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Dissertação

Uso de suplementos alimentares no controle de doenças respiratórias em bovinos de corte

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Resumo

MOCELLIN, Gabriele Santos. **Uso de suplementos alimentares no controle de doenças respiratórias em bovinos de corte.** 2025. 42f. Dissertação (Mestrado em Ciências) - Programa de Pós-Graduação em Veterinária, Faculdade de Veterinária, Universidade Federal de Pelotas, Pelotas, 2025.

A Doença Respiratória Bovina (DRB) é um dos principais desafios sanitários na produção animal, especialmente em sistemas de confinamento. A prevenção e o tratamento da DRB são amplamente baseados no uso de antimicrobianos, o que ressalta a necessidade de alternativas mais sustentáveis. Diante deste cenário, esta dissertação apresenta uma revisão sistemática sobre o uso de suplementos alimentares como estratégia para a prevenção e tratamento da DRB, já que, conforme o nosso conhecimento, não existe um trabalho que tenha coletado estes dados de forma sistemática. O objetivo é fornecer evidências dessas estratégias alimentares para mitigar os impactos da doença na bovinocultura de corte em sistemas intensivos e semi-intensivos. O estudo analisou dados de três bases científicas – PubMed, Scopus e Web of Science – para compilar evidências sobre o impacto da nutrição na saúde respiratória dos bovinos. Os resultados destacam o potencial dos suplementos alimentares na melhoria da imunidade e na redução da incidência da DRB. Apesar dos avanços apresentados, ainda são necessários novos estudos sobre o uso de suplementos alimentares em bovinos de corte, a fim de compreender mecanismos específicos de ação e estratégias de aplicação em diferentes cenários.

Palavras-chave: probióticos; prebióticos; minerais; doença respiratória bovina; imunidade

Abstract

MOCELLIN, Gabriele Santos. **Use of dietary supplements in the control of respiratory diseases in beef cattle.** 2025. 42f. Dissertation Master degree in Sciences) - Programa de Pós-Graduação em Veterinária, Faculdade de Veterinária, Universidade Federal de Pelotas, Pelotas, 2025.

Bovine Respiratory Disease (BRD), one of the major health challenges in animal production, particularly in confinement systems, is often prevented and treated using antimicrobials, highlighting the need for more sustainable alternatives. In light of this, this dissertation presents a systematic review on the use of dietary supplements as a strategy for the prevention and treatment of BRD, as, to our knowledge, no study has systematically gathered this data. The objective is to provide evidence of these feeding strategies to mitigate the impacts of the disease on beef cattle production in intensive and semi-intensive systems. The study analyzed data from three scientific databases – PubMed, Scopus, and Web of Science – to compile evidence on the impact of nutrition on the respiratory health of cattle. The results emphasize the potential of dietary supplements in improving immunity and reducing the incidence of BRD. Despite the advancements presented, further studies are still needed on the use of dietary supplements in beef cattle to better understand specific mechanisms of action and application strategies in different settings.

Keywords: probiotics; prebiotics; minerals; bovine respiratory disease; immunity

Lista de Figuras

Lista de Abreviaturas e Siglas

ACTH	Hormônio adrenocorticotrófico
Bcov	Coronavírus
BoHV-1	Herpesvírus Bovino tipo 1
bPI-3	Parainfluenza Bovino tipo 3
BRSV	Vírus Sincicial Respiratório Bovino
BVDV	Vírus da Diarreia Viral Bovina
Ca	Cálcio
Cl	Cloro
Cr	Cromo
Co	Cobalto
Cu	Cobre
DRB	Doença respiratória bovina
FAO	Food and Agriculture Organization of the United Nations
Fe	Ferro
GH	Hormônio do crescimento
HPA	Hipotálamo-hipófise-adrenal
I	Iodo
IFN-γ	Interferon gama
IgG	Imunoglobulina G
IgM	Imunoglobulina M
IL-6	Interleucina 6
K	Potássio
LPS	Lipopolissacarídeos
Mg	Magnésio
Mn	Manganês
Mo	Molibdênio

M.S.	Matéria seca
Na	Sódio
NEFA	Ácidos graxos não-esterificados
Ni	Níquel
NK	Células natural killer
ONU	Organização das Nações Unidas
P	Fósforo
Ppb	Partes por milhão
S	Enxofre
Se	Selênio
SOD	Superóxido dismutase
TGI	Trato gastrointestinal
TLR	Toll-like
UI/Kg	Unidades internacionais por quilograma
US$	Dólar americano
Zn	Zinco

Sumário

1 Introdução

Com a projeção de que a população global deverá atingir 9,7 bilhões até 2050, de acordo com estimativas da ONU (2023), a demanda por alimentos de origem animal deverá crescer significativamente. Segundo a FAO, a produção mundial de carne bovina em 2023 atingiu 76,6 milhões de toneladas, com aumento anual de 773.000 toneladas. No Brasil, observa-se uma intensificação notável na produção de carne bovina, chegando a quase 11 milhões de toneladas (FAO, 2024), evidenciada pelo crescimento no número de bovinos confinados, que passou de 7,2 milhões em 2021 para 7,62 milhões em 2022 (ABIEC, 2023).

Esse aumento de bovinos confinados e na produção demandam estratégias para assegurar a saúde e o desempenho dos bovinos de corte. Um dos principais desafios sanitários é a Doença Respiratória Bovina (DRB), representando mundialmente uma das principais causas de morbidade e mortalidade em confinamentos, afetando o desempenho zootécnico e aumentando os custos econômicos das operações de bovinos (CHAI et al., 2022). Esta doença resulta em perdas econômicas significativas na pecuária de corte, com custos anuais estimados em US$ 800 a US$ 900 milhões nos Estados Unidos (WHITE & LARSON, 2020) e US$ 11,85 milhões no Brasil (BAPTISTA et al., 2017).

De ordem multifatorial e complexa, devido a interação de patógenos, hospedeiro e fatores ambientais (STOKSTAD et al., 2020), a DRB é reconhecida como uma doença polimicrobiana (HODGINS et al., 2014), sendo comum a infecção viral primária seguida por uma superinfecção bacteriana secundária (EARLEY et al., 2017). Entre os fatores ambientais podem ser destacados momentos estressantes para estes animais como, por exemplo, desmame, mudanças de alimentação, transporte, ventilação insuficiente e superlotação, o que aumenta a susceptibilidade de transmissão de patógenos (SAEGERMAN et al., 2021).

As infecções bacterianas comumente ocorrem por *Mycoplasma bovis*, *Mannheimia haemolytica, Pasteurella multocida* e *Histophilus somni*, sendo que estes três últimos agentes são comensais no trato respiratório superior de animais saudáveis, tornam-se oportunistas quando a defesa do animal é comprometida eacabam colonizando o trato respiratório posterior (TIMSIT et al., 2013; NICOLA et al., 2017; CIRONE et al., 2019). Já os agentes virais, são o Herpesvírus Bovino tipo 1 (BoHV-1), Vírus Sincicial Respiratório Bovino (VSRB), Coronavírus (BCov), Parainfluenza Bovino tipo 3 (BPI-3V) e Vírus da Diarreia Viral Bovina (BVDV) (HEADLEY *et al*., 2017). Além destes, segundo estudos de sequenciamento, o Vírus Influenza D faz parte da lista de patógenos que causam a DRB (HAUSE et al., 2013; MITRAN et al., 2016).

Os sinais clínicos da DRB incluem febre, apatia, isolamento, anorexia, depressão e, em casos graves, secreção nasal e ocular, dispneia, tosse e salivação (APLEY et al., 2006). Segundo estudo de WHITE & RENTER (2009) a sensibilidade de detecção baseada nos sinais clínicos encontrados foi de 62%, o que nos mostra que muitos casos não são detectados, ou são detectados em estados graves.

Durante vários anos, a metafilaxia com antimicrobianos tem sido uma prática comum adotada para reduzir a morbidade e a mortalidade (HOLMAN et al., 2017). No entanto, considerando a necessidade mundial de reduzir o uso de antibióticos é essencial a utilização de outras estratégias para a mitigação da DRB e, para este propósito, estratégias nutricionais alternativas têm sido pesquisadas (VILLENA et al., 2018).

A microbiota do intestino afeta o sistema imunológico sistêmico, assim como é influenciada pelo sistema imunológico da mucosa, sendo então o trato gastrointestinal (TGI) considerado o maior órgão imunológico do organismo (CHASE, 2018). MATEER et al. (2015) relataram que o microbioma respiratório é influenciado pelo microbioma intestinal, sendo descrita esta interação intestino-pulmão em bovinos (CHASE, 2018), humanos (RASTOGI et al., 2022) e aves (SAINT-MARTIN et al., 2022). LIU et al. (2022) demonstraram que, por exemplo, prebióticos e probióticos são capazes de modular a resposta imunológica sistêmica através da sua absorção intestinal.

Os probióticos são microrganismos vivos que, quando administrados em quantidades adequadas, conferem benefícios à saúde do hospedeiro (ASHRAF & SHAH, 2014), sendo classificados em bactérias produtoras de ácido lático (*Lactobacillus, Bifidobacterium e Enterococcus*), leveduras e espécies de *Bacillus*

formadoras de esporos (GIBSON et al., 2017). Estes, podem se ligar, por exemplo, aos receptores de reconhecimento padrão, como é o caso dos receptores toll-like (TLR) que são expressos em células imunes e regulam importantes vias de sinalização (PALM et al., 2015). A resposta imune inata pode ser ativada, resultando na produção de citocinas ou quimiocinas pró e anti-inflamatórias (METZGEr et al., 2018). Já os prebióticos são um substrato seletivamente utilizado por microrganismos dos hospedeiros, conferindo benefício à saúde (GIBSON et al., 2017). Estes, podem contribuir com a regulação da resposta imune através da inibição das citocinas pró-inflamatórias, estimulando as citocinas anti-inflamatórias e, promovem também a ativação de células imunes como macrófagos, células *natural killer* (NK), e linfócitos T e B (LIU et al., 2022). Além dos pré e probióticos, os microminerais como Cr, Co, Cu, I, Fe, Mn, Mo, Ni, Se e Zn, e macrominerias como Ca, Cl, P, K, Na, Mg e S, possuem funções significativas nas vias homeostáticas e metabólicas, no equilíbrio oxidativo e nas respostas imunológicas (PALOMARES, 2022). Com relação as vitaminas, as pesquisas se concentram no seu papel imunológico e no seu papel antioxidante (KEGLEY et al., 2016).

Estas alternativas nutricionais podem ser utilizadas na prevenção de doenças respiratórias, com resultados em humanos e animais (KACZYNSKA et al., 2022; MANZOOR et al., 2022; GALYEAN et al., 2022). Em bovinos de corte, os efeitos ainda são pouco explorados. Por isso, este estudo se faz necessário, pois, até o momento e conforme nosso conhecimento, não há uma revisão sistemática sobre o uso de suplementos alimentares na prevenção e controle da DRB.

2 Objetivos

2.1 Objetivo geral

Trazer estudos com alternativas para o aumento da produtividade na bovinocultura de corte, com foco nos efeitos da utilização de suplementos alimentares (probióticos, prebióticos, vitaminas e minerais) sobre a ocorrência de doença respiratória bovina.

2.2 Objetivos específicos

- Realizar uma revisão sistemática sobre estudos conduzidos no mundo utilizando suplementos alimentares para mitigação das doenças respiratórias em bovinos de corte de todas as categorias;
- Analisar os efeitos destes suplementos alimentares na imunidade e na saúde destes animais.

3 Artigo

Bovine Respiratory Disease in beef cattle under intensive and semi-intensive systems: a systematic review on the effects of nutritional supplementation

Gabriele Santos Mocellin; Marcio Nunes Corrêa; Eliza Rossi Komninou; Thaís Casarin Barbosa; Uriel Secco Londero; Francisco Augusto Burkert Del Pino; Viviane Rohrig Rabassa

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Abstrat

Bovine Respiratory Disease (BRD) is a significant condition in animal production, particularly in feedlot cattle. Prevention and treatment generally rely on antimicrobials. Nonetheless, alternatives are necessary to reduce antimicrobial usage. Therefore, this systematic review discusses the use of dietary supplements in prevention and treatment strategies for BRD. The present review explores the use of probiotics, prebiotics, vitamins, and minerals for preventing and controlling BRD in beef cattle under intensive and semi-intensive management. Published studies were retrieved from three different databases: PubMed, Scopus, and Web of Science. Overall, the results highlight the potential of dietary supplements in improving bovine respiratory health and immune response. However, results varied between studies depending on the combination of supplements, dosage, and timing of administration. Saccharomyces cerevisiae was the most researched probiotic regarding its effects on bovine health. In conclusion, supplementation with yeasts, bacteria, minerals, and vitamins shows considerable potential for improving bovine respiratory health and the immune response.

Keywords: cattle health; probiotic; prebiotic; minerals; immunity.

Introduction

According to UN estimates, the global population will reach 9.9 billion by 2054 [(1)]. Consequently, the demand for animal-based food is expected to grow significantly. According to the DSM report [(2)], approximately 60 million cattle are feedlot-finished annually. This can lead to increased morbidity and mortality due to overcrowding, stress, transportation, dietary changes, among other factors affecting the health and well-being of these animals [(3)].

Stress is a complex biological response triggered by external stimuli to maintain or restore homeostasis and is a crucial factor in immune impairment [(4)]. The hypothalamic-pituitary-adrenal (HPA) axis is activated by stress and alters the production of hormones such as catecholamines, vasopressin, adrenocorticotropic hormone (ACTH), glucocorticoids, and growth hormone (GH), all of which influence immune function [(5)]. In acute stress situations, these hormones are beneficial to the immune response; however, under chronic stress, they can cause hormonal imbalances and impair immune function, leading to infection, including Bovine Respiratory Disease (BRD) [(6)].

BRD is a multifactorial disease, and a compromised immune response in cattle is the main triggering factor [(7)]. BRD can be caused by viral agents such as Bovine Herpesvirus type 1

(BoHV-1), Bovine Respiratory Syncytial Virus (BRSV), Coronavirus (BCoV), Bovine Parainfluenza Virus type 3 (BPI-3V), and Bovine Viral Diarrhea Virus (BVDV) as well as bacterial agents such as *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni,* and *Mycoplasma bovis*. Infections may involve multiple agents, with a primary viral infection of the respiratory tract predisposing animals to secondary bacterial infections [(8)]. BRD remains one of the main health challenges in cattle production, causing significant economic losses in the global beef industry, with estimated annual costs ranging from 800 to 900 million USD in the United States [(9)] and 11.85 million USD in Brazil [(10)].

Vaccines and antimicrobials are widely used to prevent and treat BRD [(11)]. However, there is a global effort to reduce metaphylactic antimicrobial usage due to rising antimicrobial resistance [(12)]. Recent projections indicate that by 2050, antimicrobial resistance (AMR) could be responsible for up to 10 million deaths annually worldwide, significantly impacting animal and human health [(13)].

The effectiveness of vaccines can also be compromised when administered at the time of feedlot entry due to the stress experienced by the animals at that moment. Vaccine-induced immunity may take 14 to 21 days to develop. Furthermore, many feedlots use metaphylactic antimicrobial treatments, which can interfere with vaccine efficacy [(14)]. These significant concerns warrant the optimization and use of alternative therapies, including dietary supplements, to support BRD prevention and control.

The gastrointestinal tract (GIT) the largest immune organ in the body comprised of the gut microbiome and the mucosal immune system [(15)]. Furthermore, the respiratory microbiome is influenced by the gut microbiome [(16)], and this gut-lung interaction is described in cattle [(15)], humans [(17)], and poultry [(18)]. Prebiotics and probiotics can modulate the systemic immunity through their intestinal absorption [(19)]. Additionally, mineral and vitamin supplementation, including vitamins C and E, plays a crucial role during critical production stages as these are essential components and cofactors of enzymes that drive immunity and antioxidant protection [(20, 21)].

This systematic review explores the use of dietary supplements, such as probiotics, prebiotics, vitamins, and minerals for BRD prevention and control in beef cattle under intensive and semi-intensive management.

Materials and Methods

Search Protocol

The protocol for this systematic review was based on the PRISMA 2020 [(22)] checklist. For

the literature search, the international databases PubMed, Scopus, and Web of Science were used, including the following terms: ("bronchopneumonia" OR "respiratory disease" OR "pneumonia") AND ("cattle" OR "beef cattle" OR "bovine" OR "cow" OR "calf" OR "steers" OR "heifers") AND ("feed additives" OR "probiotics" OR "prebiotics" OR "symbiotics" OR "fungi" OR "yeasts" OR "vitamins" OR "amino acids" OR "minerals" OR "Bacillus" OR "direct-fed microbial supplementation" OR "Lactobacillus" OR "Saccharomyces" OR "bacterial cultures" OR "nutritional supplements" OR "fermented feed" OR "functional feed ingredients"). All searches were conducted between June 2024 and April 2025. Initially, titles and abstracts were reviewed, and duplicate articles were excluded. Subsequently, the materials and methods sections were selected, and articles that did not meet the inclusion criteria were excluded.

To be included, articles had to meet the following criteria:

I. Published in the English language;
II. Published in peer-reviewed scientific journals;
III. Only beef cattle breeds;
IV. All categories of beef cattle;
V. Dietary supplementation with probiotics, prebiotics, symbiotics, minerals, or vitamins;
VI. Conducted in intensive systems (high animal density in smaller areas, with controlled feeding and intensive management) or pre-feeding/adaptation systems;
VII. Evaluation of BRD occurrence, with only the health and immune system parameters of the animals extracted from the articles.

Exclusion Criteria:

I. Languages other than English;
II. Reviews, abstracts, and conference presentations;
III. Duplicate articles;
IV. Undefined breed;
V. Articles focusing only on the disease assessment without the use of dietary supplements;
VI. Species and breeds other than beef cattle;
VII. Studies focusing solely on disease diagnosis;
VIII. *In vitro* studies;
IX. Outcomes related only to the use of antimicrobials, vaccines, and environmental factors;
X. Studies related to genomics, genetic variations, plasma metabolism, and microbiota;
XI. Studies not addressing the topic in question.

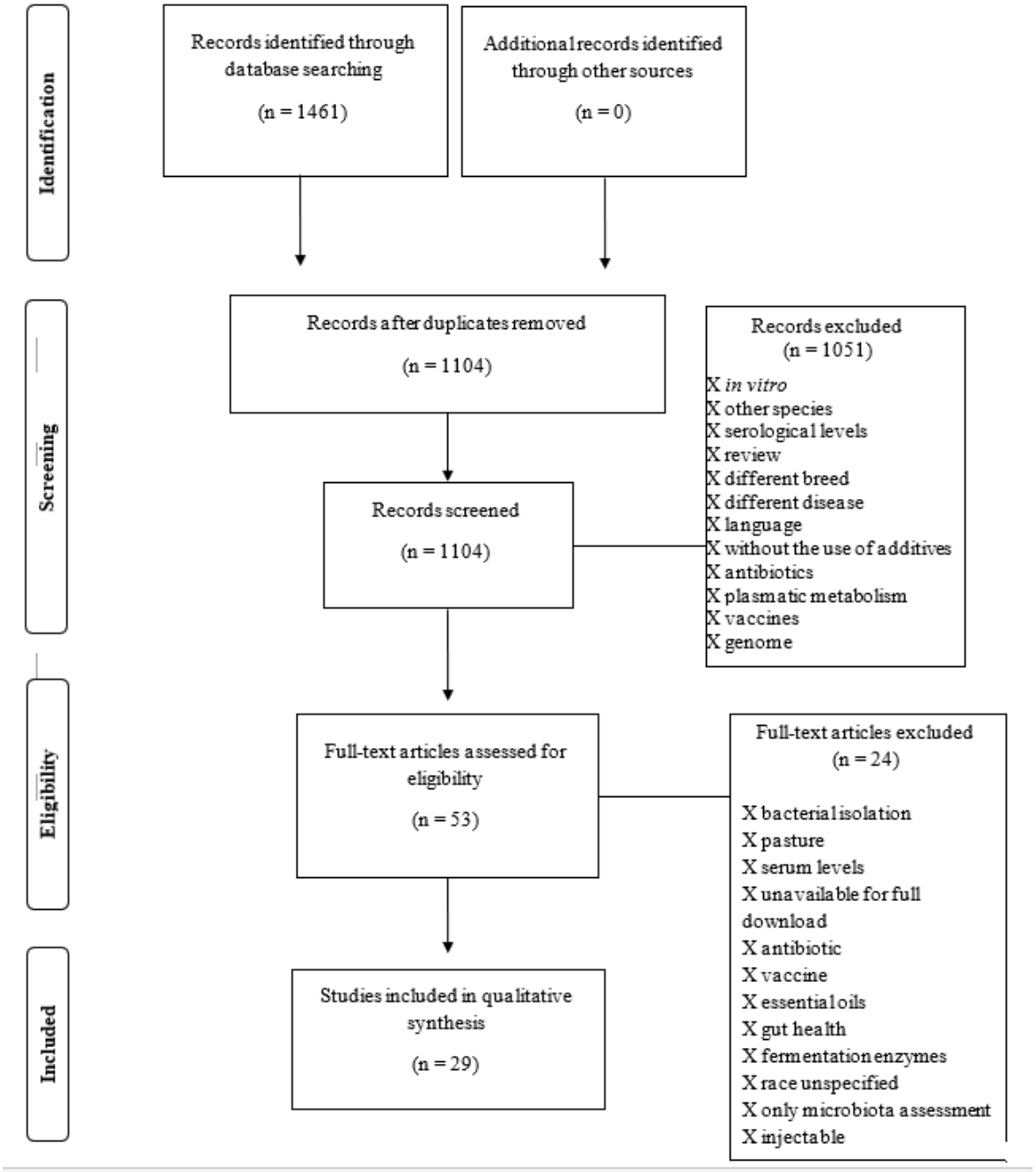
Following the described criteria and to avoid biases, two independent reviewers used the Rayyan software [23] to screen titles and abstracts. They also assessed the relevance of each study in addressing the research question and identified the eligibility criteria for inclusion in the final review, with a third person available to resolve conflicts [24]. Studies that did not meet the criteria or those lacking sufficient data to support the research question were excluded.

The obtained data were stored in a Microsoft Excel ® spreadsheet. Information regarding the dietary supplement used, animal category, study period, treatment, evaluations related to respiratory problems and immunity, and type of production system were tracked and tabulated.

1 Results

A total of 1,461 studies were identified, and after the initial screening for duplicate removal and evaluation of titles and abstracts, only 53 published manuscripts had their materials and methods section assessed. Of these, 29 were included in the review (Figure 1) and will be discussed according to the type of dietary supplementation used. The included studies were published between 1984 and 2024.

Figure 1 - PRISMA 2020 Flow Diagram for Identification and Selection of Records for the Systematic Review on the Use of Nutritional Supplements in Bovine Respiratory Disease



Fonte: Mocellin, Gabriele Santos, 2025.

The selected studies provided information on 16,882 animals, predominantly steers, followed by bulls, heifers, and cows, of taurine breeds (Angus, Hereford and their crosses, Simmental, Limousin, and Charolais). The experiments were conducted predominantly in the United States, followed by Brazil, Poland, Italy, Canada, and France. Regarding the production systems, 16,192 cattle were in intensive systems, 606 in pre-feedlot/adaptation systems, and 84

in both pre-feedlot and feedlot systems.

The types of supplements used were probiotics, prebiotics, minerals, and vitamins (https://docs.google.com/spreadsheets/d/1k1rT-ae-Axo4p6oJ1uT-uxnQbVoWmoEV/edit?gid=843932728#gid=843932728). The data extracted from the studies were only those related to the immunity and health of the cattle.

Discussion

Probiotics, Prebiotics, and Symbiotics

- **Yeasts**

The effects of yeast supplementation have been widely studied in bovine health, particularly focusing on reducing the incidence of respiratory diseases as yeast possess immunomodulatory effects[25, 26]. The majority of reviewed manuscripts used yeast, mainly *Saccharomyces cerevisiae*. Supplementation with fermented *S. cerevisiae* culture produced dose-dependent effects in feedlot steers. A dose of 28-g/animal/day elicited higher serum ceruloplasmin, interleukin (IL)-8, and haptoglobin than those elicited by 14 g/animal/day [27]. However, excessive or prolonged supplementation may lead to a harmful inflammatory state, resulting in damage to muscle and adipose tissues due to catabolism, potentially compromising animal performance and health [27]. Furthermore, the 14-g dose reduced inflammatory responses and improved feed efficiency and daily weight gain, highlighting the potentially harmful effects of inflammation on metabolism.

Fresh *S. cerevisiae* has also been used with beneficial effects on immunity and respiratory disease control [28]. Cattle supplemented with fresh yeast had greater phagocytic capacity, decreased frequency of mucopurulent nasal discharge, reduced incidence of lung lesions, and reduced haptoglobin levels compared to the control group. Live yeast modulates immunity and inflammation by reducing serum haptoglobin and neutrophil counts and increasing oxidative metabolism in phagocytes.

The effect of *S. cerevisiae boulardii*, was investigated in steers challenged with *Mannheimia haemolytica* [29]. Supplemented cattle showed a better immune response with increased immune cell counts – including T lymphocytes – enhanced neutrophil activity, and improved phagocytosis. Clinical signs of the disease were also reduced. Despite these promising results, few studies have been published with *S. cerevisiae boulardii*, highlighting the need for further research into alternative therapies to support BRD control.

Autolyzed yeast has been studied for its effects on immune function and reduction of

respiratory disease morbidity in feedlot cattle. The effects of autolyzed *S. cerevisiae* at doses of 4 or 7 g have been evaluated [30]. Animals receiving 4 g exhibited improved cellular immune efficiency, reduced inflammation, and fewer clinical cases of BRD compared to the control group. Additionally, the supplemented groups (4 or 7g) had fewer cases of mucopurulent nasal discharge and a lower occurrence of pneumonia when compared to the control group. Animals that received 7 g also showed better immune efficiency and lower BRD indicators compared to the control group. However, supplementation with 4 g resulted in fewer animals with inflammatory infiltrates in the lungs. The findings of this study indicate a positive effect on the respiratory health of feedlot cattle, improving immune response and reducing the incidence and severity of pneumonia. Autolyzed yeast acts on immunity through cellular components such as β-glucans and mannan-oligosaccharides, which can activate macrophages, stimulating phagocytic activity, reactive oxygen species production, and gene expression of immune pathways [31]. Furthermore, bronchoalveolar macrophage activation decreases susceptibility to BRD [32].

Different forms of *S. cerevisiae* supplementation have been compared, including live yeast culture versus lysed (inactivated or disrupted) yeast. Live *S. cerevisiae* culture elicited an improved immune response and a reduction in BRD cases and increased phagocytic cell activation in neutrophils and macrophages. The lysed form had a more pronounced effect on intestinal health, promoting increased villus height in the duodenum and jejunum and increased villus:crypt ratios in the duodenum, thereby improving nutrient absorption efficiency [33]. Therefore, supplementation *S. cerevisiae* can be tailored depending on the specific needs of each heard.

Live *S. cerevisiae* supplementation did not result in significant changes in the immune response of cattle facing BRD challenges [34]. The study showed no reduction in vaginal temperature and no significant differences in concentrations of non-esterified fatty acids (NEFA), cortisol, and haptoglobin. However, they did find less severe nasal mucosal lesions compared to those in the control group and lower concentrations of circulating neutrophils in the yeast-supplemented group. These results highlight the significant correlation between vaginal temperature and immune challenges [35], indicating an active immune response during the study. Regarding NEFA concentrations, the cattle had to meet the energy demands of the immune system, which explains the lack of significant differences between groups. The heifers in the study experienced stress due to handling, resulting in increased cortisol levels that decreased after adaptation. Furthermore, the haptoglobin data were collected 6 days after BHV-1 inoculation, which may not have been sufficient time to accurately measure the haptoglobin

response. Finally, the neutrophils were activated in the tissue, which may have contributed to the immune response observed in the study.

Pukrop *et al.* [36] supplemented 13 grams/day of lysed yeast rich in mannan and hydrolyzed glucan. The results suggest an improvement in overall health and a better response to immune stress, illustrated by a decrease in serum IL-6 and rectal temperature, along with an increase in serum concentrations of interferon gamma (IFN-γ) in steers after a lipopolysaccharide (LPS) challenge. These effects are attributed to β-glucan and mannan, which act as immunomodulators and improve the intestinal environment and antioxidant capacity [37].

Supplementation with a commercial yeast derivative (*S. cerevisiae* cell walls, the growth medium, and an undetermined number of live yeast cells), at a dose of 14 g across two phases (pre-feedlot and feedlot), resulted in a reduced incidence of BRD during the pre-feedlot phase. This underscores the usefulness of this nutritional strategy, especially in stressful situations where BRD morbidity and mortality are higher. Another study also observed a reduction in BRD morbidity using the same product, a result attributed to the yeast's beneficial immunomodulatory effects, which act on phagocyte function and improve the inflammatory response [39]. However, a higher dose of this commercial yeast supplement (58.8 g/day) did not affect the animals treated for BRD nor reduce antimicrobial treatment costs in newly received calves [40]. This is consistent with findings that yeast-derived β-glucans increase pro-inflammatory cytokines (IL-8, TNF-α, IL-1β, IL-6) (27, 41). Further research emphasizes the importance of supplementation prior to arrival at the feedlot to reduce the incidence of respiratory diseases [38]. Importantly, variations in product composition, management conditions, and animals health can influence the outcomes.

- **Bacteria**

Bacillus subtilis PB6 supplementation at a dose of 0.5 g/steer/day decreased morbidity in treated steers [42]. This was attributed to the immunomodulatory, anti-inflammatory, and balancing of the gut microbiome elicited by *B. subtilis* PB6. Conversely, a higher dose of *B. subtilis PB6* in a different study (13 g/animal) did not improve the health of steers, although reduced statistical power may have concealed statistical differences between groups [43]. Supplementation with *Bacillus* sp. induced both humoral and cellular immune responses, positively influencing the development of innate and adaptive immunity [44]. Additionally, increased secretion of pro-inflammatory cytokines (TNF-α, IFN-γ, IL-1β, IL-6, IL-8, and IL-12) promoted a beneficial inflammatory response.

- **Yeast and Bacteria Combined**

In studies combining yeast and bacteria, our search identified two articles, both of which used Bacillus species. Young *et al.* [45] evaluated a yeast fraction derived from *S. cerevisiae* and multi-species *Bacillus* products (*B. amyloliquefaciens, B. subtilis, B. licheniformis, and B. pumilus*) either individually or in combination. A lower percentage of respiratory disease was observed in cattle supplemented with *Bacillus* spp. alone. All individually supplemented groups showed health and growth benefits; however, no additional benefits were observed when yeast and bacteria were used simultaneously, which may be explained by a lack of synergy between the supplements. In contrast, in another study, the combination of *B. subtilis* and yeast derivatives elicited an improved response to BRD treatment and reduced removal from the experiment, suggesting greater immunocompetence [46]. These differences may be due to environmental factors, animal variability, yeast formulation, and differences in the doses used.

Minerals

Seven articles addressing the use of mineral were included in this review, with most of them comparing organic and inorganic sources of minerals.

In pre-feedlot cattle, organic and sulfate-based sources of Cu, Co, Mn, and Zn were evaluated in two separate studieswith varying results [47, 48]. In the experiment by Lippolis *et al.* [47], at a dose of 2.7 Kg/animal on a dry matter basis — either organic or inorganic sources — there was no impact on morbidity and mortality during the treatment period in the feedlot (58 days). The results suggest that for animals with adequate mineral levels, additional supplementation does not result in substantial benefits to performance and health, which may be different for animals with mineral deficiencies or in situations with greater health challenges. In contrast, animals supplemented with minerals in the organic form showed reduced plasma levels of haptoglobin and cortisol, indicating that the supplementation may have modulated the stress response; however, this organic supplementation was not significant in reducing BRD [48].

In feedlot heifers, the effects of different sources (copper sulfate and zinc sulfate, copper sulfate and zinc polysaccharide mineral complex, and copper and zinc chelate) of copper (10 mg/kg) and zinc (75 mg/kg) were evaluated in a 65% concentrate diet [49]. No differences in morbidity were observed between the groups receiving sulfate or polysaccharide complex sources. However, the source used had an impact on immunoglobulin (Ig) G levels, highlighting the importance of immune modulation, thereby improving the long-term health of the herd,

particularly concerning infections or immune stresses that may arise during critical periods. This effect occurs through the modulation of pro-inflammatory processes and the control of oxidative stress [50]. Additionally, these minerals influence T-cell-mediated immunity, cytokine production, and the activity of immune cells such as neutrophils and macrophages [51].

Vitamins

Six studies were found evaluating vitamin supplementation. Different doses of vitamin E (25 IU/kg DM, 500 IU per steer/day, and 1,000 IU per steer/day) influenced the antioxidant and immune responses of the steers [52]. At 500 IU per steer/day, there was an increase in the activity of superoxide dismutase (SOD). However, the pharmacological dose (1,000 IU per steer/day) had a negative effect on the antibody titers against BVDV, suggesting that excessive dosing could impair some immune responses. Another study showed that supplementation with 1,140 IU of vitamin E/day increased circulating antibodies against foreign antigens, improving the humoral immune response [53]. However, in the study by Stanford *et al.* [54], vitamin E supplementation, despite its antioxidant properties, did not have significant effects on the severity of acute interstitial pneumonia (AIP) or on the incidence of lung lesions. The study suggested that the isolated administration of vitamin E is not sufficient to fully neutralize the oxidative stress caused by free radicals in a disease like AIP.

Carter *et al.* [55] observed that supplementation with vitamin E had positive effects on calves in terms of morbidity, particularly BRD, with higher α-tocopherol status in the blood. This increase suggests a greater antioxidant capacity and enhanced potential to combat infections, as vitamin E is an antioxidant and plays a key role in mitigating the damage caused by free radicals.

The impact of combining vitamins E and C with antibiotics (florfenicol) and anti-inflammatory drugs (flunixin meglumine) on oxidative stress and inflammation was evaluated in feedlot calves [56, 57]. Administration of these vitamins, along with antibiotics and anti-inflammatory drugs, helped reduce oxidative stress and inflammation, with positive effects on leukocyte defence against *M. haemolytica.*

Association of different feed supplements

- **Yeasts and Minerals**

The literature search yielded 3 studies employing yeast combined with minerals, two of which involved the use of *S. cerevisiae* and selenium.

Supplementation with a nutraceutical blend of live yeast (*S. cerevisiae* CNCM-I3399, 5 g/animal/day), organic selenium (3 mg/animal/day), and mannan oligosaccharides (10 g/animal/day) reduced the incidence of BRD due to a significant improvement in immune defences [58]. This included an increase in antibody responses following vaccination and improved inflammatory responses and antioxidant effects. Consistent results were obtained when using *S. cerevisiae* CNCM-I3399 enriched with selenium (3 mg/animal/day of sodium selenite in the control group and 2 mg/day of selenium in the treatment group), which improved immune function and antioxidant status in newly received steers [59]. This showed to be a useful strategy to combat the negative effects of stress, which typically affect this category. Supplemental chromium from a chromium-rich yeast source (2 mg of Cr/g of yeast) improved immune competence as based on clinical signs and serum Ig levels (IgG1, IgG2, and IgM) with higher phagocytic activity and, consequently, a reduction in the incidence of infections.

- **Yeasts, Minerals, and Vitamins**

Regarding the use of yeasts, minerals, and vitamins in combination, one study, by Lippolis *et al.* [61], was found. This study used three distinct treatments: i) control group, ii) supplementation with active dry *S. cerevisiae* and other additives (derived from *Trichoderma longibrachiatum* fermentation, vitamins, and minerals), and iii) supplementation with products based on transfer factor proteins (extracted from bovine colostrum and egg yolks, plant-derived heteropolysaccharides, lactate-producing probiotics, vitamins, and minerals) for 30 days in confined steers. The treatments with *S. cerevisiae* or transfer factor proteins did not reduce the incidence of BRD. This could be explained by the lack of an adaptation period before immune stress and the potential ruminal degradation of certain components (such as transfer factor proteins), which may have contributed to the ineffectiveness.

- **Bacteria and Minerals**

One study was found evaluating the association of bacteria and minerals [62]. This study investigated the effects on clinical signs of BRD when *B. subtilis* PB6 (13g/animal/day) and chromium propionate (450 ppb/animal/day) were administered separately or together in 384 confined cows. *B. subtilis* PB6 and chromium propionate reduced the incidence of BRD when provided separately. *B. subtilis* PB6 had more influence at the beginning of its use, not extending until the end of the confinement period, suggesting that its effect may be more pronounced during periods of higher stress. The combination of *B. subtilis* PB6 and chromium propionate did not present superior benefits compared to their isolated use, with no significant

synergistic effect.

- **Minerals and Vitamins**

Regarding the use of minerals and vitamins together, we found the study by Vanbergue *et al.* [63], using calves in pre-feeding, with the control group on pasture and one group supplemented with micronutrients (Zn = 200 mg/kg, Se = 0.7 mg/kg, Cu = 25 mg/kg), vitamins, and plant extracts. Nonetheless the treatments in this study were ineffective in improving respiratory health. The lack of a positive response may be attributed to several factors, such as the dosage, as nutritional needs vary according to age, health status, and management conditions. Additionally, the combination of nutrients and plant extracts may not have been the most suitable to maximize benefits. Future research is needed to enhance the understanding of the factors influencing the response and develop more effective protocols.

Conclusion

Based on the studies included in this systematic review, supplementation with yeast, bacteria, minerals, and vitamins demonstrated considerable potential for improving respiratory health and immune response in beef cattle in intensive and semi-intensive systems. However, the results were varied depending on the dose, combination of supplements, and timing of administration. Furthermore, the associations between them, with a wide variety of products used in treatments (such as probiotics, transfer proteins, and minerals), may not be as synergistic as expected. Therefore, further research is needed in specific contexts to clarify the underlying mechanisms and allow optimization of these supplements in different beef cattle production scenarios including intensive and semi-intensive systems.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

Equal contribution: These authors contributed equally to this work.

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4 Considerações Finais

A crescente demanda por carne bovina, impulsionada pelo aumento da população mundial, coloca a pecuária de corte em uma posição estratégica para atender a esses desafios. Os resultados da revisão sistemática mostraram que a suplementação nutricional apresenta um grande potencial para melhorar a saúde respiratória dos bovinos, com especial destaque para os probióticos, prebióticos e minerais orgânicos. Porém, ainda existem lacunas que precisam ser pesquisadas sobre essas alternativas nutricionais, sendo essenciais para o contínuo aprimoramento da bovinocultura de corte.

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