atividade) em cada experimento de pelo menos 5 repetições. Sendo assim, temos um dado inconclusivo de uma possível atividade como agonista do 4-PSQ sob o canal TRPA1. A possível confirmação da atividade como agonista do 4-PSQ sob o canal TRPA1, provocando um aumento transitório no influxo de cálcio intracelular pode indicar um fenômeno de dessensibilização do canal, diminuindo a excitabilidade dos neurônios nociceptivos e contribuindo para os efeitos analgésicos observados *in vivo*.

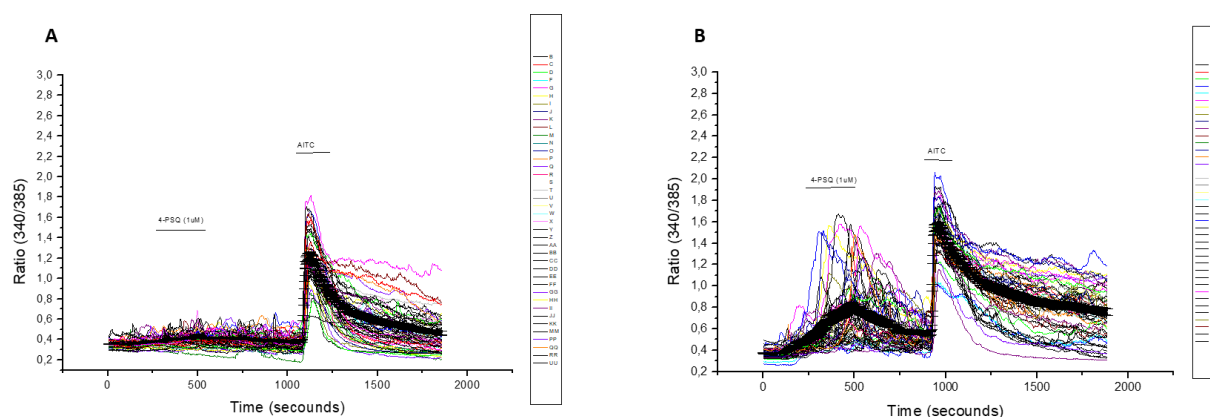


Figura 5 – Respostas de cálcio intracelular induzidas por 7-cloro-4-fenilselanil quinolina (4-PSQ) e alil isotiocianato (AITC) em células renais embrionárias humanas (HEK-293) transfectadas com TRPA1. (A–B) O possível efeito agonista do 4-PSQ sobre os canais TRPA1 foi avaliado por experimentos de calcium imaging. As células foram estimuladas sequencialmente com 4-PSQ (1 μ M), seguido por AITC (50 μ M), conforme indicado pelas barras horizontais. Os traçados representam respostas individuais registradas com o indicador fluorescente Fura-2 AM. O eixo y mostra a razão de fluorescência (340/380 nm), refletindo variações na concentração intracelular de cálcio, enquanto o eixo x corresponde ao tempo experimental (segundos).

Afim de compreender melhor as ações do 4-PSQ nos canais TRPA1 realizamos o registro de cálcio em neurônios de DRGs (Figura 6). Os resultados preliminares não sustentam totalmente a hipótese de que o 4-PSQ possa estar atuando como bloqueador ou agonista do canal TRPA1 (Figura 6A-6B) quando comparamos ao teste controle demonstrado na Figura 6C. A Figura 6C demonstra a excitabilidade cálcio padrão para um estímulo de AITC equivalente ao tempo em que foi testado 4-PSQ em conjunto com AITC.

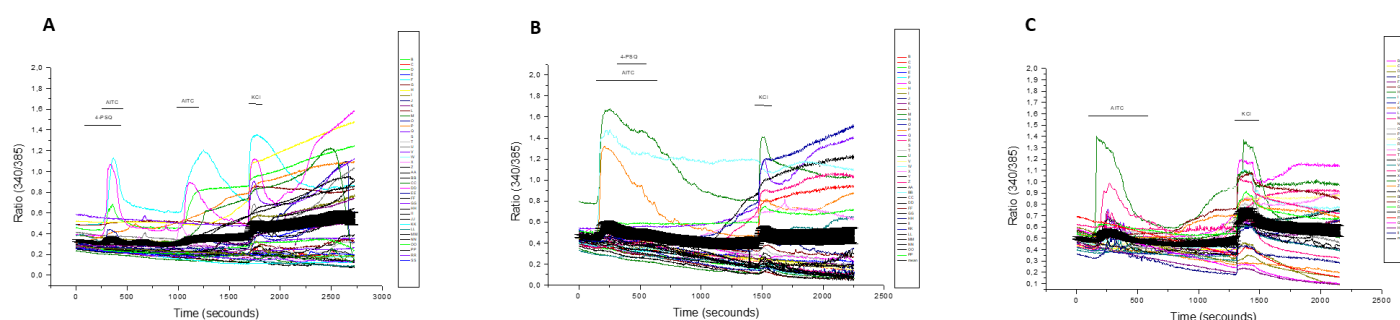


Figura 6 – Respostas de cálcio intracelular induzidas por 7-cloro-4-fenilselanil quinolina (4-PSQ) e alil isotiocianato (AITC) (50 μ M) em neurônios dissociados dos gânglios da raiz dorsal (DRG) de camundongos C57BL/6J selvagens (TRPA1+/+, *wild-type*), com 8–12 semanas de idade. (A) Avaliação do potencial efeito modulador do 4-PSQ sobre os canais TRPA1: o composto foi aplicado isoladamente, seguido por estímulo conjunto com AITC. Após o retorno dos níveis de cálcio basais, realizou-se novo estímulo com AITC e, em seguida, estímulo com cloreto de potássio (KCl) para comprovação da viabilidade neuronal. (B) Investigação do possível efeito bloqueador do 4-PSQ após estímulo prévio com AITC, seguida pela confirmação da resposta neuronal ao KCl. (C) Controle experimental com aplicação isolada de AITC pelo mesmo tempo de estímulo utilizado nos protocolos combinados com 4-PSQ, seguida pela comprovação da viabilidade neuronal pelo KCl. Os traçados representam respostas individuais registradas com o indicador fluorescente Fura-2 AM. O eixo y mostra a razão de fluorescência (340/380 nm), que reflete as variações na concentração intracelular de cálcio, enquanto o eixo x corresponde ao tempo experimental (segundos).

5. DISCUSSÃO

O presente estudo estabeleceu, de forma inédita, que a VCR embora essencial no tratamento de neoplasias hematológicas, causa neurotoxicidade multifatorial que afeta grupos vulneráveis como idosos, neonatos e fêmeas, desencadeando degeneração axonal, estresse oxidativo, desequilíbrio iônico, alterações na sinalização NF κ B e inibição da Na⁺,K⁺-ATPase, culminando em neuropatia periférica, déficits cognitivos, ansiedade e depressão. O composto 4-

PSQ demonstrou-se eficaz em reverter a hipernocicepção, restaurar parâmetros bioquímicos-chave, normalizar vias antioxidantes, regular enzimas de membrana e proteger funções cognitivas e emocionais, além de exibir seletividade citotóxica contra células leucêmicas HL-60. Esses achados posicionam o 4-PSQ como um adjuvante promissor capaz de ampliar a segurança e eficácia dos protocolos quimioterápicos com VCR, preservando qualidade de vida e funcionalidade neurológica.

Uma análise inicial foi realizada com foco na investigação inédita dos efeitos da VCR em ratos envelhecidos. No presente trabalho, investigou-se, os mecanismos estruturais e bioquímicos subjacentes à NPIV em ratos idosos, destacando-se a ocorrência de degeneração Walleriana, desequilíbrio redox e alterações na atividade de enzimas ATPases. A avaliação histopatológica evidenciou a presença de desmielinização segmentar e degeneração axonal típica do processo de degeneração Walleriana, corroborando o comprometimento estrutural de nervos periféricos, frequentemente relatado como um dos principais determinantes da neuropatia sensorial em pacientes submetidos à quimioterapia com VCR. Entretanto, não havia sido observada anteriormente em termos de condições associadas a senescência.

Os achados comportamentais demonstraram pré-sensibilização mecânica mais pronunciada em ratos idosos, sugerindo comprometimento das fibras mielinizadas associado à menor plasticidade reparadora, condição que favorece a cronificação da dor (Madsen et al., 2019; Schappacher; Styczynski; Baccei, 2017). Por outro lado, a maior hiperalgesia mecânica verificada em ratos jovens no período intermediário pode ser atribuída à maior integridade estrutural das fibras A, que, não degeneradas, mantêm alta excitabilidade nociceptiva, padrão compatível com o perfil de neurotoxicidade aguda relatado para a VCR (Gomber; Dewan; Chhonker, 2010b; Madsen et al., 2019; Schappacher; Styczynski; Baccei, 2017-).

Em relação à sensibilidade térmica, destaca-se que ratos idosos expostos ao VCR apresentaram maior redução da latência a estímulos térmicos, sugerindo maior envolvimento de fibras C amielínicas, cuja excitabilidade é modulada por alterações no metabolismo do cálcio, notadamente pela atividade da Ca^{2+} -ATPase, frequentemente desregulada em modelos de neurotoxicidade (Raasing et al., 2021). Assim, reforça-se a hipótese de que a VCR potencializa

a excitabilidade neuronal por vias dependentes de cálcio, especialmente em organismos envelhecidos, onde a capacidade de reparo neural encontra-se comprometida.

Analizou-se ainda que a VCR promoveu acúmulo de espécies reativas, refletido pelo aumento nos níveis de TBARS e pela redução de NPSH, indicando estresse oxidativo exacerbado em estruturas cerebrais. Estes achados sustentam a hipótese de que a neurotoxicidade da VCR decorre, em grande parte, da geração excessiva de radicais livres, capazes de peroxidar lipídios de membrana, lesar proteínas estruturais e comprometer a integridade axonal (Busch; Binder, 2017; Gęgotek; Skrzydlewska, 2019).

Paralelamente, observou-se modulação significativa da atividade de enzimas ATPases, destacando-se a redução da atividade da Na^+ , K^+ -ATPase e alterações na Ca^{2+} -ATPase. Tais enzimas são essenciais para a manutenção do potencial de membrana, condução do impulso nervoso e homeostase iônica; logo, sua inibição sugere perturbações funcionais que agravam a degeneração axonal iniciada pela lesão primária (Starobova; Vetter, 2017a; Sy *et al.*, 2019b; Triarico *et al.*, 2021c). Corrobora-se, assim, que a perda da função da Na^+ , K^+ -ATPase contribui para o colapso da excitabilidade neuronal e para falhas na transmissão sináptica, fenômenos centrais na manifestação da dor neuropática e perda de função sensório-motora (Canta; Pozzi; Carozzi, 2015b; Jiang; Shi; Shi, 2019b).

Neste sentido, foi possível averiguar a partir desta primeira análise que o modelo utilizado em ratos idosos permitiu verificar que o envelhecimento acentua a vulnerabilidade neuronal aos efeitos deletérios da VCR. Sabe-se que o envelhecimento reduz a capacidade antioxidante basal e prejudica mecanismos de reparo axonal, o que, somado ao impacto citotóxico da VCR, intensifica a progressão da degeneração Walleriana e limita a regeneração neural (Dagnino; Campos, 2022).

Portanto, este conjunto de dados auxiliou na conclusão de que a interação entre dano oxidativo, comprometimento enzimático e degeneração estrutural do nervo levam à sustentação da dor na NPIV. Tais evidências fortalecem o racional para o desenvolvimento de estratégias adjuvantes que priorizem a proteção axonal, o controle do estresse oxidativo e a preservação da atividade das ATPases, como alternativas promissoras para mitigar os efeitos adversos da

quimioterapia, especialmente em populações geriátricas, mais suscetíveis aos efeitos cumulativos do tratamento antineoplásico (Huang *et al.*, 2020; Kim *et al.*, 2017b).

Complementando as evidências previamente obtidas sobre os efeitos neurotóxicos periféricos da VCR, caracterizados pela degeneração Walleriana, estresse oxidativo e disfunção das ATPases, o segundo estudo da presente tese teve como objetivo investigar os mecanismos centrais associados aos déficits cognitivos e emocionais induzidos por VCR. De forma inédita, foram demonstrados os papéis da sinalização via NFkB, da expressão da proteína p21 e da atividade da Na^+ , K^+ -ATPase no desenvolvimento dessas alterações neurocomportamentais em modelos murinos de ambos os sexos.

Foi constatado que a VCR promove uma inibição significativa da atividade da Na^+ , K^+ -ATPase no córtex cerebral de camundongos, uma enzima essencial para a manutenção do potencial eletroquímico de membrana, regulação do volume celular e homeostase iônica, especialmente do gradiente de sódio e potássio (Dobretsov, 2005b; Liu; Lilly; Shapiro, 2018b; Sung *et al.*, 2015b). A redução funcional desta bomba iônica compromete a capacidade dos neurônios de realizar despolarização axonal adequada, interferindo diretamente na transmissão sináptica e na plasticidade neuronal, processos essenciais para a consolidação da memória e modulação do comportamento emocional (Dobretsov, 2005b; Magee; Grienberger, 2020b; Xu *et al.*, 2017b). A inibição da Na^+ , K^+ -ATPase pode ser atribuída ao estresse oxidativo, evidenciado pela sensibilidade dos resíduos de tiol presentes nas subunidades α e β da enzima, os quais são alvos preferenciais de radicais livres gerados em condições neurotóxicas, como previamente demonstrado (Cassol *et al.*, 2022b; Isaksen; Lykke-Hartmann, 2016b).

Paralelamente, observou-se aumento acentuado da expressão do fator de transcrição NFkB, um regulador central das respostas inflamatórias e apoptóticas, em múltiplas regiões do sistema nervoso central (Caviedes *et al.*, 2017b; Mussbacher *et al.*, 2023b). A ativação da via NFkB, correlacionada inversamente com a atividade da Na^+ , K^+ -ATPase, aponta para um mecanismo no qual o estresse oxidativo e a inflamação neurogênica interagem para perpetuar a disfunção neuronal e promover perda sináptica, conforme evidenciado pela literatura sobre neurodegeneração e transtornos

neuropsiquiátricos(Albensi, 2019b; Dobretsov, 2005b; Kinoshita *et al.*, 2016; Zheng *et al.*, 2023b). Além disso, o acúmulo de NFκB pode levar a alterações imunológicas complexas, afetando a regulação de células T, B e dendríticas, e favorecendo a manutenção anômala de células disfuncionais, que potencialmente agrava a neuroinflamação (Mussbacher *et al.*, 2023b).

A expressão aumentada de p21 exclusivamente no córtex cerebral de fêmeas, destaca um componente sexualmente dimórfico na resposta neuroinflamatória induzida pela VCR. A superexpressão de p21 em fêmeas sugere que as fêmeas podem apresentar uma maior predisposição à ativação de vias neuroinflamatórias e alteração da neuroplasticidade mediadas por hormônios sexuais, como a progesterona, que regula p21-activated kinase 4 (Pak4) e pode modular respostas inflamatórias específicas (Kim *et al.*, 2013b). Tal mecanismo pode contribuir para a maior suscetibilidade feminina à disfunção cognitiva em curto prazo, conforme sugerido pelos resultados comportamentais.

Este estudo evidenciou que os transtornos emocionais induzidos pela VCR, como ansiedade e depressão, resultam da inibição da Na⁺, K⁺-ATPase e da ativação da via NFκB, comprometendo a excitabilidade neuronal e a homeostase de glutamato e potássio, o que favorece neuroinflamação e disfunção sináptica (Lauritzen *et al.*, 2011b; Pietrobon; Moskowitz, 2013b). O composto 4-PSQ, em contrapartida, demonstrou reverter tais déficits por atenuar a neuroinflamação, restaurar a atividade da Na⁺, K⁺-ATPase, fortalecendo a neuroplasticidade e a sobrevivência neuronal. Assim, verificou-se que a neurotoxicidade central da VCR decorre de uma interação entre inibição enzimática, ativação inflamatória e expressão diferencial de p21, destacando diferenças sexuais relevantes e apontando o 4-PSQ como estratégia promissora para prevenir ou tratar os efeitos neurotóxicos da quimioterapia.

Na terceira parte deste estudo, foi avaliada a administração de VCR, buscando responder à hipótese de dimorfismo sexual em relação a NPIV. Foi observado que a VCR desencadeou de forma clara um quadro de hipernocicepção mecânica e térmica em camundongos de ambos os sexos, confirmando a já conhecida ação neurotóxica da VCR sobre fibras nervosas periféricas (Lee *et al.*, 2020; Madsen *et al.*, 2019; van de Velde *et al.*, 2021). A hipernocicepção mecânica, evidenciada pela redução do limiar de resposta a estímulos táteis, e a hipersensibilidade térmica, observada pela diminuição do

tempo de latência em testes de calor, indo de encontro com a NPIV em roedores anteriormente já evidenciada (Starobova; Vetter, 2017a). Notavelmente, verificou-se que as fêmeas mantiveram uma resposta térmica exacerbada por período prolongado, sugerindo um possível efeito modulador de fatores hormonais, como o estrogênio, que influencia processos de proliferação neural, plasticidade sináptica e inflamação (Beyer; Karolczak, 2000b; Kai *et al.*, 2006; Weeks; Levine, 1995) .

O composto organoselênio 4-PSQ demonstrou efeito neuroprotetor robusto, revertendo tanto hipernocicepção mecânica quanto térmica. Tal ação pode ser explicada pelo fato do 4-PSQ atuar como modulador redox e anti-inflamatório, conforme relatado em outros modelos de neurotoxicidade (de Oliveira *et al.*, 2022a; Paltian *et al.*, 2022a; Pinz *et al.*, 2016a, 2018a; Vogt *et al.*, 2018a; Voss *et al.*, 2017a). Ademais, o efeito do 4-PSQ em modular vias glutamatérgicas e nitrérgicas pode ser um mecanismo que corrobora o seu efeito protetor multialvo (Pinz *et al.*, 2016a; Reis *et al.*, 2017b).

No nível bioquímico, observou-se que a VCR aumenta a peroxidação lipídica, um marcador consolidado de estresse oxidativo e gatilho para inflamação neuronal (Gęgotek; Skrzydlewska, 2019). A ligação entre MDA (malondialdeído) e ativação de vias pró-inflamatórias, como NFκB e TNFα, é amplamente reconhecida (Busch; Binder, 2017; Del Rio; Stewart; Pellegrini, 2005; Gęgotek; Skrzydlewska, 2019). Nesse contexto, a reversão desse marcador pelo 4-PSQ confirma seu papel antioxidante ativo, alinhando-se a estudos que destacam sua capacidade de proteger macromoléculas contra danos oxidativos (Lemos *et al.*, 2021b; Motta *et al.*, 2021a; Reis *et al.*, 2022).

O aumento da atividade de enzimas como CAT e ATPases pode indicar uma tentativa celular de compensar o estresse redox e a disfunção mitocondrial, já que altas concentrações de espécies reativas demandam uma resposta antioxidante eficiente (Liu *et al.*, 2017; Liu, Lilly, Shapiro, 2018). Entretanto, o aumento descontrolado dessas enzimas também pode intensificar distúrbios iônicos, agravando o dano neuronal. Nesta linha, o efeito seletivo do 4-PSQ ao normalizar a Ca²⁺-ATPase, demonstra uma vantagem de especificidade terapêutica, uma vez que o composto apresenta alta lipossolubilidade, podendo este ser um fator facilitador para interagir com enzimas de membrana (Rodrigues *et al.*, 2021b).

No nível molecular, alterações no eixo Nrf2/HO-1 por meio da ação da VCR reforçam o conceito de que a falha ou desacoplamento dessa via é um marcador de neurotoxicidade crônica (An *et al.*, 2021; Minj; Upadhayay; Mehan, 2021; Su *et al.*, 2024). Basicamente, a VCR ocasionou a superexpressão seletiva de HO-1 no córtex de machos. A ação da HO-1, dissociada de alterações em Nrf2, pode ser relacionada à disfunção adaptativa típica em quadros de estresse oxidativo mantido (Sun *et al.*, 2002). O restabelecimento parcial dessa via pelo 4-PSQ reforça a hipótese de que sua eficácia neuroprotetora não se limita à ação antioxidante direta, mas inclui o suporte de mecanismos endógenos de defesa celular.

Não obstante, foi investigado o potencial antitumoral do 4-PSQ. De fato, análises *in vitro* indicaram que o 4-PSQ apresenta citotoxicidade seletiva para células de leucemia HL-60, com IC₅₀ micromolar, mantendo viabilidade em células não tumorais - células de ovário de hamster chinês (CHO). Essa seletividade é essencial, visto que a VCR, embora eficaz, tem sua aplicabilidade clínica limitada pela neurotoxicidade irreversível (Li *et al.*, 2020a; Zhu, J. *et al.*, 2021).

Logo, este terceiro estudo evidencia que o 4-PSQ reúne características desejáveis para um adjuvante quimioterápico: capacidade de modular vias de dano central e periférico, reverter desequilíbrios redox, restaurar homeostase iônica específica e exibir seletividade citotóxica frente a células tumorais. Esses aspectos consolidam o potencial do 4-PSQ em mitigar a NPV, sem comprometer sua eficácia antitumoral, alinhando-se a um paradigma terapêutico moderno que prioriza a eficácia com redução de toxicidades colaterais.

No quarto estudo, foi avaliada de forma abrangente como a exposição neonatal à VCR, embora indispensável no tratamento de leucemias infantis, compromete de modo multifacetado o neurodesenvolvimento, confirmando a robusta associação entre neurotoxicidade quimioterápica e prejuízos duradouros no sistema nervoso central em fases precoces da vida. Foi observado que a exposição neonatal a VCR reduziu significativamente o ganho de peso corporal, alterou o crescimento somático e interferiu no crescimento normal dos eixos cranianos, indicadores intimamente ligados à maturação cerebral e ao volume (Luhmann; Fukuda, 2020; Semple *et al.*, 2013). Notavelmente, o comprometimento do eixo anteroposterior do crânio em fêmeas, que não se

normalizou mesmo após o período crítico de PND 25, sugerindo uma vulnerabilidade sexual específica a neurotoxicidade neonatal induzida por VCR.

No âmbito funcional, a VCR prejudicou marcos neurocomportamentais fundamentais como: o atraso no reflexo de endireitamento, prejuízo à resposta de geotaxia negativa e a persistente deficiência no reflexo de posicionamento vibrissal, estes achados demonstram a interferência da VCR em circuitos neurais que dependem da integridade de nervos cranianos, núcleos do tronco encefálico e vias sensório-motoras. Estes achados alinham-se à literatura que descreve o impacto da interrupção da dinâmica de microtúbulos e do transporte axonal por meio da ação da VCR (da Motta *et al.*, 2024; Schappacher *et al.*, 2019b). Além disso, a análise histopatológica indicou a presença de vacúolos neuronais e câmaras de digestão em motoneurônios da medula espinhal em camundongos machos e fêmeas que receberam VCR. A análise histológica que indicou um processo neurodegenerativo induzido por VCR corrobora o que foi averiguado nos reflexos neurocomportamentais de desenvolvimento, indicando que possivelmente processos inflamatórios e degenerativos podem comprometer o neurodesenvolvimento.

A convergência entre os danos histológicos e bioquímicos foi evidenciada a partir da exposição dos animais à VCR: níveis elevados de TBARS no córtex, hipocampo e hipotálamo em fêmeas, e na medula espinhal de machos, aliados à depleção de compostos sulfidrílicos (NPSH), reforçam o papel central do estresse oxidativo como mecanismo patológico subjacente à neurotoxicidade da VCR (Alenezi, 2022, 2023a; Shayesteh *et al.*, 2022b). Paralelamente, a VCR desencadeou o desequilíbrio redox, somado à disfunção mitocondrial apontada pela modulação diferencial dos marcadores PINK-1 e PARKIN, a qual evidenciou uma resposta mitofágica sexualmente dimórfica: enquanto fêmeas ativaram mecanismos compensatórios para remoção de mitocôndrias danificadas, machos apresentaram redução na expressão de PINK-1, comprometendo a vigilância mitocondrial e intensificando a vulnerabilidade celular (Eltokhy; Toema; El-Deeb, 2022; Khidr *et al.*, 2023).

Paralelamente, VCR ocasionou supressão da expressão do MCL-1, um regulador antiapoptótico essencial, associada à elevação do BAX e à modulação de CASPASE-3, delineando um ambiente pró-apoptótico, favorecendo a ativação da via intrínseca de morte celular programada (He; Sun; Huang, 2017;

Tantawy *et al.*, 2023; Wolf *et al.*, 2023). Essa via, exacerbada pela falha na mitofagia eficiente, amplia a disfunção sináptica e a perda neuronal, refletindo-se nos atrasos de reflexos e na hipernocicepção observada.

Adicionalmente, foi observado que a VCR induziu hipernocicepção mecânica e térmica (ao calor e ao frio) em ambos os sexos, reproduzindo o perfil clássico de neuropatia periférica quimioterápica, já descrito anteriormente (Old *et al.*, 2014b; Shao *et al.*, 2024). A ativação excessiva de ATPases de membrana em ratos que receberam a VCR, como a Ca^{2+} -ATPase e Mg^{2+} -ATPase, verificada em múltiplas regiões encefálicas e na medula espinhal, sugere um aumento compensatório na tentativa de restabelecer a homeostase iônica perturbada, mas que paradoxalmente pode acentuar a excitabilidade neuronal, favorecendo a sensibilização central e a perpetuação da dor neuropática (Li, G. Zhou *et al.*, 2021a; Schappacher *et al.*, 2019b).

Somando-se a isso, os déficits motores demonstrados por meio de análises de marcha e rota-rod apontam para uma possível evolução de neuropatia sensório-motora, coerente com relatos clínicos em crianças tratadas com VCR, que frequentemente apresentam fraqueza muscular, ataxia e prejuízo no controle fino (Gilchrist; Marais; Tanner, 2014; Gilchrist; Tanner, 2016; van de Velde *et al.*, 2017a). O envolvimento do sistema nervoso autônomo, sugerido em neuropatias motoras avançadas, reforça a amplitude do impacto neurotóxico da VCR, exigindo atenção clínica especial na pediatria oncológica (Gilchrist; Tanner, 2016).

Em síntese, este quarto manuscrito demonstrou alterações inéditas em ratos neonatos expostos a VCR – prejuízo ao desenvolvimento físico e neurológico em uma janela crítica na aprendizagem e progressão física e cognitiva. Outras avaliações pioneiras deste estudo incluíram a neurodegeneração na medula espinhal, alterações mitocondriais e neuropatia sensório-motora. Portanto, este estudo amplia o conhecimento da NPIV pré-clínica em um modelo de neuropatia pediátrica, contribuindo para a elucidação de mecanismos fisiopatológicos e neurodesenvolvimento.

Por fim, no quinto estudo visou-se investigar a dor oncológica no viés da NPIV associada a dor derivada de um modelo de tumor sólido de sarcoma (S180) e os efeitos terapêuticos do 4-PSQ. Observou-se aumento progressivo tumoral por meio das medidas mediolateral e dorsoventral, evidenciando expansão do

tecido neoplásico e resposta inflamatória adjacente, fenômeno coerente com relatos prévios de desenvolvimento sólido e agressivo do Sarcoma S180 em modelos animais (Rezende *et al.*, 2021). A coadministração de VCR reduziu parcialmente essa expansão, efeito potencializado pela associação com o composto 4-PSQ, sugerindo atuação sinérgica na regressão do crescimento tumoral e/ou do edema inflamatório, achado que reforça a hipótese postulada inicialmente de ação antitumoral e anti-inflamatória combinada pelo composto.

As análises comportamentais demonstraram hiperalgesia mecânica e térmica persistente nos animais inoculados apenas com S180, corroborando o caráter inflamatório e tumoral, compatível com a literatura que descreve o envolvimento de mediadores inflamatórios, como citocinas e prostaglandinas, na gênese da dor tumoral (Gómez *et al.*, 2020; Zhu, S. *et al.*, 2021). Observou-se ainda que a administração de VCR intensificou a hiperalgesia, especialmente nas fases iniciais, evidenciando o perfil neurotóxico bem estabelecido deste quimioterápico, relacionado à disfunção dos microtúbulos, degeneração axonal e sensibilização periférica e central (Nagai; Goshima; Ohshima, 2012a; Wang *et al.*, 2000b).

Foi observado, particularmente, a partir do 11º dia, um ponto de inflexão na curva de hipersensibilidade térmica, com manutenção da hiperalgesia no grupo S180+VCR, enquanto o grupo S180 isolado apresentou atenuação parcial, sugerindo transição para estado crônico de dor mediado pela plasticidade mal-adaptativa do sistema nervoso (Chiba *et al.*, 2022). Este fenômeno pode refletir mecanismos como ativação glial, liberação sustentada de citocinas pró-inflamatórias na medula espinhal e perpetuação da sensibilização central (Chiba *et al.*, 2022; Shen *et al.*, 2015b).

Destaca-se, contudo, o efeito antinociceptivo significativo do 4-PSQ, capaz de reduzir a hiperalgesia mecânica e térmica, inclusive quando associado à VCR, evidenciando potencial modulatório tanto de vias inflamatórias quanto redox-sensíveis. De fato, dados experimentais prévios já apontam a eficácia do 4-PSQ na atenuação da hiperalgesia neuropática induzida por agentes quimioterápicos como oxaliplatina e paclitaxel (Paltian *et al.*, 2022a; Reis *et al.*, 2020a, 2022). O presente estudo amplia tais evidências, demonstrando que o 4-PSQ preserva sua ação analgésica mesmo na presença de estímulos nociceptivos combinados, o que é relevante para quadros de dor oncológica de

difícil manejo.

A análise termográfica, por sua vez, demonstrou aumento localizado da temperatura superficial na pata inoculada, reforçando a presença de inflamação e metabolismo exacerbado no sítio tumoral, fenômeno consistente com a literatura que correlaciona a hipertermia local com inflamação e angiogênese neoplásica (Kesztyüs *et al.*, 2023; Queiroz; de Cássia Fernandes de Lima, 2023). A atenuação desse padrão pelo 4-PSQ indica efeito anti-inflamatório local, compatível com suas propriedades antioxidantes e imunomodulatórias já reportadas (da Rocha *et al.*, 2025; de Freitas Couto *et al.*, 2019a; de Oliveira *et al.*, 2022a; Pinz *et al.*, 2018a; Rodrigues *et al.*, 2021b).

A resposta imune sistêmica, investigada por meio de macrófagos peritoneais, revelou disfunção funcional induzida pelo tumor, caracterizada por maior viabilidade celular, porém com proliferação reduzida, perfil compatível com polarização para um fenótipo M2 pró-tumoral (Gómez *et al.*, 2020; Maldonado *et al.*, 2022; Zhu, S. *et al.*, 2021). O co-tratamento com VCR não intensificou essa resposta, sugerindo restrição farmacocinética ou ação citostática fora do microambiente tumoral imediato. Entretanto, a associação VCR+4-PSQ restaurou a capacidade proliferativa e o equilíbrio redox dessas células, sustentando a hipótese de que o composto exerce modulação imuno-redox, relevante para o controle da progressão tumoral e da dor neuroinflamatória.

Os achados histopatológicos corroboraram o padrão agressivo do Sarcoma S180, com infiltração extensa em tecido subcutâneo, destruição de músculos e ossos e infiltrado neutrofílico proeminente, fenômenos amplamente descritos em modelos de sarcoma em roedores (Kazaryan *et al.*, 2022; Rezende *et al.*, 2021). A VCR isolada reduziu parcialmente a carga tumoral, mas não impediu necrose muscular e osteólise significativa, em consonância com relatos de eficácia citotóxica limitada, agravada por efeitos inflamatórios colaterais (Li *et al.*, 2020a; Singh *et al.*, 2019a). O 4-PSQ, isoladamente, mostrou melhora da preservação tecidual, efeito mais acentuado na combinação VCR+4-PSQ, na qual se observou redução da infiltração neoplásica, menor destruição óssea e muscular e infiltrado inflamatório atenuado. Estes achados reforçam o potencial sinérgico do 4-PSQ combinado à VCR que favorecem a manutenção da integridade tecidual.

A análise do estresse oxidativo central indicou elevação significativa dos

níveis de TBARS no córtex cerebral e medula espinhal, regiões-chave na modulação ascendente e descendente da dor (Sun *et al.*, 2023; Woolf, 2022). Este aumento reflete dano lipídico induzido por radicais livres decorrente tanto da progressão tumoral quanto da neurotoxicidade da VCR (Busch; Binder, 2017; Shayesteh *et al.*, 2022b). O restabelecimento dos níveis basais por 4-PSQ demonstra ação protetora das membranas neuronais, provavelmente relacionada à sua alta lipofilicidade e capacidade de incorporação em bicamadas lipídicas (Rodrigues *et al.*, 2021b).

Os ensaios com Na⁺, K⁺-ATPase e Mg²⁺-ATPase revelaram padrão complexo de disfunção bioenergética, com hiperatividade compensatória no córtex induzida pelo tumor e inibição acentuada pela VCR, apontando para desequilíbrios iônicos e potencial excitotoxicidade (da Motta *et al.*, 2024; Schappacher *et al.*, 2019b). O 4-PSQ restaurou parcialmente a atividade enzimática em regiões vulneráveis, reforçando seu efeito modulatório sobre a homeostase neuronal, ainda que com limitações regionais observadas no hipocampo.

Em conjunto, os dados indicam que o tratamento combinado VCR+4-PSQ mantém a eficácia citotóxica do quimioterápico, ao mesmo tempo em que atenua a progressão tumoral, limita a resposta inflamatória local e sistêmica, preserva a integridade bioenergética do sistema nervoso e reduz de forma significativa a hipersensibilidade nociceptiva. Estes achados posicionam o 4-PSQ como candidato promissor para estratégias adjuvantes no manejo da dor oncológica complexa e na mitigação de neuropatias quimioterápicas, alinhando-se a abordagens multimodais contemporâneas que combinam citotoxicidade dirigida, neuroproteção e modulação redox (Barth *et al.*, 2019a; Caraceni; Shkodra, 2019).

Por fim, realizamos análises *in vitro* avaliando o potencial do 4-PSQ sob canais TRP por meio da técnica de *calcium imaging*. Essa análise foi considerada de interesse visto uma das maiores conexões observadas em todos os modelos experimentais avaliados – a excitabilidade causada por VCR por meio do aumento de influxo de cálcio (associada com a enzima Ca²⁺ - ATPase) e o potencial efeito modulador do 4-PSQ. Ainda, os canais TRP possuem uma relação muito estrita com a dor o que nos instigou a compreender como 4-PSQ poderia atuar sob este aspecto.

Os resultados parciais demonstraram que o 4-PSQ não apresentou atividade agonista ou antagonista significativa sobre os canais TRPV1 e TRPM8, embora tenham sido observadas respostas inconsistentes frente ao TRPA1. Esses achados sugerem que o efeito antinociceptivo previamente reportado para o 4-PSQ em modelos de dor oncológica e NPIV não decorre, prioritariamente, de uma ação direta clássica sobre esses canais iônicos, mas possivelmente de mecanismos moduladores associados à excitabilidade neuronal. Entretanto, ressaltamos que estes foram ensaios *in vitro* e preliminares.

A pertinência dessa via é reforçada pelo fato de que a VCR, embora não avaliada experimentalmente em associação nesta etapa, é amplamente descrita por induzir aumento da concentração intracelular de cálcio, favorecendo estados de hiperexcitabilidade neuronal e contribuindo para a persistência da dor neuropática (Li, G. Zhou *et al.*, 2021a). Assim, o 4-PSQ poderia exercer efeitos antinociceptivos ao contrabalançar a sobrecarga de cálcio promovida pela VCR, atenuando o desbalanço eletrofisiológico que caracteriza a sensibilização neuronal crônica. Esse efeito indireto, sem ativação agonista indesejável dos canais TRP, reforça o potencial do 4-PSQ como um modulador seguro no contexto da dor crônica.

No que se refere ao TRPA1, ainda que os dados apresentem inconsistências, não se descarta a possibilidade de uma ativação transitória do canal, seguida de um processo de dessensibilização. Tal mecanismo é amplamente reconhecido para agonistas de canais TRP e pode culminar na redução da excitabilidade dos neurônios nociceptivos, o que contribuiria para os efeitos antinociceptivos *in vivo* do 4-PSQ. Desse modo, a ausência de antagonismo clássico não invalida a hipótese de que o composto exerça modulação indireta sobre vias dependentes de cálcio, reduzindo a atividade exacerbada de canais envolvidos na dor neuropática.

Em síntese, a integração dos achados sugere que a ação do 4-PSQ sobre a dor neuropática e oncológica pode estar relacionada à regulação da homeostase do cálcio intracelular, por meio da modulação da Ca^{2+} -ATPase e de possíveis efeitos secundários sobre canais TRP, especialmente em contextos de excitabilidade exacerbada induzida pela VCR. Essa perspectiva reforça o potencial translacional do 4-PSQ como adjuvante terapêutico, embora a elucidação completa de seus mecanismos dependa de investigações adicionais,

particularmente voltadas à interação funcional entre canais TRP, bombas de cálcio e vias de sinalização associadas à dor crônica.

6. CONCLUSÕES

Os resultados desta tese demonstram de forma inédita que a VCR, embora um excelente fármaco quimioterápico, apresenta uma neurotoxicidade multifatorial que compromete severamente a integridade estrutural e funcional do sistema nervoso periférico e central em grupos vulneráveis até então pouco investigados (Figura 5). Em ratos idosos, comprovou-se que o envelhecimento agrava a hipernocicepção mecânica e térmica, intensifica o estresse oxidativo, evidencia a falha da resposta antioxidante e revela a degeneração neuronal e axonal na medula espinhal como mecanismo singular da VCR associado à senescência, além de modular negativamente a Na^+, K^+ -ATPase e Ca^{2+} -ATPase. Em camundongos machos e fêmeas, verificou-se que ambos os sexos desenvolvem NPIV, sendo que fêmeas apresentaram uma nocicepção mais perpetuada, acompanhada de déficits cognitivos e comorbidades emocionais, sustentados por inibição da Na^+, K^+ -ATPase, ativação do eixo NF κ B, expressão diferencial de p21, além de alterações em Nrf2, HO-1 e desequilíbrio redox; destacando que o composto 4-PSQ foi capaz de reverter esses prejuízos de forma significativa. No modelo neonatal, evidenciou-se que a VCR compromete o crescimento craniano, atrasa marcos críticos do neurodesenvolvimento e induz neurodegeneração espinhal irreversível, mediados por estresse oxidativo, falhas mitocondriais (PINK-1/PARKIN) e modulação de marcadores apoptóticos como MCL-1, BAX e CASPASE-3. Por fim, no contexto de dor oncológica combinada à NPIV com sarcoma S180, confirmou-se que a VCR intensifica a hiperalgesia periférica e promove disfunção bioenergética central, enquanto o 4-PSQ mostrou-se promissor ao potencializar os efeitos antitumorais da VCR, reduzir danos oxidativos, modular a resposta imune e inflamatória e atenuar a nocicepção, consolidando-se como um adjuvante eficaz e inovador para protocolos quimioterápicos mais seguros. Ademais, observou-se uma possível atividade exercida pelo 4-PSQ sobre o canal TRPA1, entretanto esta hipótese ainda precisa ser confirmada. Estes achados ampliam o entendimento dos mecanismos da NPIV e reforçam a viabilidade de estratégias combinadas para proteção neurofuncional e manutenção da qualidade de vida em pacientes

oncológicos.

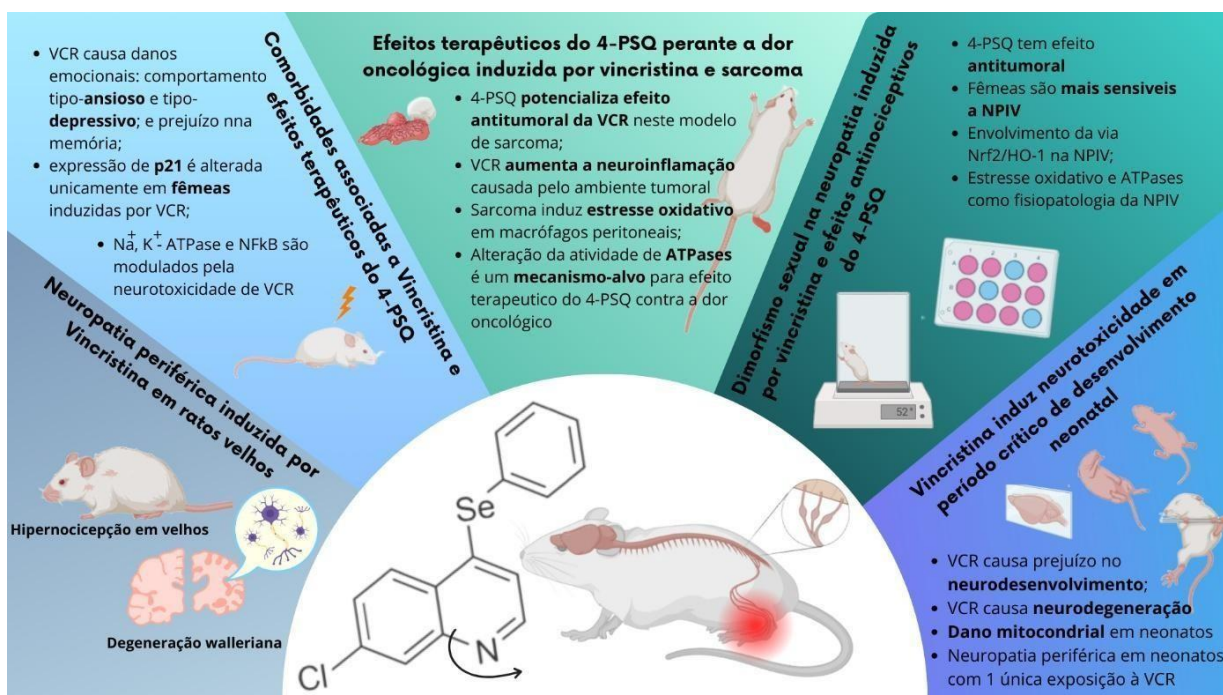


Figura 5 – Representação esquemática das principais evidências científicas reunidas nesta tese. A figura está organizada em cinco eixos temáticos: (1) Neuropatia periférica induzida pela vincristina (VCR) em animais idosos, caracterizada por hipernociceção e degeneração walleriana; (2) Comorbidades associadas à exposição à VCR, incluindo prejuízos comportamentais e alterações moleculares, bem como os efeitos terapêuticos do composto 7-cloro-4-fenilselanil quinolina (4-PSQ); (3) Dimorfismo sexual na neuropatia induzida pela VCR, com destaque para maior susceptibilidade das fêmeas, e os efeitos antinociceptivos do 4-PSQ; (4) Neurotoxicidade induzida pela VCR em janela crítica de neurodesenvolvimento neonatal, envolvendo prejuízo cognitivo, neurodegeneração e disfunção mitocondrial; e (5) Efeitos terapêuticos do 4-PSQ frente à dor oncológica induzida por VCR e sarcoma, incluindo potencialização da atividade antitumoral da VCR, modulação da neuroinflamação e do estresse oxidativo, além da regulação de ATPases como mecanismos-alvo de sua ação.

7. PERSPECTIVAS

A partir dos dados até aqui obtidos, pode-se destacar que outras análises podem complementar o já reportado. Dentre possíveis perspectivas a serem investigadas estão a avaliação a longo prazo da exposição a VCR em neonatos, avaliando-os até a fase adulta e posteriormente na velhice; analisar a associação tumoral aos efeitos de VCR em neonatos; bem como investigar os efeitos do 4-PSQ em modelos experimentais de roedores com NPIV velhos e recém-nascidos. Outras análises intrigantes que podem ser realizadas futuramente em cooperação com o grupo internacional incluem a avaliação do 4-PSQ no aspecto eletrofisiológico, observando-o por meio de técnicas como *patch-clamp* e também concluir as análises para verificação da atuação do 4-PSQ sob os canais TRPA1.

8. REFERÊNCIAS BIBLIOGRÁFICAS

- AEBI, H. Catalase in vitro. **Methods in Enzymology**, [s. l.], v. 105, p. 121–126, 1984.
- AKSENOV, M. Y.; MARKESBERY, W. R. Changes in thiol content and expression of glutathione redox system genes in the hippocampus and cerebellum in Alzheimer's disease. **Neuroscience Letters**, [s. l.], v. 302, n. 2–3, p. 141–145, 2001.
- ALAMRI, F. F. *et al.* Applicability of the grip strength and automated von Frey tactile sensitivity tests in the mouse photothrombotic model of stroke. **Behavioural Brain Research**, [s. l.], v. 336, n. August 2017, p. 250–255, 2018a.
- ALAMRI, F. F. *et al.* Applicability of the grip strength and automated von Frey tactile sensitivity tests in the mouse photothrombotic model of stroke. **Behavioural Brain Research**, [s. l.], v. 336, n. August 2017, p. 250–255, 2018b. Disponível em: <http://dx.doi.org/10.1016/j.bbr.2017.09.008>.
- ALBENSI, B. C. What Is Nuclear Factor Kappa B (NF-κB) Doing in and to the Mitochondrion?. **Frontiers in Cell and Developmental Biology**, [s. l.], v. 7, 2019a.
- ALBENSI, B. C. What Is Nuclear Factor Kappa B (NF-κB) Doing in and to the Mitochondrion?. **Frontiers in Cell and Developmental Biology**, [s. l.], v. 7, 2019b. Disponível em: <https://www.frontiersin.org/article/10.3389/fcell.2019.00154/full>.
- ALENEZI, S. K. The Ameliorative Effect of Thymoquinone on Vincristine-Induced Peripheral Neuropathy in Mice by Modulating Cellular Oxidative Stress and Cytokine. **Life**, [s. l.], v. 13, n. 1, p. 101, 2022.

ALENEZI, S. K. The Ameliorative Effect of Thymoquinone on Vincristine-Induced Peripheral Neuropathy in Mice by Modulating Cellular Oxidative Stress and Cytokine. **Life**, [s. l.], v. 13, n. 1, 2023a.

ALENEZI, S. K. The Ameliorative Effect of Thymoquinone on Vincristine-Induced Peripheral Neuropathy in Mice by Modulating Cellular Oxidative Stress and Cytokine. **Life**, [s. l.], v. 13, n. 1, 2023b.

ALWHAIBI, A. M. *et al.* Vincristine-Induced Neuropathy in Patients Diagnosed with Solid and Hematological Malignancies: The Role of Dose Rounding. **Journal of Clinical Medicine**, [s. l.], v. 12, n. 17, p. 5662, 2023.

AN, R. *et al.* Methylcobalamin Protects Melanocytes from H₂O₂-Induced Oxidative Stress by Activating the Nrf2/HO-1 Pathway. **Drug Design, Development and Therapy**, [s. l.], v. Volume 15, p. 4837–4848, 2021.

ANAND, K. J. S.; HICKEY, P. R. Pain and Its Effects in the Human Neonate and Fetus. **New England Journal of Medicine**, [s. l.], v. 317, n. 21, p. 1321–1329, 1987.

ANBALAGAN, M. *et al.* Post-translational modifications of nuclear receptors and human disease. **Nuclear receptor signaling**, [s. l.], v. 10, n. Figure 1, 2012.

ARETI, A. *et al.* Oxidative stress and nerve damage: Role in chemotherapy induced peripheral neuropathy. **Redox Biology**, [s. l.], v. 2, n. 1, p. 289–295, 2014.

BAE, E. H.; GREENWALD, M. K.; SCHWARTZ, A. G. Chemotherapy-Induced Peripheral Neuropathy: Mechanisms and Therapeutic Avenues. **Neurotherapeutics**, [s. l.], v. 18, n. 4, p. 2384–2396, 2021.

BAIG, M. A.; PANCHAL, S. S. Streptozotocin-Induced Diabetes Mellitus in Neonatal Rats: An Insight into its Applications to Induce Diabetic Complications. **Current Diabetes Reviews**, [s. l.], v. 16, n. 1, p. 26–39, 2019.

BAKER, D. W. History of The Joint Commission's Pain Standards. **JAMA**, [s. l.], v. 317, n. 11, p. 1117, 2017.

BARTH, A. *et al.* 7-Chloro-4-(Phenylselanyl) Quinoline with Memory Enhancer Action in Aging Rats: Modulation of Neuroplasticity, Acetylcholinesterase Activity, and Cholesterol Levels. **Molecular Neurobiology**, [s. l.], 2019a.

BARTH, A. *et al.* 7-Chloro-4-(Phenylselanyl) Quinoline with Memory Enhancer Action in Aging Rats: Modulation of Neuroplasticity, Acetylcholinesterase Activity, and Cholesterol Levels. **Molecular Neurobiology**, [s. l.], 2019b.

BARTLEY, E. J.; FILLINGIM, R. B. Sex differences in pain: a brief review of clinical and experimental findings. **British Journal of Anaesthesia**, [s. l.], v. 111, n. 1, p. 52–58, 2013.

BEJČEK, J. *et al.* Na⁺/K⁺-ATPase revisited: On its mechanism of action, role in cancer, and activity modulation. **Molecules**, [s. l.], v. 26, n. 7, 2021.

BENJAMIN, R. S. *et al.* Chemotherapy for Bone Sarcomas in Adults: The MD Anderson Experience. **American Society of Clinical Oncology Educational Book**, [s. l.], n. 35, p. e656–e660, 2015.

BENNETT, M. I. *et al.* Prevalence and aetiology of neuropathic pain in cancer patients: A systematic review. **Pain**, [s. l.], v. 153, n. 2, p. 359–365, 2012.

BEYER, C.; KAROLCZAK, M. Estrogenic stimulation of neurite growth in midbrain dopaminergic neurons depends on cAMP/protein kinase A signalling. **Journal of Neuroscience Research**, [s. l.], v. 59, n. 1, p. 107–116, 2000a.

BEYER, C.; KAROLCZAK, M. Estrogenic stimulation of neurite growth in midbrain dopaminergic neurons depends on cAMP/protein kinase A signalling. **Journal of Neuroscience Research**, [s. l.], v. 59, n. 1, p. 107–116, 2000b.

BHATT, S. *et al.* 5-HT₃ Receptor Antagonism: A Potential Therapeutic Approach for the Treatment of Depression and other Disorders. **Current Neuropharmacology**, [s. l.], v. 19, n. 9, p. 1545–1559, 2020.

BILBERG, A. *et al.* High prevalence of widespread pain in women with early rheumatoid arthritis. **Scandinavian Journal of Rheumatology**, [s. l.], v. 47, n. 6, p. 447–454, 2018. Disponível em: <https://doi.org/10.1080/03009742.2018.1447683>.

BLUETTE, C. T. *et al.* Behavioral, Histopathologic, and Molecular Biological Responses of Nanoparticle- and Solution-Based Formulations of Vincristine in Mice. **International Journal of Toxicology**, [s. l.], v. 40, n. 1, p. 40–51, 2021. Disponível em: <http://journals.sagepub.com/doi/10.1177/1091581820968255>.

BRADFORD, M. M. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. **Analytical biochemistry**, [s. l.], v. 72, n. 1–2, p. 248–254, 1976a.

BRADFORD, M. M. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. **Analytical biochemistry**, [s. l.], v. 72, n. 1–2, p. 248–254, 1976b. Disponível em: <https://www.sciencedirect.com/science/article/abs/pii/0003269776905273>.

BREIVIK, H. *et al.* Cancer-related pain: a pan-European survey of prevalence, treatment, and patient attitudes. **Annals of Oncology**, [s. l.], v. 20, n. 8, p. 1420–1433, 2009.

BRIGATTE, P. *et al.* Walker 256 Tumor-Bearing Rats as a Model to Study Cancer Pain. **The Journal of Pain**, [s. l.], v. 8, n. 5, p. 412–421, 2007.

BROWN, A. M.; ROSS, A.; BELSKY, J. A. Vincristine-Induced Autonomic Neuropathy Diagnosed via Quantitative Sudomotor Axon Reflex Sweat Test in an Adolescent Patient With Acute Leukemia. **Pediatric Blood & Cancer**, [s. l.], 2025.

BROZOVIĆ, G. Cancer Pain and Therapy. **Acta Clinica Croatica**, [s. l.], 2022.

BUJALSKA, M.; GUMUŁKA, S. W. Effect of cyclooxygenase and nitric oxide synthase inhibitors on vincristine induced hyperalgesia in rats. **Pharmacological Reports**, [s. l.], v. 60, n. 5, p. 735–741, 2008.

BURT, R. *et al.* Activated stromal cells transfer mitochondria to rescue acute lymphoblastic leukemia cells from oxidative stress. **Blood**, [s. l.], v. 134, n. 17, p. 1415–1429, 2019.

BUSCH, C. J.; BINDER, C. J. Malondialdehyde epitopes as mediators of sterile

inflammation. **Biochimica et Biophysica Acta - Molecular and Cell Biology of Lipids**, [s. l.], v. 1862, n. 4, p. 398–406, 2017. Disponível em: <http://dx.doi.org/10.1016/j.bbalip.2016.06.016>.

CALIXTO-CAMPOS, C. *et al.* The Ehrlich Tumor Induces Pain-Like Behavior in Mice: A Novel Model of Cancer Pain for Pathophysiological Studies and Pharmacological Screening. **BioMed Research International**, [s. l.], v. 2013, p. 1–12, 2013.

CANTA, A.; POZZI, E.; CAROZZI, V. A. Mitochondrial dysfunction in chemotherapy-induced peripheral neuropathy (CIPN). **Toxics**, [s. l.], v. 3, n. 2, p. 198–223, 2015a.

CANTA, A.; POZZI, E.; CAROZZI, V. A. Mitochondrial dysfunction in chemotherapy-induced peripheral neuropathy (CIPN). **Toxics**, [s. l.], v. 3, n. 2, p. 198–223, 2015b.

CARACENI, A.; SHKODRA, M. Cancer Pain Assessment and Classification. **Cancers**, [s. l.], v. 11, n. 4, p. 510, 2019.

CASSOL, G. *et al.* A role of Na⁺, K⁺ -ATPase in spatial memory deficits and inflammatory/oxidative stress after recurrent concussion in adolescent rats. **Brain Research Bulletin**, [s. l.], v. 180, p. 1–11, 2022a.

CASSOL, G. *et al.* A role of Na⁺, K⁺ -ATPase in spatial memory deficits and inflammatory/oxidative stress after recurrent concussion in adolescent rats. **Brain Research Bulletin**, [s. l.], v. 180, p. 1–11, 2022b. Disponível em: <https://linkinghub.elsevier.com/retrieve/pii/S0361923021003543>.

CAVIEDES, A. *et al.* BDNF/NF-κB Signaling in the Neurobiology of Depression. **Current Pharmaceutical Design**, [s. l.], v. 23, n. 21, 2017a.

CAVIEDES, A. *et al.* BDNF/NF-κB Signaling in the Neurobiology of Depression. **Current Pharmaceutical Design**, [s. l.], v. 23, n. 21, 2017b. Disponível em: <http://www.eurekaselect.com/149163/article>.

CHANCAY, M. G.; GUENDSECHADZE, S. N.; BLANCO, I. Types of pain and their psychosocial impact in women with rheumatoid arthritis. **Women's Midlife Health**, [s. l.], v. 5, n. 1, p. 1–9, 2019.

CHANTAL, T. *et al.* ACTION OF VINCA ALKALOIDES ON CALCIUM MOVEMENTS THROUGH MITOCHONDRIAL MEMBRANE. **Pharmacological Research Communications**, [s. l.], v. 18, n. 6, p. 519–528, 1986.

CHEN, C. *et al.* Body weight, frailty, and chronic pain in older adults: A cross-sectional study. **BMC Geriatrics**, [s. l.], v. 19, n. 1, p. 1–10, 2019.

CHEN, X. *et al.* Current understanding of the molecular mechanisms of chemotherapy-induced peripheral neuropathy. **Frontiers in Molecular Neuroscience**, [s. l.], v. 17, 2024.

CHEN, S. P. *et al.* Involvement of hippocampal acetylcholinergic receptors in electroacupuncture analgesia in neuropathic pain rats. **Behavioral and Brain Functions**, [s. l.], v. 12, n. 1, p. 1–10, 2016.

CHEN, Q. M. Nrf2 for protection against oxidant generation and mitochondrial damage in cardiac injury. **Free Radical Biology and Medicine**, [s. l.], v. 179, p. 133–143, 2022.

CHEN, X.-J.; WANG, L.; SONG, X.-Y. Mitoquinone alleviates vincristine-induced neuropathic pain through inhibiting oxidative stress and apoptosis via the improvement of mitochondrial dysfunction. **Biomedicine & Pharmacotherapy**, [s. l.], v. 125, p. 110003, 2020.

CHENG, H. *et al.* Case report: Wallerian degeneration: The innate-immune response to adult-onset Still's disease peripheral nerve injury. **Frontiers in Neurology**, [s. l.], v. 13, 2022.

CHEON, J. H. *et al.* P-gp Inhibition by XL019, a JAK2 Inhibitor, Increases Apoptosis of Vincristine-treated Resistant KBV20C Cells with Increased p21 and pH2AX Expression. **Anticancer Research**, [s. l.], v. 37, n. 12, 2017a.

CHEON, J. H. *et al.* P-gp Inhibition by XL019, a JAK2 Inhibitor, Increases Apoptosis of Vincristine-treated Resistant KBV20C Cells with Increased p21 and pH2AX Expression. **Anticancer Research**, [s. l.], v. 37, n. 12, 2017b. Disponível em: <http://ar.iijournals.org/content/37/12/6761.abstract>.

CHIBA, T. *et al.* Vincristine increased spinal cord substance P levels in a peripheral neuropathy rat model. **Drug and Chemical Toxicology**, [s. l.], v. 45, n. 1, p. 393–397, 2022. Disponível em: <https://www.tandfonline.com/doi/full/10.1080/01480545.2019.1706547>.

CHIECHIO, S. *et al.* L-Acetylcarnitine Induces Analgesia by Selectively Up-Regulating mGlu2 Metabotropic Glutamate Receptors. **Molecular Pharmacology**, [s. l.], v. 61, n. 5, p. 989–996, 2002.

CHO, S.-H. *et al.* Anti-inflammatory activity of Echinosophora koreensis nakai root extract in lipopolysaccharides-stimulated RAW 264.7 cells and carrageenan-induced mouse paw edema model. **Journal of Ethnopharmacology**, [s. l.], v. 302, p. 115940, 2023.

CLARK, A. K.; MALCANGIO, M. Microglial signalling mechanisms: Cathepsin S and Fractalkine. **Experimental Neurology**, [s. l.], v. 234, n. 2, p. 283–292, 2012.

COBB, C. A.; COLE, M. P. Oxidative and nitrative stress in neurodegeneration. **Neurobiology of Disease**, [s. l.], v. 84, p. 4–21, 2015. Disponível em: <http://dx.doi.org/10.1016/j.nbd.2015.04.020>.

COLUZZI, F. *et al.* Pain management in childhood leukemia: Diagnosis and available analgesic treatments. **Cancers**, [s. l.], v. 12, n. 12, p. 1–13, 2020.

COLVIN, L. A. Chemotherapy-induced peripheral neuropathy: where are we now?. **Pain**, [s. l.], v. 160, n. 1, p. S1–S10, 2019.

COOK, K. M. *et al.* Experience of early-life pain in premature infants is associated with atypical cerebellar development and later neurodevelopmental deficits. **BMC Medicine**, [s. l.], v. 21, n. 1, p. 435, 2023.

COSTA, Y. M. *et al.* Reliability of the nociceptive blink reflex evoked by electrical stimulation of the trigeminal nerve in humans. **Clinical Oral Investigations**, [s. l.], v. 21, n. 8, p. 2453–2463, 2017.

COX, B. C. *et al.* Transport of multiple nicotinic acetylcholine receptors in the rat optic nerve: High densities of receptors containing $\alpha 6$ and $\beta 3$ subunits. **Journal of**

Neurochemistry, [s. l.], v. 105, n. 5, p. 1924–1938, 2008.

CUREALL FRAMEWORK: WHO GLOBAL INITIATIVE FOR CHILDHOOD CANCER INCREASING ACCESS, ADVANCING QUALITY, SAVING LIVES. . [S. l.: s. n.], [s. d.].

DA MOTTA, K. P. *et al.* Insights into Vincristine-Induced Peripheral Neuropathy in Aged Rats: Wallerian Degeneration, Oxidative Damage, and Alterations in ATPase Enzymes. **ACS Chemical Neuroscience**, [s. l.], v. 15, n. 21, p. 3954–3969, 2024.

DA MOTTA, K. P. *et al.* The Antinociceptive Responses of MTDZ to Paclitaxel – Induced Peripheral Neuropathy and Acute Nociception in Mice : Behavioral , Pharmacological , and Biochemical Approaches. **Pharmaceuticals**, [s. l.], v. 16, n. 9, p. 1217, 2023.

DA ROCHA, V. M. E. *et al.* Structure-Activity Relationship of 7-Chloro-4-(Phenylselanyl) Quinoline: Novel Antinociceptive and Anti-Inflammatory Effects in Mice. **Chemistry & Biodiversity**, [s. l.], v. 22, n. 3, 2025.

DAGNINO, A. P. A.; CAMPOS, M. M. Chronic Pain in the Elderly: Mechanisms and Perspectives. **Frontiers in Human Neuroscience**, [s. l.], v. 16, p. 1–11, 2022.

DANG, X. *et al.* Alantolactone suppresses inflammation, apoptosis and oxidative stress in cigarette smoke-induced human bronchial epithelial cells through activation of Nrf2/HO-1 and inhibition of the NF-κB pathways. **Respiratory Research**, [s. l.], v. 21, n. 1, p. 95, 2020.

DAVIS, R. L. *et al.* Effects of mechanistically distinct NF-κB inhibitors on glial inducible nitric-oxide synthase expression. **Nitric Oxide**, [s. l.], v. 12, n. 4, p. 200–209, 2005.

DE FREITAS COUTO, S. *et al.* 7-chloro-4-(phenylselanyl) quinoline prevents dopamine depletion in a *Drosophila melanogaster* model of Parkinson's-like disease. **Journal of Trace Elements in Medicine and Biology**, [s. l.], v. 54, p. 232–243, 2019a. Disponível em: <https://linkinghub.elsevier.com/retrieve/pii/S0946672X1830405X>.

DE FREITAS COUTO, S. *et al.* 7-chloro-4-(phenylselanyl) quinoline prevents dopamine depletion in a *Drosophila melanogaster* model of Parkinson's-like disease. **Journal of Trace Elements in Medicine and Biology**, [s. l.], v. 54, p. 232–243, 2019b.

DE OLIVEIRA, R. L. *et al.* Prospecting for a quinoline containing selenium for comorbidities depression and memory impairment induced by restriction stress in mice. **Psychopharmacology**, [s. l.], v. 239, n. 1, p. 59–81, 2022a. Disponível em: <https://doi.org/10.1007/s00213-021-06039-8>.

DE OLIVEIRA, R. L. *et al.* Prospecting for a quinoline containing selenium for comorbidities depression and memory impairment induced by restriction stress in mice. **Psychopharmacology**, [s. l.], v. 239, n. 1, p. 59–81, 2022b.

DEL RIO, D.; STEWART, A. J.; PELLEGRINI, N. A review of recent studies on malondialdehyde as toxic molecule and biological marker of oxidative stress. **Nutrition, Metabolism and Cardiovascular Diseases**, [s. l.], v. 15, n. 4, p. 316–328, 2005.

DENG, G. Integrative Medicine Therapies for Pain Management in Cancer Patients. **The Cancer Journal**, [s. l.], v. 25, n. 5, p. 343–348, 2019.

DESFORGES, A. D. *et al.* Treatment and diagnosis of chemotherapy-induced

peripheral neuropathy: An update. **Biomedicine & Pharmacotherapy**, [s. l.], v. 147, p. 112671, 2022.

DIOUF, B. *et al.* Association of an inherited genetic variant with vincristine-related peripheral neuropathy in children with acute lymphoblastic leukemia Critical revision of the manuscript for important intellectual content: Barthelemy Diouf; HHS Public Access. **Jama**, [s. l.], v. 313, n. 8, p. 815–823, 2015.

DOBRETSOV, M. Neuronal function and alpha3 isoform of the Na/K-ATPase. **Frontiers in Bioscience**, [s. l.], v. 10, n. 1–3, p. 2373, 2005a.

DOBRETSOV, M. Neuronal function and alpha3 isoform of the Na/K-ATPase. **Frontiers in Bioscience**, [s. l.], v. 10, n. 1–3, p. 2373, 2005b. Disponível em: <https://imrpess.com/journal/FBL/10/3/10.2741/1704>.

DOS SANTOS, L. M. *et al.* Methionine and methionine sulfoxide treatment induces M1/classical macrophage polarization and modulates oxidative stress and purinergic signaling parameters. **Molecular and Cellular Biochemistry**, [s. l.], v. 424, n. 1–2, p. 69–78, 2017.

DUARTE, L. F. B. *et al.* A simple method for the synthesis of 4-arylselanyl-7-chloroquinolines used as in vitro acetylcholinesterase inhibitors and in vivo memory improvement. **Tetrahedron Letters**, [s. l.], v. 58, n. 33, p. 3319–3322, 2017a.

DUARTE, L. F. B. *et al.* Organoselenium compounds from purines: Synthesis of 6-arylselanylpurines with antioxidant and anticholinesterase activities and memory improvement effect. **Bioorganic & Medicinal Chemistry**, [s. l.], v. 25, n. 24, p. 6718–6723, 2017b.

DUPUIS, L. L. *et al.* Anxiety, pain, and nausea during the treatment of standard-risk childhood acute lymphoblastic leukemia: A prospective, longitudinal study from the Children's Oncology Group. **Cancer**, [s. l.], v. 122, n. 7, p. 1116–1125, 2016.

DZIECHCIAŻ, M.; BALICKA-ADAMIK, L.; FILIP, R. The problem of pain in old age. **Annals of agricultural and environmental medicine : AAEM**, [s. l.], v. 1, n. 1, p. 35–38, 2013.

EDINOFF, A. N. *et al.* Selective Serotonin Reuptake Inhibitors and Adverse Effects: A Narrative Review. **Neurology International**, [s. l.], v. 13, n. 3, p. 387–401, 2021.

EDWARDS, R. R. *et al.* The role of psychosocial processes in the development and maintenance of chronic pain disorders. **Pain**, [s. l.], v. 176, n. 1, p. 70–92, 2017.

EIDE, S.; FENG, Z. P. Doxorubicin chemotherapy-induced “chemo-brain”: Meta-analysis. **European Journal of Pharmacology**, [s. l.], v. 881, n. July 2019, p. 173078, 2020.

EL HACHEM, G. *et al.* Advances in pain management for older patients with cancer. **ecancermedicalscience**, [s. l.], v. 13, 2019.

ELDUFANI, J.; BLAISE, G. The role of acetylcholinesterase inhibitors such as neostigmine and rivastigmine on chronic pain and cognitive function in aging: A review of recent clinical applications. **Alzheimer's and Dementia: Translational Research and Clinical Interventions**, [s. l.], v. 5, p. 175–183, 2019.

ELLMAN, G. L. Tissue Sulfhydryl Groups. **Archives of biochemistry and biophysics**, [s. l.], v. 82, n. 1, p. 70–77, 1959.

ELTOKHY, A. K.; TOEMA, O.; EL-DEEB, O. S. The Correlation Between PINK-1/Parkin Mediated Mitophagy, Endoplasmic Reticulum Stress and Total Polyamines in Pediatric Bronchial Asthma: An Integrated Network of Pathways. **Molecular Biology Reports**, [s. l.], v. 49, n. 1, p. 227–235, 2022.

EVENEPOEL, M. *et al.* Pain Prevalence During Cancer Treatment: A Systematic Review and Meta-Analysis. **Journal of Pain and Symptom Management**, [s. l.], v. 63, n. 3, p. e317–e335, 2022.

FANE, M.; WEERARATNA, A. T. How the ageing microenvironment influences tumour progression. **Nature Reviews Cancer**, [s. l.], v. 20, n. 2, p. 89–106, 2020.

FANG, J. *et al.* Expression Dynamics of Heme Oxygenase-1 in Tumor Cells and the Host Contributes to the Progression of Tumors. **Journal of Personalized Medicine**, [s. l.], v. 11, n. 12, p. 1340, 2021.

FILIPPI-CHIELA, E. C. *et al.* Vincristine promotes differential levels of apoptosis, mitotic catastrophe, and senescence depending on the genetic background of glioblastoma cells. **Toxicology in Vitro**, [s. l.], v. 85, p. 105472, 2022.

FISKE, B. C. H.; SUBBAROW, Y. The colorimetric determination of phosphorus. **The Journal of Biological Chemistry**, [s. l.], v. 66, n. september, p. 375–400, 1925a.

FISKE, B. C. H.; SUBBAROW, Y. The colorimetric determination of phosphorus. **The Journal of Biological Chemistry**, [s. l.], v. 66, n. september, p. 375–400, 1925b.

FITZMAURICE, C. *et al.* Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study Global Burden. **JAMA Oncology**, [s. l.], v. 3, n. 4, p. 524–548, 2017.

FLATTERS, S. J. L.; DOUGHERTY, P. M.; COLVIN, L. A. Clinical and preclinical perspectives on Chemotherapy-Induced Peripheral Neuropathy (CIPN): A narrative review. **British Journal of Anaesthesia**, [s. l.], v. 119, n. 4, p. 737–749, 2017.

FRANÇOIS, A. *et al.* The Low-Threshold Calcium Channel Cav3.2 Determines Low-Threshold Mechanoreceptor Function. **Cell Reports**, [s. l.], v. 10, n. 3, p. 370–382, 2015.

GAUTHIER, I.; TARR, M. J. Visual Object Recognition: Do We (Finally) Know More Now Than We Did?. **Annual Review of Vision Science**, [s. l.], v. 2, n. 1, p. 377–396, 2016.

GEŃGOTEK, A.; SKRZYDLEWSKA, E. Biological effect of protein modifications by lipid peroxidation products. **Chemistry and Physics of Lipids**, [s. l.], v. 221, n. February, p. 46–52, 2019.

GEŃGOTEK, A.; SKRZYDLEWSKA, E. Lipid peroxidation products' role in autophagy regulation. **Free Radical Biology and Medicine**, [s. l.], v. 212, p. 375–383, 2024.

GEISLER, S. Vincristine- and bortezomib-induced neuropathies – from bedside to bench and back. **Experimental Neurology**, [s. l.], v. 336, p. 113519, 2021a.

GEISLER, S. Vincristine- and bortezomib-induced neuropathies – from bedside to bench and back. **Experimental Neurology**, [s. l.], v. 336, p. 113519, 2021b. Disponível em: <https://doi.org/10.1016/j.expneurol.2020.113519>.

GEORGE, E. B.; GLASS, J. D.; GRIFFIN, J. W. Axotomy-induced axonal degeneration is mediated by calcium influx through ion-specific channels. **Journal of Neuroscience**, [s. l.], v. 15, n. 10, p. 6445–6452, 1995.

GILCHRIST, L. S.; MARAIS, L.; TANNER, L. Comparison of two chemotherapy-induced peripheral neuropathy measurement approaches in children. **Supportive Care in Cancer**, [s. l.], v. 22, n. 2, p. 359–366, 2014.

GILCHRIST, L.; TANNER, L. Gait Patterns in Children With Cancer and Vincristine Neuropathy. **Pediatric Physical Therapy**, [s. l.], v. 28, n. 1, p. 16–22, 2016.

GLOBAL CANCER BURDEN GROWING, AMIDST MOUNTING NEED FOR SERVICES. **Saudi medical journal**, [s. l.], v. 45, n. 3, p. 326–327, 2024.

GOESLING, J.; LIN, L. A.; CLAUW, D. J. Psychiatry and Pain Management: at the Intersection of Chronic Pain and Mental Health. **Current Psychiatry Reports**, [s. l.], v. 20, n. 2, 2018.

GOLCHIN, L. *et al.* Pistachio supplementation attenuates motor and cognition impairments induced by cisplatin or vincristine in rats. **Advanced Biomedical Research**, [s. l.], v. 4, n. 1, p. 92, 2015.

GOMBER, S.; DEWAN, P.; CHHONKER, D. Vincristine induced neurotoxicity in cancer patients. **Indian Journal of Pediatrics**, [s. l.], v. 77, n. 1, p. 97–100, 2010a.

GOMBER, S.; DEWAN, P.; CHHONKER, D. Vincristine induced neurotoxicity in cancer patients. **Indian Journal of Pediatrics**, [s. l.], v. 77, n. 1, p. 97–100, 2010b.

GÓMEZ, V. *et al.* Breast cancer–associated macrophages promote tumorigenesis by suppressing succinate dehydrogenase in tumor cells. **Science Signaling**, [s. l.], v. 13, n. 652, 2020.

GOUVEIA, D. N. *et al.* α -Terpineol reduces cancer pain via modulation of oxidative stress and inhibition of iNOS. **Biomedicine & Pharmacotherapy**, [s. l.], v. 105, p. 652–661, 2018.

GRANT, C. H. *et al.* Multimorbidity and analgesic-related harms: a systematic review. **British Journal of Anaesthesia**, [s. l.], v. 134, n. 6, p. 1717–1745, 2025.

GROTEN, C. J.; MACVICAR, B. A. Mitochondrial Ca²⁺ uptake by the MCU facilitates pyramidal neuron excitability and metabolism during action potential firing. **Communications Biology**, [s. l.], v. 5, n. 1, p. 900, 2022.

GU, C. *et al.* Cancer Cells Promote Immune Regulatory Function of Macrophages by Upregulating Scavenger Receptor MARCO Expression. **The Journal of Immunology**, [s. l.], v. 211, n. 1, p. 57–70, 2023.

GUHA, L.; SINGH, N.; KUMAR, H. Different Ways to Die: Cell Death Pathways and Their Association With Spinal Cord Injury. **Neurospine**, [s. l.], v. 20, n. 2, p. 430–448, 2023a.

GUHA, L.; SINGH, N.; KUMAR, H. Different Ways to Die: Cell Death Pathways and Their Association With Spinal Cord Injury. **Neurospine**, [s. l.], v. 20, n. 2, p. 430–448, 2023b.

HABIF, M. *et al.* Early Long-Term Memory Impairment and Changes in the Expression of Synaptic Plasticity-Associated Genes, in the McGill-R-Thy1-APP Rat Model of Alzheimer's-Like Brain Amyloidosis. **Frontiers in Aging Neuroscience**, [s. l.], v. 12, 2021. Disponível em: <https://www.frontiersin.org/articles/10.3389/fnagi.2020.585873/full>.

HABIG, W. H.; JAKOBY, M. J. P.; B., W. J. Glutathione S-Transferases: The first enzymatic step in mercapturic acid formation. **THE JOURNAL OF BIOLOGICAL CHEMISTRY**, [s. l.], v. 249, n. 22, p. 7130–7139, 1974.

HARRIS, J. C. *et al.* Sustained delivery of vincristine inside an orthotopic mouse sarcoma model decreases tumor growth. **Journal of Pediatric Surgery**, [s. l.], v. 51, n. 12, p. 2058–2062, 2016.

HASHMI, J. A.; DAVIS, K. D. Women experience greater heat pain adaptation and habituation than men. **Pain**, [s. l.], v. 145, n. 3, p. 350–357, 2009a.

HASHMI, J. A.; DAVIS, K. D. Women experience greater heat pain adaptation and habituation than men. **Pain**, [s. l.], v. 145, n. 3, p. 350–357, 2009b. Disponível em: <http://dx.doi.org/10.1016/j.pain.2009.07.002>.

HATHWAY, G. J. *et al.* Cancer Chemotherapy in Early Life Significantly Alters the Maturation of Pain Processing. **Neuroscience**, [s. l.], v. 387, p. 214–229, 2018.

HE, X.; SUN, J.; HUANG, X. Expression of caspase-3, Bax and Bcl-2 in hippocampus of rats with diabetes and subarachnoid hemorrhage. **Experimental and Therapeutic Medicine**, [s. l.], 2017.

HODAPP, J. W.; ALI, S.; DRENDEL, A. L. Bringing It All Together: A Review of the Challenges in Measuring Children's Satisfaction as a Key Component of Acute Pain Management. **Children**, [s. l.], v. 7, n. 11, p. 243, 2020.

HOLLIDAY, L. S. Vacuolar H⁺-ATPases (V-ATPases) as therapeutic targets: a brief review and recent developments. **Biotarget**, [s. l.], v. 1, n. 7, p. 18–18, 2017.

HONE, A. J.; MCINTOSH, J. M. **Nicotinic Acetylcholine Receptors in Neuropathic and Inflammatory Pain**. [S. l.: s. n.], 2018-. ISSN 1751553X.v. 592

HOOGEN, N. J. van den *et al.* Neonatal Plasticity of the Nociceptive System: Mechanisms, Effects, and Treatment of Repetitive Painful Procedures During NICU Admittance. **Current Pharmaceutical Design**, [s. l.], v. 23, n. 38, p. 5902–5910, 2018.

HORIE, K.; MA, J.; UMEZAWA, K. Inhibition of Canonical NF- κ B Nuclear Localization by (–)-DHMEQ via Impairment of DNA Binding. **Oncology Research Featuring Preclinical and Clinical Cancer Therapeutics**, [s. l.], v. 22, n. 2, p. 105–115, 2015.

HOU, Y. *et al.* Ageing as a risk factor for neurodegenerative disease. **Nature Reviews Neurology**, [s. l.], v. 15, n. 10, p. 565–581, 2019.

HUANG, Y. L. *et al.* Chronic pain and use of analgesics in the elderly: A nationwide

population-based study. **Archives of Medical Science**, [s. l.], v. 16, n. 2, p. 627–634, 2020.

ISAKSEN, T. J.; LYKKE-HARTMANN, K. Insights into the Pathology of the $\alpha 2$ -Na⁺/K⁺-ATPase in Neurological Disorders; Lessons from Animal Models. **Frontiers in Physiology**, [s. l.], v. 7, 2016a.

ISAKSEN, T. J.; LYKKE-HARTMANN, K. Insights into the Pathology of the $\alpha 2$ -Na⁺/K⁺-ATPase in Neurological Disorders; Lessons from Animal Models. **Frontiers in Physiology**, [s. l.], v. 7, 2016b. Disponível em: <http://journal.frontiersin.org/Article/10.3389/fphys.2016.00161/abstract>.

JAGANJAC, M. *et al.* The relevance of pathophysiological alterations in redox signaling of 4-hydroxynonenal for pharmacological therapies of major stress-associated diseases. **Free Radical Biology and Medicine**, [s. l.], v. 157, p. 128–153, 2020.

JIANG, K.; SHI, Jinshan; SHI, Jing. Morin Alleviates Vincristine-Induced Neuropathic Pain via Nerve protective Effect and Inhibition of NF- κ B Pathway in Rats. **Cellular and Molecular Neurobiology**, [s. l.], v. 39, n. 6, p. 799–808, 2019a.

JIANG, K.; SHI, Jinshan; SHI, Jing. Morin Alleviates Vincristine-Induced Neuropathic Pain via Nerve protective Effect and Inhibition of NF- κ B Pathway in Rats. **Cellular and Molecular Neurobiology**, [s. l.], v. 39, n. 6, p. 799–808, 2019b. Disponível em: <https://doi.org/10.1007/s10571-019-00679-3>.

JIN, T.; LENG, B. Cynaropicrin Averts the Oxidative Stress and Neuroinflammation in Ischemic/Reperfusion Injury Through the Modulation of NF- κ B. **Applied Biochemistry and Biotechnology**, [s. l.], v. 195, n. 9, p. 5424–5438, 2023.

JOSEPH, E. K.; LEVINE, J. D. Mitochondrial electron transport in models of neuropathic and inflammatory pain. **Pain**, [s. l.], v. 121, n. 1–2, p. 105–114, 2006.

KAI, K. *et al.* Species and Sex Differences in Susceptibility to Olfactory Lesions Among the Mouse, Rat and Monkey Following an Intravenous Injection of Vincristine Sulphate. **Toxicologic Pathology**, [s. l.], v. 34, n. 3, p. 223–231, 2006.

KAKATKAR, S.; NARAYAN, A.; BALKRISHNAN, R. Prescription analgesic overuse in older adults: Can we mitigate this growing problem?. **AGING MEDICINE**, [s. l.], v. 5, n. 4, p. 294–296, 2022.

KALTSCHMIDT, B.; KALTSCHMIDT, C. NF-KappaB in Long-Term Memory and Structural Plasticity in the Adult Mammalian Brain. **Frontiers in Molecular Neuroscience**, [s. l.], v. 8, 2015.

KANG, L. *et al.* Oxaliplatin-induced peripheral neuropathy: clinical features, mechanisms, prevention and treatment. **Journal of Neurology**, [s. l.], n. 0123456789, 2020. Disponível em: <https://doi.org/10.1007/s00415-020-09942-w>.

KANZAKI, H. *et al.* Disabling the Nuclear Translocalization of RelA/NF- κ B by a Small Molecule Inhibits Triple-Negative Breast Cancer Growth. **Breast Cancer: Targets and Therapy**, [s. l.], v. Volume 13, p. 419–430, 2021.

KASAI, S. *et al.* Regulation of Nrf2 by Mitochondrial Reactive Oxygen Species in Physiology and Pathology. **Biomolecules**, [s. l.], v. 10, n. 2, p. 320, 2020.

KATSUYAMA, S. *et al.* Antinociceptive Effects of the Serotonin and Noradrenaline Reuptake Inhibitors Milnacipran and Duloxetine on Vincristine-Induced Neuropathic Pain Model in Mice. **ISRN Pain**, [s. l.], v. 2014, p. 1–7, 2014.

KAZARYAN, S. *et al.* Oxidative stress and histopathological changes in several organs of mice injected with biogenic silver nanoparticles. **Artificial Cells, Nanomedicine, and Biotechnology**, [s. l.], v. 50, n. 1, p. 331–342, 2022.

KESZTYÜS, D. *et al.* Use of Infrared Thermography in Medical Diagnosis, Screening, and Disease Monitoring: A Scoping Review. **Medicina**, [s. l.], v. 59, n. 12, p. 2139, 2023.

KHALILZADEH, M. *et al.* Aripiprazole prevents from development of vincristine-induced neuropathic nociception by limiting neural NOS overexpression and NF- κ B hyperactivation. **Cancer Chemotherapy and Pharmacology**, [s. l.], v. 86, n. 3, p. 393–404, 2020a.

KHALILZADEH, M. *et al.* Aripiprazole prevents from development of vincristine-induced neuropathic nociception by limiting neural NOS overexpression and NF- κ B hyperactivation. **Cancer Chemotherapy and Pharmacology**, [s. l.], v. 86, n. 3, p. 393–404, 2020b. Disponível em: <https://doi.org/10.1007/s00280-020-04127-8>.

KHIDR, H. Y. *et al.* Formoterol attenuated mitochondrial dysfunction in rotenone-induced Parkinson's disease in a rat model: Role of PINK-1/PARKIN and PI3K/Akt/CREB/BDNF/TrkB axis. **International Immunopharmacology**, [s. l.], v. 125, p. 111207, 2023.

KIGUCHI, N. *et al.* The critical role of invading peripheral macrophage-derived interleukin-6 in vincristine-induced mechanical allodynia in mice. **European Journal of Pharmacology**, [s. l.], v. 592, n. 1–3, p. 87–92, 2008.

KIM, S. J. *et al.* Antitumor Effects of Selenium. **International Journal of Molecular Sciences**, [s. l.], v. 22, n. 21, p. 11844, 2021.

KIM, Y. S. *et al.* Assessment of pain in the elderly: A literature review. **National Medical Journal of India**, [s. l.], v. 30, n. 4, p. 203–207, 2017a.

KIM, Y. S. *et al.* Assessment of pain in the elderly: A literature review. **National Medical Journal of India**, [s. l.], v. 30, n. 4, p. 203–207, 2017b.

KIM, S. H. *et al.* Regulation of P21-Activated Kinase-4 by Progesterone and Tumor Necrosis Factor- α in Human Endometrium and Its Increased Expression in Advanced-Stage Endometriosis. **The Journal of Clinical Endocrinology & Metabolism**, [s. l.], v. 98, n. 2, p. E238–E248, 2013a.

KIM, S. H. *et al.* Regulation of P21-Activated Kinase-4 by Progesterone and Tumor Necrosis Factor- α in Human Endometrium and Its Increased Expression in Advanced-Stage Endometriosis. **The Journal of Clinical Endocrinology & Metabolism**, [s. l.], v. 98, n. 2, p. E238–E248, 2013b. Disponível em: <https://academic.oup.com/jcem/article-lookup/doi/10.1210/jc.2012-2969>.

KIM, J.; SHARMA, R. P. Calcium-mediated activation of c-Jun NH₂-terminal kinase (JNK and apoptosis in response to cadmium in murine macrophages. **Toxicological Sciences**, [s. l.], v. 81, n. 2, p. 518–527, 2004.

KINOSHITA, P. F. *et al.* The influence of Na⁺, K⁺-ATPase on glutamate signaling in neurodegenerative diseases and senescence. **Frontiers in Physiology**, [s. l.], v. 7, n. JUN, p. 1–19, 2016.

KINTOSSOU, A. K. *et al.* Early Life Nutrition Factors and Risk of Acute Leukemia in Children: Systematic Review and Meta-Analysis. **Nutrients**, [s. l.], v. 15, n. 17, p. 3775, 2023.

KOHNO, T. *et al.* Peripheral nerve injury alters excitatory synaptic transmission in laminal II of the rat dorsal horn. **Journal of Physiology**, [s. l.], v. 548, n. 1, p. 131–138, 2003.

KOSTIĆ, M.; MARJANOVIĆ, J.; DIVAC, V. Organoselenium transition metal complexes as promising candidates in medicine area. **JBIC Journal of Biological Inorganic Chemistry**, [s. l.], v. 29, n. 6, p. 555–571, 2024.

KREMER, M. *et al.* How to study anxiety and depression in rodent models of chronic pain?. **European Journal of Neuroscience**, [s. l.], v. 53, n. 1, p. 236–270, 2021.

KUPPUSAMY, P. *et al.* Targeting metabolic pathways alleviates bortezomib-induced neuropathic pain without compromising anticancer efficacy in a sex-specific manner. **Frontiers in Pain Research**, [s. l.], v. 5, 2024.

LAFORGIA, M. *et al.* Peripheral Neuropathy under Oncologic Therapies: A Literature Review on Pathogenetic Mechanisms. **International Journal of Molecular Sciences**, [s. l.], v. 22, n. 4, p. 1980, 2021.

LAURITZEN, M. *et al.* Clinical Relevance of Cortical Spreading Depression in Neurological Disorders: Migraine, Malignant Stroke, Subarachnoid and Intracranial Hemorrhage, and Traumatic Brain Injury. **Journal of Cerebral Blood Flow & Metabolism**, [s. l.], v. 31, n. 1, p. 17–35, 2011a.

LAURITZEN, M. *et al.* Clinical Relevance of Cortical Spreading Depression in Neurological Disorders: Migraine, Malignant Stroke, Subarachnoid and Intracranial Hemorrhage, and Traumatic Brain Injury. **Journal of Cerebral Blood Flow & Metabolism**, [s. l.], v. 31, n. 1, p. 17–35, 2011b. Disponível em: <http://journals.sagepub.com/doi/10.1038/jcbfm.2010.191>.

LAW, A. Y. S. *et al.* Histone deacetylase inhibitor-induced cellular apoptosis involves stanniocalcin-1 activation. **Experimental Cell Research**, [s. l.], v. 314, n. 16, p. 2975–2984, 2008.

LEE, S. J. *et al.* Fetal Pain. **JAMA**, [s. l.], v. 294, n. 8, p. 947, 2005.

LEE, J. Y. *et al.* The Antiallodynic Effect of Nefopam on Vincristine-Induced Neuropathy in Mice. **Journal of Pain Research**, [s. l.], v. Volume 13, p. 323–329, 2020. Disponível em: <https://www.dovepress.com/the-antiallodynic-effect-of-nefopam-on-vincristine-induced-neuropathy-peer-reviewed-article-JPR>.

LEE, B. Y.; HUR, E. M. A role of microtubules in oligodendrocyte differentiation. **International Journal of Molecular Sciences**, [s. l.], v. 21, n. 3, 2020.

LEGAKIS, L. P.; BIGBEE, J. W.; NEGUS, S. S. Lack of paclitaxel effects on intracranial Self-Stimulation in male and female rats: Comparison to mechanical sensitivity. **Behavioural Pharmacology**, [s. l.], v. 29, p. 290–298, 2018.

LEMOS, B. B. *et al.* ROLE OF 7-CHLORO-4- (PHENYLSELANYL) QUINOLINE IN THE TREATMENT. **Canadian physiology and pharmacology**, [s. l.], v. 99(4), n. 378–388, p. 1–50, 2021a.

LEMOS, B. B. *et al.* ROLE OF 7-CHLORO-4- (PHENYLSELANYL) QUINOLINE IN THE TREATMENT. **Canadian physiology and pharmacology**, [s. l.], v. 99(4), n. 378–388, p. 1–50, 2021b.

LI, H. *et al.* Adipocyte Fatty Acid-Binding Protein Promotes Palmitate-Induced Mitochondrial Dysfunction and Apoptosis in Macrophages. **Frontiers in Immunology**, [s. l.], v. 9, 2018.

LI, G. zhou *et al.* CaMKII and CaV3.2 T-type calcium channel mediate Connexin-43-dependent inflammation by activating astrocytes in vincristine-induced neuropathic pain. **Cell Biology and Toxicology**, [s. l.], p. 679–702, 2021a.

LI, G. zhou *et al.* CaMKII and CaV3.2 T-type calcium channel mediate Connexin-43-dependent inflammation by activating astrocytes in vincristine-induced neuropathic pain. **Cell Biology and Toxicology**, [s. l.], p. 679–702, 2021b.

LI, T. *et al.* Characterising vincristine-induced peripheral neuropathy in adults: symptom development and long-term persistent outcomes. **Supportive Care in Cancer**, [s. l.], v. 32, n. 5, p. 278, 2024.

LI, Y. *et al.* Dorsal root ganglion neurons become hyperexcitable and increase expression of voltage-gated T-type calcium channels (Cav3.2) in paclitaxel-induced peripheral neuropathy. **Pain**, [s. l.], v. 158, n. 3, p. 417–429, 2017.

LI, W. *et al.* Ibrutinib alleviates LPS-induced neuroinflammation and synaptic defects in a mouse model of depression. **Brain, Behavior, and Immunity**, [s. l.], v. 92, p. 10–24, 2021.

LI, G. zhou *et al.* Vincristine-induced peripheral neuropathy: A mini-review. **NeuroToxicology**, [s. l.], v. 81, p. 161–171, 2020a.

LI, G. zhou *et al.* Vincristine-induced peripheral neuropathy: A mini-review. **NeuroToxicology**, [s. l.], v. 81, p. 161–171, 2020b.

LIU, J. *et al.* Glutamatergic Neurons in the Amygdala Are Involved in Paclitaxel-Induced Pain and Anxiety. **Frontiers in Psychiatry**, [s. l.], v. 13, n. April, p. 1–11, 2022.

LIU, J. *et al.* Na/K-ATPase signaling and salt sensitivity: The role of oxidative stress. **Antioxidants**, [s. l.], v. 6, n. 1, p. 12–14, 2017a.

LIU, J. *et al.* Na/K-ATPase signaling and salt sensitivity: The role of oxidative stress. **Antioxidants**, [s. l.], v. 6, n. 1, p. 12–14, 2017b.

LIU, J.; LILLY, M. N.; SHAPIRO, J. I. Targeting Na/K-ATPase Signaling: A New Approach to Control Oxidative Stress. **Current Pharmaceutical Design**, [s. l.], v. 24, n. 3, p. 359–364, 2018a.

LIU, J.; LILLY, M. N.; SHAPIRO, J. I. Targeting Na/K-ATPase Signaling: A New Approach to Control Oxidative Stress. **Current Pharmaceutical Design**, [s. l.], v. 24,

n. 3, p. 359–364, 2018b. Disponível em: <https://www.eurekaselect.com/158913/article>.

LIVAK, K. J.; SCHMITTGEN, T. D. Analysis of Relative Gene Expression Data Using Real-Time Quantitative PCR and the $2^{-\Delta\Delta CT}$ Method. **Methods**, [s. l.], v. 25, n. 4, p. 402–408, 2001a.

LIVAK, K. J.; SCHMITTGEN, T. D. Analysis of relative gene expression data using real-time quantitative PCR and the $2^{-\Delta\Delta CT}$ method. **Methods**, [s. l.], v. 25, n. 4, p. 402–408, 2001b.

LOWRY, Oliver H. *et al.* PROTEIN MEASUREMENT WITH THE FOLIN PHENOL REAGENT. **Journal of Biological Chemistry**, [s. l.], v. 193, n. 1, p. 265–275, 1951.

LUHMANN, H. J.; FUKUDA, A. Can we understand human brain development from experimental studies in rodents?. **Pediatrics International**, [s. l.], v. 62, n. 10, p. 1139–1144, 2020.

MACDONALD, A. D.; WOOLFE, G. Analgesic action of pethidine derivatives and related compounds. **British journal of pharmacology and chemotherapy**, [s. l.], v. 1, p. 4–14, 1946.

MADSEN, M. L. *et al.* Aspects of vincristine-induced neuropathy in hematologic malignancies: a systematic review. **Cancer Chemotherapy and Pharmacology**, [s. l.], v. 84, n. 3, p. 471–485, 2019. Disponível em: <https://doi.org/10.1007/s00280-019-03884-5>.

MAGEE, J. C.; GRIENBERGER, C. Synaptic Plasticity Forms and Functions. **Annual Review of Neuroscience**, [s. l.], v. 43, n. 1, p. 95–117, 2020a.

MAGEE, J. C.; GRIENBERGER, C. Synaptic Plasticity Forms and Functions. **Annual Review of Neuroscience**, [s. l.], v. 43, n. 1, p. 95–117, 2020b. Disponível em: <https://www.annualreviews.org/doi/10.1146/annurev-neuro-090919-022842>.

MALDONADO, L. A. G. *et al.* Influence of tumor cell-derived TGF- β on macrophage phenotype and macrophage-mediated tumor cell invasion. **The International Journal of Biochemistry & Cell Biology**, [s. l.], v. 153, p. 106330, 2022.

MALONEYHUSS, M. A. *et al.* Efficacy and toxicity of mustargen, vincristine, procarbazine and prednisone (MOPP) for the treatment of relapsed or resistant lymphoma in cats. **Journal of Feline Medicine and Surgery**, [s. l.], v. 22, n. 4, p. 299–304, 2020.

MARKOVIC, T. *et al.* Pain induces adaptations in ventral tegmental area dopamine neurons to drive anhedonia-like behavior. **Nature Neuroscience**, [s. l.], v. 24, n. 11, p. 1601–1613, 2021.

MASKO, M. *et al.* A novel approach to thermographic images analysis of equine thoracolumbar region: the effect of effort and rider's body weight on structural image complexity. **BMC Veterinary Research**, [s. l.], v. 17, n. 1, p. 99, 2021.

MCCALLUM, J. B. *et al.* Loss of T-type calcium current in sensory neurons of rats with neuropathic pain. **Anesthesiology**, [s. l.], v. 98, n. 1, p. 209–216, 2003.

MCILWAIN, K. L. *et al.* The use of behavioral test batteries: Effects of training history. **Physiology & Behavior**, [s. l.], v. 73, n. 5, p. 705–717, 2001.

MCKELVEY, R. *et al.* Neuropathic pain is constitutively suppressed in early life by anti-inflammatory neuroimmune regulation. **Journal of Neuroscience**, [s. l.], v. 35, n. 2, p. 457–466, 2015.

MEFFERT, M. K. *et al.* NF- κ B functions in synaptic signaling and behavior. **Nature Neuroscience**, [s. l.], v. 6, n. 10, p. 1072–1078, 2003.

MELÉNDEZ, D. M. *et al.* Spatial memory deficits after vincristine-induced lesions to the dorsal hippocampus. **PLoS ONE**, [s. l.], v. 15, n. 4, p. 1–16, 2020.

MESTDAGH, F.; STEYAERT, A.; LAVAND'HOMME, P. Cancer Pain Management: A Narrative Review of Current Concepts, Strategies, and Techniques. **Current Oncology**, [s. l.], v. 30, n. 7, p. 6838–6858, 2023.

MICLESCU, A. A. *et al.* Association between systemic inflammation and experimental pain sensitivity in subjects with pain and painless neuropathy after traumatic nerve injuries. **Scandinavian Journal of Pain**, [s. l.], v. 7, 2022.

MINJ, E.; UPADHAYAY, S.; MEHAN, S. Nrf2/HO-1 Signaling Activator Acetyl-11-keto-beta Boswellic Acid (AKBA)-Mediated Neuroprotection in Methyl Mercury-Induced Experimental Model of ALS. **Neurochemical Research**, [s. l.], v. 46, n. 11, p. 2867–2884, 2021.

MISRA, H. P.; FRIDOVICH, I. The role of superoxide anion in the autoxidation of epinephrine and a simple assay for superoxide dismutase. **Journal of Biological Chemistry**, [s. l.], v. 247, n. 10, p. 3170–3175, 1972.

MOJARAD-JABALI, S. *et al.* Comparison of three synthetic transferrin mimetic small peptides to promote the blood–brain barrier penetration of vincristine liposomes for improved glioma targeted therapy. **International Journal of Pharmaceutics**, [s. l.], v. 613, p. 121395, 2022.

MOK, C. C.; LOK, E. Y. C.; CHEUNG, E. F. C. Concurrent psychiatric disorders are associated with significantly poorer quality of life in patients with rheumatoid arthritis. **Scandinavian Journal of Rheumatology**, [s. l.], v. 41, n. 4, p. 253–259, 2012.

MONTAGUE, K. *et al.* A novel interaction between CX 3 CR 1 and CCR 2 signalling in monocytes constitutes an underlying mechanism for persistent vincristine-induced pain. **Journal of Neuroinflammation**, [s. l.], v. 15, n. 1, p. 1–15, 2018.

MONTAGUE-CARDOSO, K.; MALCANGIO, M. Changes in blood–spinal cord barrier permeability and neuroimmune interactions in the underlying mechanisms of chronic pain. **Pain Reports**, [s. l.], v. 6, n. 1, p. 1–7, 2021.

MORA, E. *et al.* Vincristine-induced peripheral neuropathy in pediatric cancer patients. **American Journal of Cancer Research**, [s. l.], v. 6, n. 11, p. 2416–2430, 2016.

MORTAZAVI, H. Balance training as a promising intervention for reducing the risk of fall in elderly patients with chemotherapy-induced peripheral neuropathy. **Journal of Cancer Research and Therapeutics**, [s. l.], v. 15, n. 5, p. 1192, 2019.

MOSCHETTI, G. *et al.* Prokineticin 2 promotes and sustains neuroinflammation in vincristine treated mice: Focus on pain and emotional like behavior. **Brain, Behavior, and Immunity**, [s. l.], v. 82, n. September, p. 422–431, 2019a.

MOSCHETTI, G. *et al.* Prokineticin 2 promotes and sustains neuroinflammation in vincristine treated mice: Focus on pain and emotional like behavior. **Brain, Behavior, and Immunity**, [s. l.], v. 82, n. September, p. 422–431, 2019b.

MOSELEY, A. E. *et al.* Deficiency in Na,K-ATPase α isoform genes alters spatial learning, motor activity, and anxiety in mice. **Journal of Neuroscience**, [s. l.], v. 27, n. 3, p. 616–626, 2007.

MOTTA, K. P. da *et al.* **7-Chloro-4- (phenylselanyl) quinoline reduces renal oxidative stress induced by oxaliplatin in mice.** [S. l.: s. n.], 2021a.

MOTTA, K. P. da *et al.* 7-Chloro-4- (phenylselanyl) quinoline reduces renal oxidative stress induced by oxaliplatin in mice. **Canadian physiology and pharmacology**, [s. l.], p. 1–37, 2021b.

MOTTA, K. P. da *et al.* 7-Chloro-4- (phenylselanyl) quinoline reduces renal oxidative stress induced by oxaliplatin in mice. **Canadian physiology and pharmacology**, [s. l.], p. 1–37, 2021c.

MOTTA, K. P. da *et al.* Target enzymes in oxaliplatin-induced peripheral neuropathy in Swiss mice: A new acetylcholinesterase inhibitor as therapeutic strategy. **Chemico-Biological Interactions**, [s. l.], v. 352, n. November 2021, p. 109772, 2022. Disponível em: <https://doi.org/10.1016/j.cbi.2021.109772>.

MOWLAVI, A. *et al.* Increased cutaneous nerve fibers in female specimens. **Plastic and Reconstructive Surgery**, [s. l.], v. 116, n. 5, p. 1407–1410, 2005.

MUSSBACHER, M. *et al.* NF- κ B in monocytes and macrophages – an inflammatory master regulator in multitasked immune cells. **Frontiers in Immunology**, [s. l.], v. 14, 2023a.

MUSSBACHER, M. *et al.* NF- κ B in monocytes and macrophages – an inflammatory master regulator in multitasked immune cells. **Frontiers in Immunology**, [s. l.], v. 14, 2023b. Disponível em: <https://www.frontiersin.org/articles/10.3389/fimmu.2023.1134661/full>.

NAGAI, J.; GOSHIMA, Y.; OHSHIMA, T. CRMP4 mediates MAG-induced inhibition of axonal outgrowth and protection against Vincristine-induced axonal degeneration. **Neuroscience Letters**, [s. l.], v. 519, n. 1, p. 56–61, 2012a. Disponível em: <http://dx.doi.org/10.1016/j.neulet.2012.05.020>.

NAGAI, J.; GOSHIMA, Y.; OHSHIMA, T. CRMP4 mediates MAG-induced inhibition of axonal outgrowth and protection against Vincristine-induced axonal degeneration. **Neuroscience Letters**, [s. l.], v. 519, n. 1, p. 56–61, 2012b.

NGO, V.; DUENNWALD, M. L. Nrf2 and Oxidative Stress: A General Overview of Mechanisms and Implications in Human Disease. **Antioxidants**, [s. l.], v. 11, n. 12, p. 2345, 2022.

NOGUEIRA, C. W.; ROCHA, J. B. T. Toxicology and pharmacology of selenium: Emphasis on synthetic organoselenium compounds. **Archives of Toxicology**, [s. l.], v. 85, n. 11, p. 1313–1359, 2011.

NOGUEIRA, C. W.; ZENI, G.; ROCHA, J. B. T. Organoselenium and organotellurium

compounds: Toxicology and pharmacology. **Chemical Reviews**, [s. l.], v. 104, n. 12, p. 6255–6285, 2004.

NOVELLE, M. G.; CAMACHO-MORALES, A.; MARTÍNEZ DE MORENTIN, P. B. Editorial: Role of estrogens as key regulators of energy homeostasis. **Frontiers in Endocrinology**, [s. l.], v. 14, 2023.

OHKAWA, H.; OHISHI, N.; YAGI, K. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. **Analytical Biochemistry**, [s. l.], v. 95, n. 2, p. 351–358, 1979.

OLD, E. A. *et al.* Monocytes expressing CX3CR1 orchestrate the development of vincristine-induced pain. **Journal of Clinical Investigation**, [s. l.], v. 124, n. 5, p. 2023–2036, 2014a.

OLD, E. A. *et al.* Monocytes expressing CX3CR1 orchestrate the development of vincristine-induced pain. **Journal of Clinical Investigation**, [s. l.], v. 124, n. 5, p. 2023–2036, 2014b.

O'ROURKE, S. A.; SHANLEY, L. C.; DUNNE, A. The Nrf2-HO-1 system and inflammaging. **Frontiers in Immunology**, [s. l.], v. 15, 2024.

PAICE, J. A. *et al.* Management of Chronic Pain in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. **Journal of Clinical Oncology**, [s. l.], v. 34, n. 27, p. 3325–3345, 2016.

PALTIAN, J. J. *et al.* 7-chloro-4-(phenylselanyl) quinoline incorporation into polymeric nanocapsules improves its pharmacological action: Physicochemical, toxicological, and behavioral studies. **International Journal of Pharmaceutics**, [s. l.], v. 673, p. 125370, 2025.

PALTIAN, J. J. *et al.* 7-Chloro-4-(Phenylselanyl) Quinoline Is a Novel Multitarget Therapy to Combat Peripheral Neuropathy and Comorbidities Induced by Paclitaxel in Mice. **Molecular Neurobiology**, [s. l.], n. 0123456789, 2022a. Disponível em: <https://doi.org/10.1007/s12035-022-02991-4>.

PALTIAN, J. J. *et al.* 7-Chloro-4-(Phenylselanyl) Quinoline Is a Novel Multitarget Therapy to Combat Peripheral Neuropathy and Comorbidities Induced by Paclitaxel in Mice. **Molecular Neurobiology**, [s. l.], n. 0123456789, 2022b.

PALTIAN, J. J. *et al.* The anxiolytic effect of a promising quinoline containing selenium with the contribution of the serotonergic and GABAergic pathways: Modulation of parameters associated with anxiety in mice. **Behavioural Brain Research**, [s. l.], v. 393, n. June, p. 112797, 2020a. Disponível em: <https://doi.org/10.1016/j.bbr.2020.112797>.

PALTIAN, J. J. *et al.* The anxiolytic effect of a promising quinoline containing selenium with the contribution of the serotonergic and GABAergic pathways: Modulation of parameters associated with anxiety in mice. **Behavioural Brain Research**, [s. l.], v. 393, n. June, p. 112797, 2020b.

PATIL, M. J. *et al.* Ginger Constituent 6-Shogaol Attenuates Vincristine-Induced Activation of Mouse Gastroesophageal Vagal Afferent C-Fibers. **Molecules**, [s. l.], v. 27, n. 21, 2022.

PAUWELS, B. *et al.* Comparison of the sulforhodamine B assay and the clonogenic assay for in vitro chemoradiation studies. **Cancer Chemotherapy and Pharmacology**, [s. l.], v. 51, n. 3, p. 221–226, 2003.

PEDRA, N. S. *et al.* Impact of gallic acid on tumor suppression: Modulation of redox homeostasis and purinergic response in in vitro and a preclinical glioblastoma model. **The Journal of Nutritional Biochemistry**, [s. l.], v. 110, p. 109156, 2022.

PELLOW, S. *et al.* Validation of open : closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. **Journal of Neuroscience Methods**, [s. l.], v. 14, n. 3, p. 149–167, 1985.

PÉREZ-GONZÁLEZ, M. Z. *et al.* Anti-inflammatory, antioxidant, and acute toxicity of *Brugmansia arborea* extracts from wild plants and shoots obtained by indirect organogenesis. A thermographic assay to anti-inflammatory evaluation. **Biomedicine & Pharmacotherapy**, [s. l.], v. 186, p. 117972, 2025.

PIETROBON, D.; MOSKOWITZ, M. A. Pathophysiology of Migraine. **Annual Review of Physiology**, [s. l.], v. 75, n. 1, p. 365–391, 2013a.

PIETROBON, D.; MOSKOWITZ, M. A. Pathophysiology of Migraine. **Annual Review of Physiology**, [s. l.], v. 75, n. 1, p. 365–391, 2013b. Disponível em: <https://www.annualreviews.org/doi/10.1146/annurev-physiol-030212-183717>.

PINZ, M. *et al.* 4-Phenylselenyl-7-chloroquinoline, a new quinoline derivative containing selenium, has potential antinociceptive and anti-inflammatory actions. **European Journal of Pharmacology**, [s. l.], v. 780, p. 122–128, 2016a. Disponível em: <http://dx.doi.org/10.1016/j.ejphar.2016.03.039>.

PINZ, M. *et al.* 4-Phenylselenyl-7-chloroquinoline, a new quinoline derivative containing selenium, has potential antinociceptive and anti-inflammatory actions. **European Journal of Pharmacology**, [s. l.], v. 780, p. 122–128, 2016b.

PINZ, M. P. *et al.* Current advances of pharmacological properties of 7-chloro-4-(phenylselenyl) quinoline: Prevention of cognitive deficit and anxiety in Alzheimer's disease model. **Biomedicine and Pharmacotherapy**, [s. l.], v. 105, n. June, p. 1006–1014, 2018a. Disponível em: <https://doi.org/10.1016/j.biopha.2018.06.049>.

PINZ, M. P. *et al.* Current advances of pharmacological properties of 7-chloro-4-(phenylselenyl) quinoline: Prevention of cognitive deficit and anxiety in Alzheimer's disease model. **Biomedicine and Pharmacotherapy**, [s. l.], v. 105, n. June, p. 1006–1014, 2018b.

PURSER, M. J.; JOHNSTON, D. L.; MCMILLAN, H. J. Chemotherapy-induced Peripheral Neuropathy Among Paediatric Oncology Patients. **Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques**, [s. l.], v. 41, n. 4, p. 442–447, 2014.

QUEIROZ, M. P. *et al.* Effect of Conjugated Linoleic Acid on Memory and Reflex Maturation in Rats Treated During Early Life. **Frontiers in Neuroscience**, [s. l.], v. 13, 2019.

QUEIROZ, K. F. F. da C.; DE CÁSSIA FERNANDES DE LIMA, R. Smart screening system for breast cancer: the use of thermographic images, evolutionary algorithms, and oversampling. **Biomedical Physics & Engineering Express**, [s. l.], v. 9, n. 5, p.

055027, 2023.

QUINES, C. B. *et al.* Involvement of the serotonergic system in the anxiolytic-like effect of 2-phenylethynyl butyltellurium in mice. **Behavioural Brain Research**, [s. l.], v. 277, p. 221–227, 2015.

QUINN, R. Comparing rat's to human's age: How old is my rat in people years? **Nutrition**, [s. l.], v. 21, n. 6, p. 775–777, 2005.

QUITON, R. L.; GREENSPAN, J. D. Sex differences in endogenous pain modulation by distracting and painful conditioning stimulation. **Pain**, [s. l.], p. 132–149, 2007.

RAASING, L. R. M. *et al.* Current View of Diagnosing Small Fiber Neuropathy. **Journal of Neuromuscular Diseases**, [s. l.], v. 8, n. 2, p. 185–207, 2021.

REIS, A. S. *et al.* 4-phenylselenenyl-7-chloroquinoline, a novel multitarget compound with anxiolytic activity: Contribution of the glutamatergic system. **Journal of Psychiatric Research**, [s. l.], v. 84, p. 191–199, 2017a.

REIS, A. S. *et al.* 4-phenylselenenyl-7-chloroquinoline, a novel multitarget compound with anxiolytic activity: Contribution of the glutamatergic system. **Journal of Psychiatric Research**, [s. l.], v. 84, p. 191–199, 2017b.

REIS, A. S. *et al.* 4-phenylselenenyl-7-chloroquinoline, a novel multitarget compound with anxiolytic activity: Contribution of the glutamatergic system. **Journal of Psychiatric Research**, [s. l.], v. 84, p. 191–199, 2017c. Disponível em: <https://linkinghub.elsevier.com/retrieve/pii/S0022395616304976>.

REIS, A. S. *et al.* Advances in the Understanding of Oxaliplatin-Induced Peripheral Neuropathy in Mice: 7-Chloro-4-(Phenylselenenyl) Quinoline as a Promising Therapeutic Agent. **Molecular Neurobiology**, [s. l.], v. 57, n. 12, p. 5219–5234, 2020a.

REIS, A. S. *et al.* Advances in the Understanding of Oxaliplatin-Induced Peripheral Neuropathy in Mice: 7-Chloro-4-(Phenylselenenyl) Quinoline as a Promising Therapeutic Agent. **Molecular Neurobiology**, [s. l.], v. 57, n. 12, p. 5219–5234, 2020b.

REIS, A. S. *et al.* Interface of Aging and Acute Peripheral Neuropathy Induced by Oxaliplatin in Mice: Target-Directed Approaches for Na⁺, K⁺—ATPase, Oxidative Stress, and 7-Chloro-4-(phenylselenenyl) quinoline Therapy. **Molecular Neurobiology**, [s. l.], v. 59, n. 3, p. 1766–1780, 2022. Disponível em: <https://doi.org/10.1007/s12035-021-02659-5>.

REIS, A. S. *et al.* Pharmacological modulation of Na⁺, K⁺-ATPase as a potential target for OXA-induced neurotoxicity: Correlation between anxiety and cognitive decline and beneficial effects of 7-chloro-4-(phenylselenenyl) quinoline. **Brain Research Bulletin**, [s. l.], v. 162, n. June, p. 282–290, 2020c.

REIS, A. S. *et al.* Pharmacological modulation of Na⁺, K⁺-ATPase as a potential target for OXA-induced neurotoxicity: Correlation between anxiety and cognitive decline and beneficial effects of 7-chloro-4-(phenylselenenyl) quinoline. **Brain Research Bulletin**, [s. l.], v. 162, n. June, p. 282–290, 2020d.

REIS, A. S. *et al.* Platinum Deposition in the Central Nervous System: A Novel Insight into Oxaliplatin-induced Peripheral Neuropathy in Young and Old Mice. **Molecular Neurobiology**, [s. l.], v. 62, n. 3, p. 3712–3729, 2025.

REZENDE, A. A. *et al.* Anti-Tumor Efficiency of Perillyl alcohol/ β -Cyclodextrin Inclusion Complexes in a Sarcoma S180-Induced Mice Model. **Pharmaceutics**, [s. l.], v. 13, n. 2, p. 245, 2021.

RODRIGUES, K. C. *et al.* The neurotherapeutic role of a selenium-functionalized quinoline in hypothalamic obese rats. **Psychopharmacology**, [s. l.], v. 238, n. 7, p. 1937–1951, 2021a.

RODRIGUES, K. C. *et al.* The neurotherapeutic role of a selenium-functionalized quinoline in hypothalamic obese rats. **Psychopharmacology**, [s. l.], v. 238, n. 7, p. 1937–1951, 2021b.

ROHN, T. T.; HINDS, T. R.; VINCENZI, F. F. Ion transport ATPases as targets for free radical damage. **Biochemical Pharmacology**, [s. l.], v. 46, n. 3, p. 525–534, 1993.

RUAN, Y. *et al.* An effective and concise device for detecting cold allodynia in mice. **Scientific Reports**, [s. l.], v. 8, n. 1, 2018.

RUBIO, M. *et al.* The immunosuppressive effect of vincristine on allostimulatory potential of human dendritic cells interferes with their function and survival. **International Journal of Oncology**, [s. l.], 2004.

RUDNITSKAYA, E. A. *et al.* Features of Postnatal Hippocampal Development in a Rat Model of Sporadic Alzheimer's Disease. **Frontiers in Neuroscience**, [s. l.], v. 14, 2020.

RUHEE, R. T. *et al.* Organosulfur Compounds: A Review of Their Anti-inflammatory Effects in Human Health. **Frontiers in Nutrition**, [s. l.], v. 7, 2020.

SAGALAJEV, B. *et al.* Bidirectional amygdaloid control of neuropathic hypersensitivity mediated by descending serotonergic pathways acting on spinal 5-HT₃ and 5-HT_{1A} receptors. **Behavioural Brain Research**, [s. l.], v. 282, p. 14–24, 2015.

SAHRANAVARD, S. *et al.* Hydroethanolic extract of *Lavandula angustifolia* ameliorates vincristine-induced peripheral neuropathy in rats. **Research in Pharmaceutical Sciences**, [s. l.], v. 17, n. 3, p. 265, 2022. Disponível em: <https://journals.lww.com/10.4103/1735-5362.343080>.

SALAT, K.; FILIPEK, B. Antinociceptive activity of transient receptor potential channel TRPV1, TRPA1, and TRPM8 antagonists in neurogenic and neuropathic pain models in mice. **Journal of Zhejiang University-SCIENCE B**, [s. l.], v. 16, n. 3, p. 167–178, 2015.

SAMPATHKUMAR, V. *et al.* Integration of signals from different cortical areas in higher order thalamic neurons. **Proceedings of the National Academy of Sciences**, [s. l.], v. 118, n. 30, 2021.

SANTOS, G. J. L. *et al.* *Himatanthus drasticus* (Apocynaceae) latex reduces oxidative stress and modulates CD4⁺, CD8⁺, FoxP3⁺ and HSP-60⁺ expressions in Sarcoma 180-bearing mice. **Journal of Ethnopharmacology**, [s. l.], v. 220, p. 159–168, 2018.

SAVEGNAGO, L. *et al.* Synthesis and antioxidant properties of novel quinoline-chalcogenium compounds. **Tetrahedron Letters**, [s. l.], v. 54, n. 1, p. 40–44, 2013a.

SAVEGNAGO, L. *et al.* Synthesis and antioxidant properties of novel quinoline-chalcogenium compounds. **Tetrahedron Letters**, [s. l.], v. 54, n. 1, p. 40–44, 2013b. Disponível em: <http://dx.doi.org/10.1016/j.tetlet.2012.10.067>.

SCHAPPACHER, K. A. *et al.* Neonatal vincristine administration modulates intrinsic neuronal excitability in the rat dorsal root ganglion and spinal dorsal horn during adolescence. **Pain**, [s. l.], v. 160, n. 3, p. 645–657, 2019a.

SCHAPPACHER, K. A. *et al.* Neonatal vincristine administration modulates intrinsic neuronal excitability in the rat dorsal root ganglion and spinal dorsal horn during adolescence. **Pain**, [s. l.], v. 160, n. 3, p. 645–657, 2019b.

SCHAPPACHER, K. A. *et al.* Neonatal vincristine administration modulates intrinsic neuronal excitability in the rat dorsal root ganglion and spinal dorsal horn during adolescence. **Pain**, [s. l.], v. 160, n. 3, p. 645–657, 2019c.

SCHAPPACHER, K. A.; STYCZYNSKI, L.; BACCEI, M. L. **Early life vincristine exposure evokes mechanical pain hypersensitivity in the developing rat.** [S. l.: s. n.], 2017-. ISSN 18726623.v. 158

SEKERES, M. J.; WINOCUR, G.; MOSCOVITCH, M. The hippocampus and related neocortical structures in memory transformation. **Neuroscience Letters**, [s. l.], v. 680, p. 39–53, 2018.

SEMPLE, B. D. *et al.* Brain development in rodents and humans: Identifying benchmarks of maturation and vulnerability to injury across species. **Progress in Neurobiology**, [s. l.], v. 106–107, p. 1–16, 2013.

SENGUPTA, S. *et al.* Adverse Neonatal Outcomes Associated With Early-Term Birth. **JAMA Pediatrics**, [s. l.], v. 167, n. 11, p. 1053, 2013.

SHABANI, M. *et al.* Profound destructive effects of adolescent exposure to Vincristine accompanied with some sex differences in motor and memory performance. **Canadian Journal of Physiology and Pharmacology**, [s. l.], v. 90, n. 4, p. 379–386, 2012a.

SHABANI, M. *et al.* Profound destructive effects of adolescent exposure to Vincristine accompanied with some sex differences in motor and memory performance. **Canadian Journal of Physiology and Pharmacology**, [s. l.], v. 90, n. 4, p. 379–386, 2012b.

SHAO, Y. *et al.* Morin Regulates M1/M2 Microglial Polarization via NF-κB p65 to Alleviate Vincristine-Induced Neuropathic Pain. **Drug Design, Development and Therapy**, [s. l.], v. Volume 18, p. 3143–3156, 2024.

SHAYESTEH, S. *et al.* Dapsone improves the vincristine-induced neuropathic nociception by modulating neuroinflammation and oxidative stress. **DARU, Journal of Pharmaceutical Sciences**, [s. l.], v. 30, n. 2, p. 303–310, 2022a.

SHAYESTEH, S. *et al.* Dapsone improves the vincristine-induced neuropathic nociception by modulating neuroinflammation and oxidative stress. **DARU, Journal of Pharmaceutical Sciences**, [s. l.], v. 30, n. 2, p. 303–310, 2022b. Disponível em: <https://doi.org/10.1007/s40199-022-00448-6>.

SHEN, Y. *et al.* Exogenous induction of HO-1 alleviates vincristine-induced neuropathic pain by reducing spinal glial activation in mice. **Neurobiology of Disease**, [s. l.], v. 79, p. 100–110, 2015a.

SHEN, Y. *et al.* Exogenous induction of HO-1 alleviates vincristine-induced neuropathic pain by reducing spinal glial activation in mice. **Neurobiology of Disease**, [s. l.], v. 79, p. 100–110, 2015b. Disponível em: <http://dx.doi.org/10.1016/j.nbd.2015.04.012>.

SHINWARI, Z. *et al.* Vincristine and lomustine induce apoptosis and p21WAF1 up-regulation in medulloblastoma and normal human epithelial and fibroblast cells. **Journal of Neuro-Oncology**, [s. l.], v. 87, n. 2, p. 123–132, 2008.

SILVA, A. V. Associations between clinical signs and pathological findings in toxicity testing. **ALTEX**, [s. l.], 2020.

SILVA, V. D. G. *et al.* Further analysis of acute antinociceptive and anti-inflammatory actions of 4-phenylselenyl-7-chloroquinoline in mice. **Fundamental and Clinical Pharmacology**, [s. l.], v. 31, n. 5, p. 513–525, 2017a.

SILVA, V. D. G. *et al.* Further analysis of acute antinociceptive and anti-inflammatory actions of 4-phenylselenyl-7-chloroquinoline in mice. **Fundamental and Clinical Pharmacology**, [s. l.], v. 31, n. 5, p. 513–525, 2017b.

SIMÃO, D. A. da S. *et al.* Chemotherapy-induced peripheral neuropathy: review for clinical practice. **Revista Dor**, [s. l.], v. 16, n. 3, p. 215–220, 2015.

ŞİMŞEK, Ş.; OYMAK SOYSAL, A. N.; KAŞ ÖZDEMİR, A. Association between Pain Intensity, Pain Belief, and Coping Strategies in Older Adults. **Experimental Aging Research**, [s. l.], v. 49, n. 3, p. 244–251, 2023a. Disponível em: <https://doi.org/10.1080/0361073X.2022.2101304>.

ŞİMŞEK, Ş.; OYMAK SOYSAL, A. N.; KAŞ ÖZDEMİR, A. Association between Pain Intensity, Pain Belief, and Coping Strategies in Older Adults. **Experimental Aging Research**, [s. l.], v. 49, n. 3, p. 244–251, 2023b.

SINGH, G. *et al.* Bergapten Ameliorates Vincristine-Induced Peripheral Neuropathy by Inhibition of Inflammatory Cytokines and NFκB Signaling. research-article. **ACS Chemical Neuroscience**, [s. l.], v. 10, n. 6, p. 3008–3017, 2019a.

SINGH, G. *et al.* Bergapten Ameliorates Vincristine-Induced Peripheral Neuropathy by Inhibition of Inflammatory Cytokines and NFκB Signaling. research-article. **ACS Chemical Neuroscience**, [s. l.], v. 10, n. 6, p. 3008–3017, 2019b.

SMART, J. L.; DOBBING, J. Vulnerability of developing brain. II. Effects of early nutritional deprivation on reflex ontogeny and development of behaviour in the rat. **Brain Research**, [s. l.], v. 28, n. 1, p. 85–95, 1971.

SMITH, E. M. L. *et al.* Predictors of duloxetine response in patients with oxaliplatin-induced painful chemotherapy-induced peripheral neuropathy (CIPN): a secondary analysis of randomised controlled trial – CALGB/alliance 170601. **European Journal of Cancer Care**, [s. l.], v. 26, n. 2, 2017.

SNIJDERS, R. *et al.* Update on Prevalence of Pain in Patients with Cancer 2022: A Systematic Literature Review and Meta-Analysis. **Cancers**, [s. l.], v. 15, n. 3, p. 591, 2023.

SONG, B. *et al.* Inhibitory phosphorylation of GSK-3 by CaMKII couples depolarization to neuronal survival. **Journal of Biological Chemistry**, [s. l.], v. 285, n. 52, p. 41122–

41134, 2010.

SORIANO, D. *et al.* Chemotherapy-induced neuropathy and pain in pediatric oncology patients: impact of combination therapies. **European Journal of Pediatrics**, [s. l.], v. 183, n. 9, p. 3749–3756, 2024.

SOYOCAK, A. *et al.* Tannic acid exhibits anti-inflammatory effects on formalin-induced paw edema model of inflammation in rats. **Human & Experimental Toxicology**, [s. l.], v. 38, n. 11, p. 1296–1301, 2019.

STANGHERLIN, E. C.; ROCHA, J. B. T.; NOGUEIRA, C. W. Diphenyl ditelluride impairs short-term memory and alters neurochemical parameters in young rats. **Pharmacology Biochemistry and Behavior**, [s. l.], v. 91, n. 3, p. 430–435, 2009.

STAROBOVA, H. *et al.* Minocycline prevents the development of mechanical allodynia in mouse models of vincristine-induced peripheral neuropathy. **Frontiers in Neuroscience**, [s. l.], v. 13, n. JUN, p. 1–10, 2019.

STAROBOVA, H.; VETTER, I. Pathophysiology of chemotherapy-induced peripheral neuropathy. **Frontiers in Molecular Neuroscience**, [s. l.], v. 10, n. May, p. 1–21, 2017a.

STAROBOVA, H.; VETTER, I. Pathophysiology of chemotherapy-induced peripheral neuropathy. **Frontiers in Molecular Neuroscience**, [s. l.], v. 10, n. May, p. 1–21, 2017b.

STEEL, A. *et al.* A network linking scene perception and spatial memory systems in posterior cerebral cortex. **Nature Communications**, [s. l.], v. 12, n. 1, p. 2632, 2021.

STERU, L. *et al.* The tail suspension test: A new method for screening antidepressants in mice. **Psychopharmacology**, [s. l.], v. 85, n. 3, p. 367–370, 1985.

STYCZYNSKI, L. M.; SCHAPPACHER, K. A.; BACCEI, M. L. Early life vincristine fails to prime developing pain pathways. **Neuroscience Letters**, [s. l.], v. 720, n. January, p. 134764, 2020. Disponível em: <https://doi.org/10.1016/j.neulet.2020.134764>.

SU, H. *et al.* Regulation of the Nrf2/HO-1 axis by mesenchymal stem cells-derived extracellular vesicles: implications for disease treatment. **Frontiers in Cell and Developmental Biology**, [s. l.], v. 12, 2024.

SU, Y.-C. *et al.* Survivors of Non-Hodgkin's Lymphoma: A Comparative Study on Patients With Vincristine-Induced Neuropathy and Their Quality of Life. **Journal of Nursing Research**, [s. l.], v. 33, n. 3, p. e393, 2025.

SUN, J. *et al.* Hemoprotein Bach1 regulates enhancer availability of heme oxygenase-1 gene. **The EMBO Journal**, [s. l.], v. 21, n. 19, p. 5216–5224, 2002.

SUN, G. *et al.* Temporal pain processing in the primary somatosensory cortex and anterior cingulate cortex. **Molecular Brain**, [s. l.], v. 16, n. 1, p. 3, 2023.

SUNG, J. Y. *et al.* Sensory axonal dysfunction in cervical radiculopathy. **Journal of Neurology, Neurosurgery and Psychiatry**, [s. l.], v. 86, n. 6, p. 640–645, 2015a.

SUNG, J. Y. *et al.* Sensory axonal dysfunction in cervical radiculopathy. **Journal of Neurology, Neurosurgery and Psychiatry**, [s. l.], v. 86, n. 6, p. 640–645, 2015b.

SWARM, R. A. *et al.* Adult Cancer Pain. **Journal of the National Comprehensive Cancer Network**, [s. l.], v. 11, n. 8, p. 992–1022, 2013.

SY, A. *et al.* Heterozygosity for CMT Type 4 Predicts a Severe Vincristine-induced Polyneuropathy Phenotype: A Case Report and Review of Literature. **Journal of Pediatric Hematology/Oncology**, [s. l.], v. 41, n. 1, p. E41–E43, 2019a.

SY, A. *et al.* Heterozygosity for CMT Type 4 Predicts a Severe Vincristine-induced Polyneuropathy Phenotype: A Case Report and Review of Literature. **Journal of Pediatric Hematology/Oncology**, [s. l.], v. 41, n. 1, p. E41–E43, 2019b.

TAKEDA, M.; TAKAHASHI, M.; MATSUMOTO, S. Suppression of neurokinin-1 receptor in trigeminal ganglia attenuates central sensitization following inflammation. **Journal of the Peripheral Nervous System**, [s. l.], v. 17, n. 2, p. 169–181, 2012.

TANTAWY, S. I. *et al.* Targeting MCL-1 protein to treat cancer: opportunities and challenges. **Frontiers in Oncology**, [s. l.], v. 13, 2023.

TAVES, S. *et al.* Microglia and Spinal Cord Synaptic Plasticity in Persistent Pain. **Neural Plasticity**, [s. l.], v. 2013, p. 1–10, 2013. Disponível em: <http://www.hindawi.com/journals/np/2013/753656/>.

TAY, N. *et al.* Chemotherapy-induced peripheral neuropathy in children and adolescent cancer patients. **Frontiers in Molecular Biosciences**, [s. l.], v. 9, 2022.

TAY, S. Y. *et al.* Pediatric Oncology Patients With Vincristine-Induced Recurrent Laryngeal Nerve Palsy: Two Case Reports and a Brief Review of Literature. **Ear, Nose and Throat Journal**, [s. l.], v. 100, n. 10, p. NP459–NP463, 2021a.

TAY, S. Y. *et al.* Pediatric Oncology Patients With Vincristine-Induced Recurrent Laryngeal Nerve Palsy: Two Case Reports and a Brief Review of Literature. **Ear, Nose and Throat Journal**, [s. l.], v. 100, n. 10, p. NP459–NP463, 2021b.

TIMMINS, H. C. *et al.* The impact of obesity on neuropathy outcomes for paclitaxel- and oxaliplatin-treated cancer survivors. **Journal of Cancer Survivorship**, [s. l.], v. 16, n. 2, p. 223–232, 2022.

TINNIRELLO, A.; MAZZOLENI, S.; SANTI, C. Chronic Pain in the Elderly: Mechanisms and Perspectives. **Biomolecules**, [s. l.], v. 11, n. March, p. 1256, 2021.

TOWER, J.; POMATTO, L. C. D.; DAVIES, K. J. A. Sex differences in the response to oxidative and proteolytic stress. **Redox Biology**, [s. l.], v. 31, p. 101488, 2020.

TREEDE, R. D. The International Association for the Study of Pain definition of pain: As valid in 2018 as in 1979, but in need of regularly updated footnotes. **Pain Reports**, [s. l.], v. 3, n. 2, p. 1–3, 2018.

TREVISAN, G. *et al.* Antinociceptive Effects of 14-Membered Cyclopeptide Alkaloids. **Journal of natural products**, [s. l.], v. 72, p. 608–612, 2009.

TRIARICO, S. *et al.* Vincristine-induced peripheral neuropathy (Vipn) in pediatric tumors: Mechanisms, risk factors, strategies of prevention and treatment. **International Journal of Molecular Sciences**, [s. l.], v. 22, n. 8, 2021a.

TRIARICO, S. *et al.* Vincristine-induced peripheral neuropathy (Vipn) in pediatric tumors: Mechanisms, risk factors, strategies of prevention and treatment. **International Journal of Molecular Sciences**, [s. l.], v. 22, n. 8, 2021b.

TRIARICO, S. *et al.* Vincristine-Induced Peripheral Neuropathy (VIPN) in Pediatric Tumors: Mechanisms, Risk Factors, Strategies of Prevention and Treatment. **International Journal of Molecular Sciences**, [s. l.], v. 22, n. 8, p. 4112, 2021c.

TUCKER, M. H.; TIWARI, P.; CARTER, B. S. The physiology, assessment, and treatment of neonatal pain. **Seminars in Fetal and Neonatal Medicine**, [s. l.], v. 28, n. 4, p. 101465, 2023.

TUMMALA, R. *et al.* Expression of Na,K-ATPase- β 1 subunit increases uptake and sensitizes carcinoma cells to oxaliplatin. **Cancer Chemotherapy and Pharmacology**, [s. l.], v. 64, n. 6, p. 1187–1194, 2009.

TUNJUNGSARI, D. A.; GUNAWAN, P. I.; UGRASENA, I. D. G. RISK FACTORS OF VINCRISTINE-INDUCED PERIPHERAL NEUROPATHY IN ACUTE LYMPHOBLASTIC LEUKAEMIA CHILDREN. **The Journal of Medical Investigation**, [s. l.], v. 68, n. 3.4, p. 232–237, 2021.

TURCU-STIOLICA, A. *et al.* Diagnostic Accuracy of Machine-Learning Models on Predicting Chemo-Brain in Breast Cancer Survivors Previously Treated with Chemotherapy: A Meta-Analysis. **International Journal of Environmental Research and Public Health**, [s. l.], v. 19, n. 24, p. 16832, 2022.

UITTENBOOGAARD, A. *et al.* Pharmacogenomics of Vincristine-Induced Peripheral Neuropathy in Children with Cancer: A Systematic Review and Meta-Analysis. **Cancers**, [s. l.], v. 14, n. 3, p. 612, 2022.

UMANA, I. C. *et al.* **Nicotinic modulation of descending pain control circuitry**. [S. l.: s. n.], 2017-. ISSN 18726623.v. 158

VAN DE VELDE, M. E. *et al.* The association between vincristine-induced peripheral neuropathy and health-related quality of life in children with cancer. **Cancer Medicine**, [s. l.], v. 10, n. 22, p. 8172–8181, 2021.

VAN DE VELDE, M. E. *et al.* Vincristine-induced peripheral neuropathy in children with cancer: A systematic review. **Critical Reviews in Oncology/Hematology**, [s. l.], v. 114, p. 114–130, 2017a. Disponível em: <https://doi.org/10.1016/j.critrevonc.2017.04.004>.

VAN DE VELDE, M. E. *et al.* Vincristine-induced peripheral neuropathy in children with cancer: A systematic review. **Critical Reviews in Oncology/Hematology**, [s. l.], v. 114, p. 114–130, 2017b.

VAN DEN BEUKEN-VAN EVERDINGEN, M. H. J. *et al.* Prevalence of pain in patients with cancer: a systematic review of the past 40 years. **Annals of Oncology**, [s. l.], v. 18, n. 9, p. 1437–1449, 2007.

VEGA-AVELAIRA, D.; MOSS, A.; FITZGERALD, M. Age-related changes in the spinal cord microglial and astrocytic response profile to nerve injury. **Brain, Behavior, and Immunity**, [s. l.], v. 21, n. 5, p. 617–623, 2007.

VOGT, A. G. *et al.* Organoselenium group is critical for antioxidant activity of 7-chloro-

4-phenylselenyl-quinoline. **Chemico-Biological Interactions**, [s. l.], v. 282, p. 7–12, 2018a. Disponível em: <https://doi.org/10.1016/j.cbi.2018.01.003>.

VOGT, A. G. *et al.* Organoselenium group is critical for antioxidant activity of 7-chloro-4-phenylselenyl-quinoline. **Chemico-Biological Interactions**, [s. l.], v. 282, p. 7–12, 2018b.

VOSS, G. T. *et al.* Therapeutic and technological potential of 7-chloro-4-phenylselenyl quinoline for the treatment of atopic dermatitis-like skin lesions in mice. **Materials Science and Engineering C**, [s. l.], v. 84, n. August 2017, p. 90–98, 2017a. Disponível em: <https://doi.org/10.1016/j.msec.2017.11.026>.

VOSS, G. T. *et al.* Therapeutic and technological potential of 7-chloro-4-phenylselenyl quinoline for the treatment of atopic dermatitis-like skin lesions in mice. **Materials Science and Engineering C**, [s. l.], v. 84, n. August 2017, p. 90–98, 2017b.

WALKER, J. L. *et al.* Gait-stance duration as a measure of injury and recovery in the rat sciatic nerve model. **Journal of Neuroscience Methods**, [s. l.], v. 52, n. 1, p. 47–52, 1994.

WALSH, R. N.; CUMMINS, R. A. The open-field test: A critical review. **Psychological Bulletin**, [s. l.], v. 83, n. 3, p. 482–504, 1976.

WANG, F. *et al.* Influence of blood-brain barrier efflux pumps on the distribution of vincristine in brain and brain tumors. **Neuro-Oncology**, [s. l.], v. 12, n. 10, p. 1043–1049, 2010.

WANG, X. *et al.* Observation of Acetylcholinesterase in Stress-Induced Depression Phenotypes by Two-Photon Fluorescence Imaging in the Mouse Brain. **Journal of the American Chemical Society**, [s. l.], v. 141, n. 5, p. 2061–2068, 2019.

WANG, M. S. *et al.* Pathogenesis of axonal degeneration: Parallels between Wallerian degeneration and vincristine neuropathy. **Journal of Neuropathology and Experimental Neurology**, [s. l.], v. 59, n. 7, p. 599–606, 2000a.

WANG, M. S. *et al.* Pathogenesis of axonal degeneration: Parallels between Wallerian degeneration and vincristine neuropathy. **Journal of Neuropathology and Experimental Neurology**, [s. l.], v. 59, n. 7, p. 599–606, 2000b.

WANG, J. H. *et al.* Relationship between prescribed opioids, pain management satisfaction, and pain intensity in oncology outpatients. **Supportive Care in Cancer**, [s. l.], v. 30, n. 4, p. 3233–3240, 2022. Disponível em: <https://doi.org/10.1007/s00520-021-06722-8>.

WANG, L.; AHN, Y. J.; ASMIS, R. Sexual dimorphism in glutathione metabolism and glutathione-dependent responses. **Redox Biology**, [s. l.], v. 31, p. 101410, 2020.

WEEKS, J. C.; LEVINE, R. B. Steroid hormone effects on neurons subserving behavior. **Current Opinion in Neurobiology**, [s. l.], v. 5, n. 6, p. 809–815, 1995.

WHITE, D. *et al.* Targeting translation: A review of preclinical animal models in the development of treatments for chemotherapy-induced peripheral neuropathy. **Journal of the Peripheral Nervous System**, [s. l.], v. 28, n. 2, p. 179–190, 2023.

WIESKOPF, J. S. *et al.* The nicotinic $\alpha 6$ subunit gene determines variability in chronic

pain sensitivity via cross-inhibition of P2X2/3 receptors. **Science Translational Medicine**, [s. l.], v. 7, n. 287, 2015.

WILHELM, E. A. *et al.* Antioxidant effect of quinoline derivatives containing or not selenium: Relationship with antinociceptive action quinolines are antioxidant and antinociceptive. **Anais da Academia Brasileira de Ciencias**, [s. l.], v. 89, n. 1, p. 457–467, 2017.

WILLIAMS, M. D.; LASCELLES, B. D. X. Early Neonatal Pain—A Review of Clinical and Experimental Implications on Painful Conditions Later in Life. **Frontiers in Pediatrics**, [s. l.], v. 8, 2020a.

WILLIAMS, M. D.; LASCELLES, B. D. X. Early Neonatal Pain—A Review of Clinical and Experimental Implications on Painful Conditions Later in Life. **Frontiers in Pediatrics**, [s. l.], v. 8, 2020b.

WOLF, E. *et al.* Innate Conformational Dynamics Drive Binding Specificity in Anti-Apoptotic Proteins Mcl-1 and Bcl-2. **Biochemistry**, [s. l.], v. 62, n. 11, p. 1619–1630, 2023.

WOOLF, C. J. Pain modulation in the spinal cord. **Frontiers in Pain Research**, [s. l.], v. 3, 2022.

WOOLFE, G.; MACDONALD, A. D. The Evaluation of the analgesic action of pethidine hydrochloride (demerol). **Journal of Pharmacology and Experimental Therapeutics**, [s. l.], v. 80, n. 3, p. 300–307, 1944.

WORLD HEALTH ORGANIZATION (WHO). **Global cancer burden growing, amidst mounting need for services**. [S. l.: s. n.], 2024. Disponível em: : <https://www.who.int/news/item/01-02-2024-global-cancer-burden-growing--amidstmounting-need-for-services>. Acesso em: 14 jul. 2025.

XIAOHONG, G. *et al.* [Effects of glucocorticoid receptor agonists on hyperalgesia of rats with neuropathic pain and its mechanisms]. **Chinese Journal of Applied Physiology**, [s. l.], v. 38, n. 5, p. 470–474, 2022.

XU, T. *et al.* Epigenetic upregulation of CXCL12 expression mediates antitubulin chemotherapeutics-induced neuropathic pain. **Pain**, [s. l.], v. 158, n. 4, p. 637–648, 2017a.

XU, T. *et al.* Epigenetic upregulation of CXCL12 expression mediates antitubulin chemotherapeutics-induced neuropathic pain. **Pain**, [s. l.], v. 158, n. 4, p. 637–648, 2017b.

XU, J. *et al.* Longer versus Shorter Schedules of Vincristine, Irinotecan, and Temozolomide (VIT) for Relapsed or Refractory Ewing Sarcoma: A Randomized Controlled Phase 2 Trial. **Clinical Cancer Research**, [s. l.], v. 29, n. 6, p. 1040–1046, 2023.

XUE, V. W. *et al.* Transforming Growth Factor- β : A Multifunctional Regulator of Cancer Immunity. **Cancers**, [s. l.], v. 12, n. 11, p. 3099, 2020.

YOHAN, C. N.; GERGUES, M. M.; SAMUELS, B. A. The role of 5-HT receptors in depression Tim Bliss. **Molecular Brain**, [s. l.], v. 10, n. 1, p. 1–12, 2017.

YOON, S. Y.; OH, J. Neuropathic cancer pain: Prevalence, pathophysiology, and management. **Korean Journal of Internal Medicine**, [s. l.], v. 33, n. 6, p. 1058–1069, 2018.

ZAJĄCZKOWSKA, R. *et al.* Mechanisms of Chemotherapy-Induced Peripheral Neuropathy. **International Journal of Molecular Sciences**, [s. l.], v. 20, n. 6, p. 1451, 2019.

ŽARKOVIĆ, N. *et al.* Spontaneous Regression of Cancer: Revealing Granulocytes and Oxidative Stress as the Crucial Double-edge Sword. **Frontiers in Bioscience-Landmark**, [s. l.], v. 27, n. 4, 2022.

ZHAN, X.; LI, J.; ZHOU, T. Targeting Nrf2-Mediated Oxidative Stress Response Signaling Pathways as New Therapeutic Strategy for Pituitary Adenomas. **Frontiers in Pharmacology**, [s. l.], v. 12, 2021.

ZHANG, H. Cancer Pain Management—New Therapies. **Current Oncology Reports**, [s. l.], v. 24, n. 2, p. 223–226, 2022.

ZHANG, S. Chemotherapy-induced peripheral neuropathy and rehabilitation: A review. **Seminars in Oncology**, [s. l.], v. 48, n. 3, p. 193–207, 2021.

ZHAO, J. Y. *et al.* DNA methyltransferase DNMT3a contributes to neuropathic pain by repressing Kcna2 in primary afferent neurons. **Nature Communications**, [s. l.], v. 8, n. May 2016, p. 1–15, 2017.

ZHAO, B. *et al.* Supplementation of lycopene attenuates oxidative stress induced neuroinflammation and cognitive impairment via Nrf2/NF-κB transcriptional pathway. **Food and Chemical Toxicology**, [s. l.], v. 109, p. 505–516, 2017a.

ZHAO, B. *et al.* Supplementation of lycopene attenuates oxidative stress induced neuroinflammation and cognitive impairment via Nrf2/NF-κB transcriptional pathway. **Food and Chemical Toxicology**, [s. l.], v. 109, p. 505–516, 2017b. Disponível em: <https://doi.org/10.1016/j.fct.2017.09.050>.

ZHENG, S. *et al.* TNF-α Impairs Pericyte-Mediated Cerebral Microcirculation via the NF-κB/iNOS Axis after Experimental Traumatic Brain Injury. **Journal of Neurotrauma**, [s. l.], v. 40, n. 3–4, p. 349–364, 2023a.

ZHENG, S. *et al.* TNF-α Impairs Pericyte-Mediated Cerebral Microcirculation via the NF-κB/iNOS Axis after Experimental Traumatic Brain Injury. **Journal of Neurotrauma**, [s. l.], v. 40, n. 3–4, p. 349–364, 2023b. Disponível em: <https://www.liebertpub.com/doi/10.1089/neu.2022.0016>.

ZHU, Y. *et al.* Inhibition of PINK1 senses ROS signaling to facilitate neuroblastoma cell pyroptosis. **Autophagy**, [s. l.], p. 1–20, 2025.

ZHU, M. *et al.* Na⁺/K⁺-ATPase-dependent autophagy protects brain against ischemic injury. **Signal Transduction and Targeted Therapy**, [s. l.], v. 5, n. 1, p. 55, 2020.

ZHU, S. *et al.* Roles of tumor-associated macrophages in tumor progression: implications on therapeutic strategies. **Experimental Hematology & Oncology**, [s. l.], v. 10, n. 1, p. 60, 2021.

ZHU, J. *et al.* The neuroprotective effect of oxytocin on vincristine-induced neurotoxicity

in mice. **Toxicology Letters**, [s. l.], v. 340, p. 67–76, 2021. Disponível em: <https://linkinghub.elsevier.com/retrieve/pii/S0378427421000096>.

9. ANEXOS

Anexo I – Carta de aprovação dos protocolos experimentais pela Comissão de Ética em Experimentação Animal da Universidade Federal de Pelotas



PARECER Nº
PROCESSO Nº

12/2022/CEUA/REITORIA
23110.035767/2021-41

Certificado

Certificamos que a proposta intitulada “**Avaliação da contribuição do envelhecimento e do estresse na dor oncológica e comorbidades correlatas: prospecção de uma estratégia terapêutica**”, registrada com o nº **23110.035767/2021-41**, sob a responsabilidade de **Ethel Antunes Wilhelm** - que envolve a produção, manutenção ou utilização de animais pertencentes ao filo Chordata, subfilo Vertebrata (exceto humanos), para fins de pesquisa científica (ou ensino) – encontra-se de acordo com os preceitos da Lei nº 11.794, de 8 de outubro de 2008, do Decreto nº 6.899, de 15 de julho de 2009, e com as normas editadas pelo Conselho Nacional de Controle de Experimentação Animal (CONCEA), e recebeu parecer **FAVORÁVEL** a sua execução pela Comissão de Ética no Uso de Animais da Universidade Federal de Pelotas, em reunião de 15/12/2021.

Finalidade	(x) Pesquisa () Ensino
Vigência da autorização	Início = 10 /02 / 2022 Término = 10 / 01 /2027
Espécie/linhagem/raça	<i>Mus musculus</i> / Swiss
Nº de animais	624 (312 machos e 312 fêmeas)
Idade	60 dias
Sexo	Machos e fêmeas
Origem	Biotério Central - UFPel

Código para cadastro nº **CEUA 035767/2021-41**

Priscila Marques Moura de Leon

Coordenadora da CEUA



Documento assinado eletronicamente por **PRISCILA MARQUES MOURA DE LEON**,
Professor do Magistério Superior/Adjunto, em 26/01/2022, às 20:39, conforme horário oficial
de Brasília, com fundamento no art. 4º, § 3º, do [Decreto nº 10.543, de 13 de novembro de 2020](#).



A autenticidade deste documento pode ser conferida no site
[http://sei.ufpel.edu.br/sei/controlador_externo.php?](http://sei.ufpel.edu.br/sei/controlador_externo.php?acao=documento_conferir&id_orgao_acesso_externo=0)
[acao=documento_conferir&id_orgao_acesso_externo=0](http://sei.ufpel.edu.br/sei/controlador_externo.php?acao=documento_conferir&id_orgao_acesso_externo=0), informando o código verificador
1571841 e o código CRC **51508AB4**.



UNIVERSIDADE FEDERAL DE PELOTAS
PARECER Nº 144/2019/CEEA/REITORIA
PROCESSO Nº 23110.046701/2019-61

Certificado

Certificamos que a solicitação de **adendo** à proposta intitulada "**Investigação do papel do envelhecimento na neuropatia induzida por quimioterápicos: 7-cloro-4-(fenilseleno) quinolina como alternativa terapêutica**" (CEEA 4506-2017), registrada com o nº 23110.046701/2019-61, sob a responsabilidade de **Ethel Antunes Wilhelm** - que envolve a produção, manutenção ou utilização de animais pertencentes ao filo Chordata, subfilo Vertebrata (exceto humanos), para fins de pesquisa científica (ou ensino) – encontra-se de acordo com os preceitos da Lei nº 11.794, de 8 de outubro de 2008, do Decreto nº 6.899, de 15 de julho de 2009, e com as normas editadas pelo Conselho Nacional de Controle de Experimentação Animal (CONCEA), e recebeu parecer **FAVORÁVEL** a sua execução pela Comissão de Ética em Experimentação Animal, em reunião de **13 de novembro de 2019**.

Solicitação: Acréscimo de 156 camundongos Swiss, sendo 78 machos e 78 fêmeas de 60 dias.

M.V. Dra. Anelize de Oliveira Campello Felix

Presidente da CEEA



Documento assinado eletronicamente por **ANELIZE DE OLIVEIRA CAMPELLO FELIX**, **Médico Veterinário**, em 19/11/2019, às 10:02, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do [Decreto nº 8.539, de 8 de outubro de 2015](#).



A autenticidade deste documento pode ser conferida no site http://sei.ufpel.edu.br/sei/controlador_externo.php?acao=documento_conferir&id_orgao_acesso_externo=0, informando o código verificador **0788243** e o código CRC **1D324FB7**.

Anexo II – Carta de aprovação dos protocolos experimentais pela Comissão de Ética em Experimentação Animal da Universidade Federal de Pelotas



PARECER Nº
PROCESSO Nº

72/2022/CEUA/REITORIA
23110.038650/2021-19

Certificado

Certificamos que a proposta intitulada “**Avaliação da exposição pediátrica de vincristina na alteração da sensibilidade a dor na adolescência e fase adulta: mecanismos envolvidos, avaliação do neurodesenvolvimento e possível estratégia terapêutica**”, registrada com o nº **23110.038650/2021-19**, sob a responsabilidade de **Ethel Antunes Wilhelm** - que envolve a produção, manutenção ou utilização de animais pertencentes ao filo Chordata, subfilo Vertebrata (exceto humanos), para fins de pesquisa científica (ou ensino) – encontra-se de acordo com os preceitos da Lei nº 11.794, de 8 de outubro de 2008, do Decreto nº 6.899, de 15 de julho de 2009, e com as normas editadas pelo Conselho Nacional de Controle de Experimentação Animal (CONCEA), e recebeu parecer **FAVORÁVEL** a sua execução pela Comissão de Ética no Uso de Animais da Universidade Federal de Pelotas, em reunião de **16 de maio de 2022**.

Finalidade	(x) Pesquisa () Ensino
Vigência da autorização	Início = 16/05/22 Término = 01/05/25
Espécie/linhagem/raça	<i>Rattus norvegicus</i> / Wistar
Nº de animais	635
Idade	60 dias (68 fêmeas prenhes) e Recém nascidos (272 machos + 272 fêmeas)
Sexo	Machos (272 animais) e fêmeas (68 prenhes e 272 recém nascidos)
Origem	Biotério Central - UFPel

Código para cadastro nº CEUA 038650/2021-19

Priscila Marques Moura de Leon

Coordenadora da CEUA



Documento assinado eletronicamente por **PRISCILA MARQUES MOURA DE LEON**, **Professor do Magistério Superior**, em 16/05/2022, às 18:58, conforme horário oficial de Brasília, com fundamento no art. 4º, § 3º, do [Decreto nº 10.543, de 13 de novembro de 2020](#).



A autenticidade deste documento pode ser conferida no site http://sei.ufpel.edu.br/sei/controlador_externo.php?acao=documento_conferir&id_orgao_acesso_externo=0, informando o código verificador **1698934** e o código CRC **CA377697**.

Referência: Processo nº 23110.038650/2021-19

SEI nº 1698934

Anexo III - Comprovante de submissão do manuscrito 1 na revista científica ACS Omega

ACS | ACS Publications | C&EN | CAS

ACS Publishing Center
Powered by ChronosHub

Author ▾ EW

Article In Peer Review

Correlation between NFκB Signaling and Na⁺, K⁺-ATPase Inhibition in Vincristine-Induced Emotional and Cognitive Comorbidities in Mice: Neuroprotective Potential of 4-PSQ

ao-2025-074235

Email Editor

Abstract

Vincristine (VCR), a widely used chemotherapeutic agent, is associated with persistent neurotoxic effects, including psychiatric and cognitive impairments in cancer survivors. This study investigated the neurobehavioral and molecular effects of VCR in male and female Swiss mice, with a focus on sex-specific outcomes and the neuroprotective efficacy of 7-chloro-4-(phenylselanyl)quinoline (4-PSQ). Mice received daily intraperitoneal injections of VCR (0.1 mg/kg) or vehicle for five days, followed by daily oral administration of 4-PSQ (1 mg/kg) or vehicle from day 7 to 16. Behavioral assessments for depressive- and anxiety-like responses and cognitive performance were conducted, followed by biochemical analyses of the cerebral cortex and spinal cord. VCR significantly increased nuclear factor kappa B (NFκB) expression and inhibited Na⁺,K⁺-ATPase activity in both sexes, while selectively upregulating protein-21 (p21) mRNA in the cerebral cortex of females. These molecular alterations correlated with behavioral impairments, as shown by a robust pattern of sex-specific associations: in males, behavioral changes were strongly correlated with Na⁺,K⁺-ATPase inhibition, while in females, increased NFκB expression was more strongly associated with emotional and cognitive deficits. Notably, p21 overexpression emerged as a unique marker of neurotoxicity in females. Treatment with 4-PSQ attenuated molecular and behavioral alterations in both sexes, supporting its neuroprotective efficacy. By establishing specific correlations between biochemical and behavioral parameters, this study provides mechanistic insights into VCR-induced neurotoxicity. It proposes 4-PSQ as a promising therapeutic candidate for preventing or reversing chemotherapy-related cognitive and emotional dysfunctions.

Previous Submission

Help?

Feedback