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Dissertação

**Suplementação de leveduras e *Aspergillus oryzae* para vacas leiteiras: uma meta-análise.**

**Melina Calegaro Tamiozzo**

Pelotas, 2021

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**Suplementação de leveduras e *Aspergillus oryzae* para vacas leiteiras: uma meta-análise.**

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*“Você nunca poderá cruzar o oceano até ter coragem de perder a costa de vista.”- Cristovão Colombo*

*“Nada se inventaria se nos sentíssemos satisfeitos com as coisas descobertas.” - Sêneca.*

## Resumo

TAMIOZZO, Melina Calegaro. **Suplementação de leveduras e *Aspergillus oryzae* para vacas leiteiras: uma meta-análise.** 2021. 73f. Dissertação (Mestrado em Zootecnia) - Programa de Pós-Graduação em Zootecnia, Faculdade de Agronomia Eliseu Maciel, Universidade Federal de Pelotas, Pelotas, 2021.

Os avanços na nutrição de ruminantes demandam novas estratégias nutricionais, para que os efeitos benéficos sejam aprimorados e os deletérios minimizados ou excluídos. Como estratégia tem-se adotado o uso de aditivos alimentares. Desta forma, os aditivos reguladores da flora intestinal, como os probióticos e prebióticos tornam-se uma alternativa ao uso dos antibióticos na nutrição de ruminantes. Existem muitos estudos avaliando os efeitos do uso de probióticos, prebióticos na alimentação de bovinos leiteiros, principalmente utilizando leveduras vivas do gênero *Saccharomyces cerevisiae*, bem como parede celular e extrato de fermentação de *Aspergillus oryzae*. Apesar disso, os resultados observados ainda são distintos e controversos. Portanto um estudo meta-analítico em relação ao assunto abordado pode auxiliar na constituição de alguns conceitos e melhor estabelecê-los. Assim, o objetivo foi o de avaliar através de uma meta-análise os benefícios do uso de leveduras vivas do gênero *Saccharomyces cerevisiae* (LY), produtos da fermentação de leveduras (SCFP) e extrato de fermentação de *Aspergillus oryzae* (AO) na dieta de vacas leiteiras, bem como, qual o melhor aditivo para melhorar parâmetros ruminais, desempenho e saúde dos animais. Para isso, foram compilados 116 estudos que avaliaram a ingestão, parâmetros ruminais e de digestibilidade dos nutrientes e produção e composição do leite de vacas leiteiras suplementadas ou não com esses aditivos. Observou-se que a produção de leite de vacas suplementadas com LY aumentou 7,08% frente às vacas não suplementadas ( $P<0,0001$ ), bem como reduziu a perda de leite durante a lactação em 44,54% ( $P<0,05$ ). Ainda, gordura, sólidos totais, sólidos não gordurosos e lactose do leite também foram aumentados com a suplementação de LY, enquanto que a contagem de células somáticas foi reduzida em 39,8% ( $P<0,05$ ). A digestibilidade aparente da fibra em detergente neutro e proteína bruta da dieta foram aumentadas pela adição de LY, porém, aumentos na concentração de ácidos graxos voláteis no rúmen não foram observados por nenhum dos tratamentos. Ainda, o consumo de matéria seca foi aumentado em 1,07% com a suplementação de AO comparada aos outros tratamentos. Desta forma, pode – se inferir que a suplementação com LY é a melhor opção entre os aditivos avaliados para melhorar parâmetros ruminais e de digestibilidade, e o desempenho de vacas leiteiras.

**Palavras-chave:** *Saccharomyces cerevisiae*; *Aspergillus oryzae*; prebióticos; nutrição; bovinos leiteiros.

## Abstract

TAMIOZZO, Melina Calegaro. **Supplementation of yeasts and *Aspergillus oryzae* for dairy cows: a meta-analysis**. 2021. 73f. Dissertation (Master Degree in Zootecnics) - Programa de Pós-Graduação em Zootecnia, Faculdade de Agronomia Eliseu Maciel, Universidade Federal de Pelotas, Pelotas, 2021.

Advances in the ruminant nutrition demand new nutritional strategies, so that the beneficial effects are improved and the deleterious ones are minimized or excluded. As a strategy, the use of feed additives has been adopted. In this way, additives for intestinal flora regulators, such as probiotics and prebiotics, become an alternative to the use of antibiotics in ruminants' nutrition. There are many studies evaluating the effects of the use of probiotics and prebiotics in dairy cattle feeding, mainly using live yeasts of the genus *Saccharomyces cerevisiae*, as well as cell wall, and *Aspergillus oryzae* fermentation extract. Despite this, the results observed are still controversial. Therefore, a meta-analytical study in relation to the subject addressed can assist in the constitution of some concepts and better establish them. Thus, the objective was to evaluate through meta-analysis the benefits of using live yeasts of the genus *Saccharomyces cerevisiae* (LY), yeast fermentation products (SCFP) and fermentation extract of *Aspergillus oryzae* (AO) in the diet of dairy cows, as well as, which is the best additive to improve ruminal parameters, performance and animal health. For that, 116 studies were compiled that evaluated the intake, ruminal parameters and digestibility of nutrients and milk production and composition of dairy cows supplemented or not with these additives. It was observed that the milk production of cows supplemented with LY increased 7.08% compared to non-supplemented cows ( $P < 0.0001$ ), as well as reduced losses during lactation by 44.54% ( $P < 0.05$ ). In addition, fat, total solids, solids not fat and milk lactose were also increased with LY supplementation, while somatic cell counts were reduced by 39.8% ( $P < 0.05$ ). The apparent digestibility of the neutral detergent fiber and crude protein in the diet was increased by the addition of LY, however, increases in the concentration of volatile fatty acids in the rumen were not observed by any of the treatments. In addition, dry matter intake was increased by 1.07% with AO supplementation compared to other treatments. Thus, it can be inferred that supplementation with LY is the best option among the additives evaluated to improve ruminal and digestibility parameters, and the productive efficiency of dairy cows.

**Key words:** *Saccharomyces cerevisiae*; *Aspergillus oryzae*; prebiotics; nutrition; dairy cows.

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## **Capítulo 1.**

### **1. Introdução**

A vaca é atualmente, o principal animal doméstico usado para a produção de leite, o qual está presente na alimentação de 80% da população. A produção mundial de leite aumentou 339 milhões de toneladas entre os anos de 1998 e 2018 e apenas cinco países produzem 47% do total do leite no mundo, estando o Brasil na quarta posição seguido da Alemanha, ficando atrás da Índia, Estados Unidos e Paquistão (ROCHA e CARVALHO, 2020).

No Brasil, o Instituto Brasileiro de Geografia e Estatística (IBGE, 2020) aponta que em 2020 foram adquiridos pela indústria 25,5 bilhões de litros de leite, e o Sul do país (Paraná, Santa Catarina e Rio Grande do Sul) continua sendo a maior região produtora de leite. Mesmo em crescimento, a cadeia produtiva do leite tem experimentado importantes transformações nas últimas décadas, acompanhada de desafios e da intensa modernização do setor. Dessa forma, os avanços na nutrição dos rebanhos leiteiros tornam-se ferramentas importantes para o aumento de produção, aliando máximo desempenho dos animais com saúde e bem estar. Assim, o uso de aditivos na nutrição de ruminantes é uma estratégia na busca por melhores resultados.

Os aditivos são considerados substâncias adicionadas intencionalmente às dietas dos animais, com objetivo de melhorar seu desempenho (BRASIL, 2009). A classe dos antibióticos é usada, em sua grande maioria, para melhorar os parâmetros de produtividade dos animais, sendo o principal foco de discussões, especialmente em relação à segurança alimentar humana. O uso de antibióticos na nutrição animal já é banido na União Europeia, mesmo que os utilizados na terapêutica humana não sejam os mesmos utilizados como aditivos (BERTECHINI, 2012). Essa discussão abriu caminho para a utilização de aditivos alternativos com finalidade antimicrobiana e promotora de desempenho, como os prebióticos e probióticos, porém, a literatura ainda não é clara quanto aos seus efeitos na nutrição de vacas leiteiras (SUN et al, 2017; DESNOYERS et al., 2009; CHIQUETTE, 1995).

## **2. Objetivos**

### **2.1 Geral**

Avaliar através de um estudo meta-analítico os benefícios da suplementação de prebióticos e probióticos na dieta de vacas leiteiras.

### **2.2 Específicos**

- Avaliar o efeito da suplementação de prebióticos e probióticos na produção e composição do leite de vacas em lactação, bem como consumo de matéria seca e escore de condição corporal;
- Avaliar o efeito da suplementação de probióticos e prebióticos sobre os parâmetros ruminais e de digestibilidade de dieta de vacas em lactação;

## **3. Hipótese**

### **3.1 Nula**

A suplementação de leveduras e *Aspergillus oryzae* não influencia a produção e composição do leite, e o consumo de vacas leiteiras, bem como parâmetros ruminais e de digestibilidade.

### **3.2 Alternativa**

A suplementação de leveduras e *Aspergillus oryzae* influencia de forma positiva a produção e composição do leite, e o consumo de vacas leiteiras, bem como parâmetros ruminais e de digestibilidade.

## **4. Revisão de Literatura**

### **4.1 Aditivos probióticos e prebióticos**

Segundo a Instrução Normativa 15/2009 do Ministério da Agricultura, Pecuária e Desenvolvimento, aditivo pode ser “*substância, microorganismo ou produto formulado,*

*adicionado intencionalmente aos produtos, que não é utilizada normalmente como ingrediente, tenha ou não valor nutritivo e que melhore as características dos produtos destinados à alimentação animal ou dos produtos animais, melhore o desempenho dos animais sadios e atenda às necessidades nutricionais ou tenha efeito anticoccidiano*“. Além disso, os aditivos utilizados na alimentação animal são classificados pela Instrução Normativa 13/2004 do Ministério da Agricultura, Pecuária e Desenvolvimento de acordo com suas funções e propriedades em:

- Tecnológicos: substância adicionada ao produto destinado à alimentação animal com fins tecnológicos, a fim de manter ou melhorar propriedades físicas (adsorvente, aglomerante, antiaglomerante, antioxidante, antiumectante, conservante, emulsificante, estabilizante, espessantes, gelificantes e umectante);
- Sensoriais: substância adicionada ao produto para melhorar ou modificar as propriedades organolépticas destes ou as características visuais dos produtos (corantes e pigmentantes, aromatizantes e palatabilizantes);
- Nutricionais: substância utilizada para manter ou melhorar as propriedades nutricionais do produto (vitaminas, oligoelementos, aminoácidos e ureia);
- Zootécnicos: substância utilizada na promoção e melhoria do desempenho dos animais (enzimas, micro-organismos e ácidos orgânicos).

Durante décadas a comunidade acadêmica tem se dedicado ao estudo de como melhorar a eficiência produtiva de animais ruminantes, e atualmente, a adição de aditivos alimentares microbianos, denominados “*direct - fed microbials*” (DFM) vem sendo amplamente utilizado como aditivos melhoradores de desempenho reguladores da flora. O FDA (*Food and Drug Administration*), órgão do departamento de Saúde e Serviços Humanos dos Estados Unidos que controla os alimentos, cosméticos, medicamentos e dispositivos médicos define DFM como aditivo que contém microorganismos vivos (viáveis). No Brasil, o termo *probiótico* é usado para classificar aditivos com cepas de microrganismos vivos, o qual teve origem a partir das palavras gregas “pro” e “bios”, que significam “para a vida” (Gismondo et al., 1999); enquanto o termo prebiótico é designado para aditivos com ingredientes que não são digeridos pelas enzimas digestivas do hospedeiro, mas que são fermentados pela microbiota do

trato digestório dos animais, ambos contribuindo para a regulação da flora do hospedeiro (BRASIL, 2004).

A cadeia produtiva do leite vem usando DFMs principalmente com o objetivo de aumentar a produção de leite e melhorar a eficiência alimentar dos animais, ainda, atualmente o desenvolvimento desses aditivos para ruminantes vem sendo focado também para melhoria da saúde dos animais (LEHLOENYA et al., 2008; MAMMI et al., 2018). Porém, os resultados dos estudos com DFMs em vacas leiteiras ao longo dos anos, infelizmente ainda são inconsistentes, principalmente devido à falta de compreensão dos microrganismos utilizados, uma vez que as respostas podem variar amplamente com base no tipo de produto (ou seja, fúngico versus levedura; cultura viva versus extrato de fermentação, etc.) (WINDSCHITL, 1992). Bactérias, fungos e leveduras podem ser utilizados como aditivos alimentares microbianos probióticos, entretanto, os mais utilizados para animais ruminantes adultos são leveduras e fungos do gênero *Saccharomyces cerevisiae* e *Aspergillus oryzae*, respectivamente, bem como seus extratos e culturas (prebióticos).

## 4.2 Leveduras

As leveduras são fungos encontrados em grandes quantidades em quase todos os lugares do meio ambiente, tendo sido isoladas em água, solo, vegetais, mel (U.S. EPA, 1997) e estão naturalmente presentes em ingredientes alimentares comuns, como grãos, coprodutos de grãos, silagem e feno para alimentação de animais. Alguns gêneros de leveduras são conhecidos por serem patogênicos (*Candida*, *Cryptococcus*, *Torulopsis* e *Trichosporon*) (KANDEL e STERN, 1979), enquanto algumas espécies (*Saccharomyces cerevisiae*, *Kluyveromyces marxianus*, *Candida utilis*) fornecem efeitos benéficos (STONE, 2006).

Considerados microrganismos unicelulares, as leveduras medem cerca de 3-4 µm de tamanho. Possuem membrana nuclear e paredes celulares, mas, ao contrário das plantas, não contêm cloroplastos (BENNETT, 1998). Sua parede celular é composta por combinações de glucanos, glicoproteínas, mananas e quitina (ALEXANDRE e GUILLOUX-BENATIER, 2006; KOLLÁR et al., 1997). Além disso, as

leveduras são classificadas como fungos anaeróbicos facultativos, podendo sobreviver e se multiplicar na presença ou ausência de oxigênio (STONE, 2006). Em condições aeróbicas, as células convertem oxigênio e açúcares em dióxido de carbono e energia através do metabolismo oxidativo, e, já em condições anaeróbicas as leveduras são muito menos eficientes nesse processo, o que resulta na produção de etanol (BEKATOROU et al., 2006).

Atualmente as aplicações comerciais das leveduras são diversas e incluem produção de bebidas alcoólicas e não alcoólicas, panificação e suplementos alimentares. Existem hoje cerca de 60 gêneros diferentes de leveduras, que são compostos por cerca de 500 espécies diferentes, porém apenas algumas destas são usadas comercialmente. As espécies variam quanto a sua morfologia celular, uso de substrato como energia e metabolismo (STONE, 2006) e a mais utilizada como aditivo em dietas para animais de produção é a levedura seca ativa (*active dry yeast*). Para ser considerada cultura de levedura viva ou ativa, o aditivo deve consistir em produtos secos puros (95% de matéria seca (MS)) com alta concentração de células viáveis sem seu meio de cultura (LYNCH e MARTIN, 2002), variando de 15 a 25 bilhões de unidades formadoras de colônia por grama (UFC/g) (STONE, 2006; CHAUCHEYRAS-DURAND et al., 2008). A levedura seca ativa é produzida em biorreatores de cultura que fornecem substrato (oxigênio, nitrogênio e carboidratos), permitindo que as leveduras se multipliquem. Quando se alcança a concentração efetiva, o fermento é centrifugado, dando origem ao “creme de fermento”, que posteriormente é filtrado e seco a temperaturas que não prejudiquem o potencial fermentativo da levedura. Os métodos de processamento de secagem mais comuns são os realizados em túnel, dando origem a um pó granular; o realizado em leito fluido, que origina um produto em formato oval e é o mais amplamente utilizado por causar menos danos às células e manter sua viabilidade, e, ainda, o realizado em rotulouwer, que produz pequenas esferas (STONE, 2006).

A cepa de levedura mais utilizada e estudada mundialmente é a *Saccharomyces cerevisiae* e seu modo de ação já foi investigado em muitos experimentos. A primeira teoria é que a levedura estimula o crescimento da microbiota benéfica aos ruminantes de forma indireta (NISBET e MARTIN, 1991; ARAKAKI et al., 2000; ABD EL-GHANI,

2004, NEWBOLD, 1996), através da interação de mecanismos que envolvem a consumo de oxigênio, regulação de pH ruminal e produção de fatores de crescimento (VOHRA et al., 2016), como vitaminas do complexo B, ácidos orgânicos e aminoácidos (NISBET e MARTIN, 1991; ROSSI et al., 2004).

O rúmen é o principal local de digestão em ruminantes adultos e é considerado um ecossistema microbiano diverso e único (FURLAN et al., 2016; KOZLOSKI, 2019). Além disso, o rúmen representa o melhor sistema digestivo com rendimento bioquímico em condições anaeróbias e pH adequado, onde uma grande diversidade de protozoários ciliados, bactérias e fungos anaeróbicos são responsáveis pela degradação e fermentação de 70-75% dos nutrientes da dieta (CHAUCHEYRAS-DURAND E DURAN, 2010). Moléculas de oxigênio ( $60 \mu\text{mol/min/L}$  a  $100 \mu\text{mol/min/L}$ ) entram no rúmen através do alimento e da saliva e são tóxicas para os microrganismos ruminais, principalmente para bactérias celulolíticas (FURLAN et al., 2006). Dessa forma, a atividade respiratória de captação de oxigênio da levedura ( $200 \mu\text{mol/min/g}$  a  $300 \mu\text{mol/min/g}$ ) (BARFORD e HALL, 1979) no fluído ruminal impulsiona a melhoria das condições ruminais para os microrganismos (WALLACE, 1994). Newbold et al. (1996b) concluíram que uma cepa comercial de levedura viva teve a capacidade de remover de 46 a 89% do oxigênio introduzido no fluído ruminal incubado *in vitro* e estimular dessa forma o crescimento bacteriano. Como consequência, a adição de leveduras vivas parece aumentar o número de total de bactérias ruminais anaeróbicas (DAWSON et al., 1990; NEWBOLD et al., 1998), em especial bactérias celulolíticas (NEWBOLD et al., 1998) e protozoários no rúmen. O aumento da população de protozoários pode ser explicado pelo aumento do número de bactérias, que são usadas como fonte de proteína e energia pelos protozoários para seu crescimento (ARAKAKI et al., 2000). Ainda, Marden et al. (2013) descobriram mais tarde que a eliminação de oxigênio foi devido ao potencial redox reduzido do fluido ruminal, criando condições ambientais favoráveis no rúmen para o desenvolvimento da microflora anaeróbia.

A capacidade da levedura de estimular específicos grupos de bactérias é consistente (WIEDMEIER et al., 1987; CALLAWAY e MARTIN, 1997) e pode explicar também os efeitos na estabilização de pH ruminal, através da redução das concentrações de lactato no rúmen, reduzindo assim os efeitos negativos associados

com a acidose láctica. Sempre que há ingestão de alimentos, costuma-se observar declínios no pH ruminal devido à rápida fermentação dos componentes da dieta (NOCEK, 1997). Com o pH mais baixo, bactérias produtoras de ácido láctico, como o *Streptococcus bovis*, se desenvolvem mais do que usuárias de ácido láctico, ocasionando aumentos nas concentrações desse ácido. Quando o pH ruminal permanece baixo, ocorre redução da população microbiana, principalmente de espécies que degradam a fibra, particularmente sensíveis ao baixo pH, como *Fibrobacter succinogenes*, *Ruminococcus albus* e *R. flavfaciens* (RUSSELL e WILSON, 1996). Se o pH ainda estiver baixo, ocorre acidose metabólica devido ao acúmulo de lactato (RUSSELL e HINO, 1985). Marden et al. (2013) avaliaram a inclusão 4g de leveduras vivas nas dietas para indução de acidose de vacas holandesas não lactantes e observaram que a suplementação com leveduras vivas foi capaz de estabilizar o pH ruminal, devido ao menor acúmulo de lactato no rúmen. *Selenomonas ruminantium* são bactérias gram-negativas que utilizam lactato como substrato e parece ser estimulada pelo ácido málico (QUIGLEY et al., 1992; WALLACE, 1994) e vitaminas do complexo B e aminoácidos presentes na composição da levedura (NISBET e MARTIN, 1991). Por outro lado, Newbold et al. (1995), citado por Newbold (1996) testaram esta hipótese para comparar os efeitos da adição de levedura (4g) ou ácido málico (100g) sobre a fermentação ruminal em ovinos, e observaram aumento na contagem total de bactérias ruminais com uso da levedura, porém não com o uso de ácido málico, sugerindo que esse aumento nas concentrações de bactérias ocorreu em função da atividade respiratória das leveduras.

Além disso, algumas frações de leveduras se tornaram importantes na alimentação animal. A levedura pode ser fonte de selênio na dieta, estando geralmente na forma de seleniometionina, que é uma forma orgânica de selênio (Se), onde o Se substitui o enxofre na molécula de metionina (STONE, 2006). O Se é um micromineral essencial que está envolvido no sistema antioxidante do organismo, através da enzima glutathione peroxidase (GSH-px), que converte peróxido de hidrogênio em água (MILLER e BRZEZINSKA-SLEBODZINSKA, 1993). Gong et al. (2018) avaliaram os efeitos da suplementação de selênio orgânico oriundo de leveduras no estresse oxidativo e antioxidante de vacas leiteiras durante o pré-parto e concluíram que o Se

pode melhorar a função antioxidante e atenuar efetivamente o estresse oxidativo no início da lactação. Em contra partida, a atividade da GSH-px de vacas leiteiras de alta produção não foi influenciada pela suplementação de selênio levedura no estudo de Cerri et al. (2009). Ainda, a levedura pode fornecer cromo (Cr), que está presente na forma orgânica, ligado a aminoácidos, atuando junto com a insulina no metabolismo de carboidratos (LASHKARI et al., 2018). Em vacas leiteiras os resultados com a suplementação de cromo levedura ainda são inconsistentes e os estudos mostram-se divergentes em alguns parâmetros. A suplementação de cromo levedura na dieta de vacas Holandesas no terço médio da lactação aumentou a produção de leite sem interferir na sua composição, devido ao aumento no consumo de ração e eficiência na utilização de energia (AL-SAIADY et al., 2004). Mais recentemente, Shan et al. (2020) forneceram a vacas leiteiras também em terço médio de lactação 0,18, 0,36 e 0,54 mg de Cr levedura por quilo de MS gradativamente e observaram que o consumo de MS das vacas suplementadas aumentou conforme o aumento da dosagem de Cr, da mesma forma que a lactose do leite. Diferentemente do observado por Al-Saiady et al. (2004), a produção de leite não foi influenciada pela adição de Cr levedura na dieta, além das concentrações de glicose.

O efeito benéfico da suplementação com leveduras vivas na fermentação ruminal acaba influenciando de forma positiva, na maioria dos casos, a digestibilidade e a utilização dos nutrientes e, conseqüentemente, o desempenho dos animais. Esses efeitos parecem estar ligados principalmente a estabilização do pH e melhora no ambiente ruminal, proporcionando melhores condições para a atuação e desenvolvimento da microflora ruminal. Entretanto, Bakr et al. (2015) observaram redução no pH ruminal de vacas suplementadas com leveduras vivas. Eles concluíram que essa diminuição foi ocasionada em função do aumento da produção de ácidos graxos voláteis (AGVs), a qual foi atribuída à diminuição na produção de metano e conseqüente redução de perda de energia, disponibilizando energia para a síntese de AGV. Ainda, Jiang et al. (2017) não observaram nenhuma influência das leveduras vivas no pH ruminal, bem como na produção de AGVs.

Alguns estudos mostraram que a adição de leveduras vivas na dieta de vacas leiteiras não influenciou a digestibilidade da MS (SALVATI et al., 2015; EILERAS, 2019;

FERREIRA et al., 2019), da fibra em detergente neutro (FDN) (SALVATI et al., 2015; EILERAS, 2019; FERREIRA et al., 2019), do amido (BEDROSIAN, 2009; SALVATI et al., 2015; EILERAS, 2019; FERREIRA et al., 2019) e da PB (EILERAS, 2019; FERREIRA et al., 2019), bem como no pH ruminal (EILERAS, 2019), concentração de AGVs (BEDROSIAN, 2009; EILERAS, 2019), e consumo de MS das vacas suplementadas (SALVATI et al., 2015; JIANG et al., 2017; EILERAS, 2019). Por outro lado, aumentos no consumo de MS (BEDROSIAN, 2009) na digestibilidade da MS (BAGHERI et al., 2009; JIANG et al., 2017), da FDN (BAGHERI et al., 2009; JIANG et al., 2017), da fibra em detergente ácido (FDA) (JIANG et al., 2017), da hemicelulose (JIANG et al., 2017) e da PB (BAGHERI et al., 2009) também foram observados com a suplementação de leveduras.

Além disso, foram observados também resultados em que as leveduras vivas não influenciaram a produção de leite (ONDARZA et al., 2010; EILERAS, 2019; FERREIRA et al., 2019) e a composição do leite (EILERAS, 2019; FERREIRA et al., 2019). Entretanto, outros estudos mostram que a produção de leite (SALVATI et al., 2015; JIANG et al., 2017) e concentrações de gordura (BAGHERI et al., 2009), proteína (JIANG et al., 2017), lactose (ONDARZA et al., 2010; SALVATI et al., 2015), sólidos totais (SALVATI et al., 2015) e sólidos desengordurados (ONDARZA et al., 2010) parecem ser aumentados com a suplementação de levedura viva, independentemente da fase de lactação do animal.

### **4.3 Prebióticos**

Segundo Gibson et al. (1997), os prebióticos são ingredientes alimentares não digeríveis que afetam benéficamente o hospedeiro. Para isso, não devem ser hidrolisados nem absorvidos na parte superior do trato gastrointestinal; ser substrato seletivo para um ou um número limitado de potencialmente bactérias benéficas; e consequentemente, serem capazes de alterar a microflora do cólon, reduzindo o número de espécies indesejáveis e nocivas à saúde. Os grupos de prebióticos mais utilizados atualmente são os frutoligosacarídeos (FOS), galactoligosacarídeos (GOS), os mananoligosacarídeos (MOS) e as beta-glucanas. Os FOS e os GOS são açúcares

produzidos pela indústria que fornecem energia para as bactérias benéficas que habitam o trato gastrointestinal, podendo alterar a população da microflora benéfica. Já os MOS e as beta-glucanas são derivadas da parede celular de leveduras, e seu mecanismo de ação é mais complexo que o do FOS e do GOS (SCAPINELLO et al., 2001).

A parede celular das leveduras é uma estrutura robusta com função protetora e de suporte osmótico (SMITH et al., 2000). Descrita da parte externa para interna, a parede celular da levedura é composta por 35 a 40% do peso total da parede seca de manoproteínas (DEAN, 1999); 55 a 65% de beta-glucanas, sendo 5 a 10% beta 1,6-glucanas (MANNERS et al., 1973A) e 50 a 55% beta 1,3 glucanas (MANNERS et al., 1973B); e 1 a 2% de quitina (HOLAN et al., 1981) (Figura 1).

As manoproteínas são fontes de mananoligosacarídeos (MOS), e se apresentam ligadas covalentemente a um glucano (OSUMI, 1998) atuando como barreira de proteção para a levedura (ZLOTNIK et al., 1984). Além disso, os MOS são capazes de se ligar a uma variedade de bactérias, inclusive bactérias patogênicas como *Escherichia coli* e *Salmonella*, impedindo a aderência dessas bactérias no intestino, prevenindo consequentemente algumas enfermidades (SPRING et al., 2000). Em bezerros, a *E. coli* e a *Salmonella* são os principais agentes etiológicos causadores de diarreia (GILL, 2001), a qual pode ser quantificada a partir do escore fecal, como proposto por Larson et al. (1977), onde o escore 1 são fezes consistentes, normais, mas não rígidas (desejável); escore 2 as fezes moles; escore 3 considera evacuações fáceis; e escore 4 as fezes não possuem material sólido. Com base nisso, Ghosh e Mehla (2017) avaliaram o escore fecal de bezerros com dois meses de idade suplementados com 4g de MOS por cinco dias e concluíram que a adição de MOS pode prevenir a diarreia, uma vez que o escore fecal foi menor ( $1,6 \pm 0,06$ ) do que os bezerros não suplementos ( $2,1 \pm 0,05$ ) ( $P < 0,01$ ), comprovando a eficiência do MOS em prevenir diarreia a partir da competição por sítios de ligação no intestino com agentes patogênicos (SPRING et al., 2000). Ainda, por ser um polissacarídeo com aproximadamente 50 unidades de manose, MOS também pode ser considerado um substrato que atua estimulando o crescimento ou ativando o metabolismo da microbiota benéfica do hospedeiro (SPRING et al., 2000).

A estrutura química das beta-glucanas é semelhante à do amido ou da celulose, porém, os açúcares são ligados entre si por ligações beta 1,3 e beta 1,6 (OSUMI, 1998) ao invés de alfa 1,4 e alfa 1,6 (amido) e beta 1,4 (celulose) (NELSON e COX, 2014). Portanto, diferentes enzimas são necessárias para quebrá-los em moléculas de açúcar absorvíveis (STONE, 2006). A solubilidade, peso molecular, estrutura terciária, extensão de ramificação e conformação dos  $\beta$ -glucanos variam entre as fontes (VOLMAN et al., 2008). As beta-glucanas vem sendo utilizados como agentes terapêuticos ou profiláticos para aumentar a resposta imune inespecífica e específica, reduzindo o número de doenças por infecções oportunistas, através da produção de citocinas e quimiocinas pró-inflamatórias, como as IL-1 $\beta$ , IL-6 e TNF- $\alpha$ , que auxiliam no recrutamento de leucócitos adicionais para o local da infecção (VETVICKA e YVIN, 2004). Em ruminantes, os efeitos imunomodulatórios das beta-glucanas vem sendo estudados, principalmente em bezerros em fase de aleitamento, entretanto, a maioria dos estudos não utiliza beta-glucanas de leveduras isoladas, e sim a parede de levedura em si. Kim et al. (2011) avaliaram os efeitos da suplementação de parede de levedura contendo 7 a 9% de manose e 10 a 12% de beta-glucanas no desempenho de crescimento, parâmetros de saúde e imunofisiológicos em bezerros da raça holandesa e concluíram que o aditivo melhorou as condições gerais de saúde durante o período neonatal. Em outro estudo utilizando produtos da fermentação de *Saccharomyces cerevisiae* adicionados a ração inicial de bezerros leiteiros, Xiao et al. (2016) observaram melhoria na morfologia ruminal. Em vacas leiteiras, a parede de levedura parece aumentar a saúde da glândula mamária, através da redução da contagem de células somáticas (DANN et al., 2000; ZHU et al., 2017), e aumento na eficiência produtiva através do aumento na produção de leite e nas concentrações de gordura e proteína, sem afetar o consumo de MS (ZHANG et al., 2013).

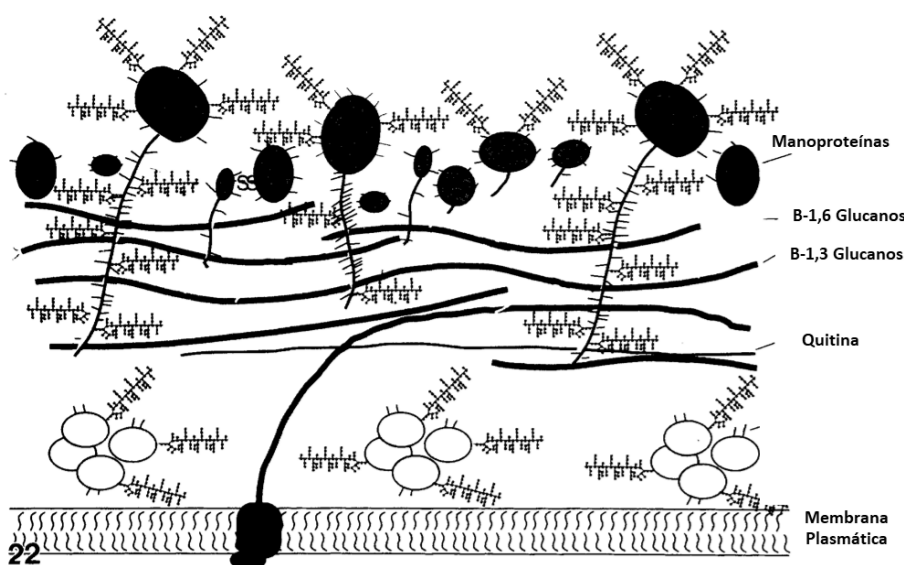


Figura 1. Composição e estrutura da parede celular de *Saccharomyces cerevisiae*. Adaptado de Osumi (1998)

#### 4.4 *Aspergillus oryzae*

Especialmente na cultura oriental, como Japão, Coréia e China, o *Aspergillus oryzae* (*A. oryzae*) tem importante destaque no desenvolvimento de processos fermentativos de muitos alimentos e bebidas, como *sake*, *seishu*, *shoyu* e *mirin* a mais de mil anos (KOBAYASHI et al., 2007).

Embora o interesse pela utilização de *Aspergillus oryzae* na dieta de ruminantes seja constante, pouco se sabe sobre seu mecanismo de atuação no rúmen, principalmente devido à limitação do conhecimento da biologia de *A. oryzae* em decorrência das dificuldades em analisar o organismo por métodos genéticos convencionais, uma vez que o *A. oryzae* forma conídios multinucleados e não tem ciclo de vida sexual (KOBAYASHI et al., 2007). Sobretudo, com os avanços da genômica, esse desafio foi vencido e algumas cepas, como por exemplo, o *Aspergillus oryzae* RIB40 e o 100-8 já foram sequenciados (KOBAYASHI et al., 2007; ZHAO et al., 2014). A presença de genes específicos para secreção de enzimas hidrolíticas no *A. oryzae* indicam o vantajoso uso deste microrganismo em processos de fermentação

(KOBAYASHI et al., 2007). Porém, a dificuldade em identificar seus efeitos na alimentação de ruminantes levou pesquisadores a suspeitar da eficácia do *A. oryzae* como aditivo alimentar (CHIOU et al., 2001), principalmente por que se observou que o tempo de atuação no rúmen das as enzimas secretadas era muito pequena antes de ser inativada por microrganismos ruminais (MORAIS et al., 2006). Além disso, as condições ideais (50°C e pH 4,5) para as atividades enzimáticas são diferentes das encontradas no rúmen (39°C e pH em torno de 5,8 a 6,8) (KUNG et al., 2002). Entretanto, Varel et al. (1993) demonstraram em um experimento in vitro, simulando as mesmas condições ruminais, que *A. oryzae* pode aumentar a taxa in vitro de degradação de frações de fibra, através do fornecimento de celulases e hemicelulases adicionais.

Durante a fermentação, *A. oryzae* secreta quantidades significativas de amilases, celulases e hemicelulases para quebrar carboidratos complexos em unidades menores, que são posteriormente fermentados por leveduras e bactérias no rúmen (KOBAYASHI et al., 2007). Cerca de 40 a 70% da MS das forragens é parede celular de plantas, compostas principalmente por celulose, hemicelulose e lignina, e mesmo em condições ideais de alimentação, a digestibilidade da parede celular no trato digestivo ainda é geralmente inferior a 65% (VAN SOEST, 1994). Um estudo dirigido por Sun et al., (2017) demonstrou que a inclusão de *A. oryzae* na dieta de vacas leiteiras aumentou as concentrações de acetato muito provavelmente em decorrência do aumento no número de bactérias celulolíticas e da ação da enzima carboximetilcelulase. Todavia, Gomez-Alarcon et al. (1991) observaram que vacas suplementadas com *A. oryzae* no início de lactação produziram mais leite do que vacas suplementadas no terço médio da lactação. Isso se deu em decorrência do maior consumo de concentrado das vacas em início de lactação, uma vez que a digestibilidade da MS, PB, FDN e FDA da dieta foram melhoradas pela suplementação de *A.oryzae*, muito provavelmente pela ação das enzimas liberadas no processo de fermentação.

Além disso, *A. oryzae*, produz ácido málico através de diferentes fontes de carbono, sendo a glicose a fonte com maior rendimento, além da possibilidade de sua obtenção utilizando lignoceluloses (DÖRSAM, 2017), bem como maltodextrinas

(TRICARICO et al., 2008), e estimulando o desenvolvimento de *Selenomonas ruminantium*, que são bactérias consumidoras de ácido láctico, que é um ácido mais forte que os AGVs. Em consequência da diminuição de ácido láctico, as concentrações de acetato, propionato e AGVs totais podem ser aumentadas (NISBET e MARTIN, 1990; SUN et al., 2017), além de suprimir o declínio de pH ruminal após a ingestão de alimentos (NISBET e MARTIN, 1990; TRICARICO et al., 2008). Outros microrganismos também parecem ser estimulados com a suplementação de *A. oryzae*. Estudos avaliando os efeitos de extrato de fermentação de *A. oryzae* no crescimento de microrganismos mostraram que houve aumento de pelo menos 30% no número total de culturas de bactérias e de 94% no número de bactérias celulolíticas em ovelhas suplementadas com *A. oryzae* (NEWBOLD et al., 1992), e de 40% no número de bactérias celulolíticas em vacas holandesas não lactantes (WIEDMEIER et al., 1987), provavelmente em função da estabilização do pH a partir do consumo de lactato. Entretanto, este aumento não foi capaz de influenciar a digestibilidade da fibra ingerida pelos animais (DENIGAN et al., 1992; WIEDMEIER et al., 1987). Por outro lado, em um estudo in vitro, Frumholtz et al. (1989) não observaram aumento do pH ruminal, igualmente encontrado por Higginbotham et al. (2004), porém o número de bactérias celulolíticas também foi aumentado com o uso de *A. oryzae*, também sem afetar a digestibilidade da MS. Em contra partida, outros estudos mostraram melhoria na digestibilidade da MS (WIEDMEIER et al., 1987; GOMEZ-ALARCON et al., 1991) FDN e PB (GOMEZ-ALARCON et al., 1991).

Denigan et al. (1992) observaram aumento de 14,6% no consumo de MS de vacas holandesas em lactação suplementadas com 1,5g/dia de extrato fermentado de *A. oryzae* comparado as não suplementadas. Atualmente, Sallam et al. (2019) comprovaram esse resultado ao adicionar 3,5g/dia de extrato fermentado de *A. oryzae* na dieta de vacas leiteiras, aumentando em 6,25% o consumo da MS, bem como 1,1kg de leite a mais por dia. Embora a adição de *A. oryzae* na dieta de ruminantes pareça melhorar o ambiente ruminal e a digestibilidade do alimento, diferente do esperado, onde houve aumento na produção de leite (GOMEZ-ALARCON et al., 1991; SALLAM et al., 2019) e lactose (SUN et al., 2017) em alguns estudos esses efeitos não foram

estendidos à essas variáveis (DENIGAN et al., 1992; CHIQUETTE et al., 1995; HIGGINBOTHAM et al., 2004; KIM et al., 2006).

## 5. Considerações gerais

A suplementação de leveduras e *A. oryzae* na dieta de vacas leiteiras é uma ferramenta que pode contribuir para a melhoria do desempenho animal, entretanto, seu uso deve sempre ser planejado e executado aliado as boas práticas de manejo, nutrição e sanidade, e nunca de forma isolada para corrigir ou substituir alguns desses manejos.

Como apresentado na pesquisa de revisão, ainda são observadas disparidades de resultados entre os estudos que avaliaram os efeitos das leveduras vivas e seus produtos de fermentação, bem como de *A. oryzae* na alimentação de vacas leiteiras. Dessa forma, um estudo meta-analítico pode auxiliar na constituição de alguns conceitos e melhor estabelece-los, além de conhecer a eficácia destes aditivos na produção de leite para tomar decisões apropriadas sobre o uso desses produtos. Assim, no capítulo a seguir será apresentada uma meta-análise, elaborada na forma de artigo e formatado nas normas da revista que será submetido, a *Journal of Dairy Science*.

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## Capítulo 2. Artigo

### **Supplementation of yeasts and *Aspergillus oryzae* for dairy cows: a meta-analysis.**

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## **Additives supplementation to dairy cows**

### **Supplementation of yeasts and *Aspergillus oryzae* for dairy cows: a meta-analysis.**

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**Abstract**

The aim of this study was to identify which is the better additive supplementation for dairy cows to improve milk yield and composition, BCS, dry matter intake, digestibility, and ruminal parameters. For this, one hundred sixteen studies (332 observations) were compiled to be evaluated across a meta-analysis, from mixed models regressions, using the MIXED procedure of SAS, according to the additive used: *Saccharomyces cerevisiae* (LY), *Aspergillus oryzae* (AO) and prebiotics (SCFP). LY supplementation increased rumen pH ( $P < 0.0001$ ) and apparent total tract digestibility of neutral detergent fiber and crude protein ( $P < 0.0001$ ). Thereby, compared with the control, the dry matter intake (DMI) was increased by 1.07% when cows were supplemented with AO ( $P = 0.0314$ ), while the other treatments had no positive effects. LY increased milk yield by 7.16% compared with the control, 5.07% compared to AO and 4.62% compared to SCFP ( $P < 0.01$ ), and reduced milk yield losses by 44.54% according to the lactation advance compared to the other additives and the control ( $P < 0.01$ ). Yet, LY and SCFP increased productive efficiency. Milk fat and total solids were increased by LY, followed by SCFP. Solids not fat and lactose were increased by LY; however, AO also increased milk lactose contents. The somatic cell count was reduced by LY by 39.8% ( $P < 0.0001$ ). In conclusion, LY are the best option to increase milk yield, improve milk composition, decrease somatic cell count and improve feed efficiency.

**Keywords:** additives, milk yield, yeast, ruminal pH, *Saccharomyces cerevisiae*, prebiotics, *Aspergillus oryzae*.

## **1. Introduction**

Several factors could affect milk yield and composition, such as herd management, genetic factors, animal health and welfare, and physiological factors, like the lactation stage; however, the success in the productive efficiency of dairy cows is mainly dependent on nutrition (Peres, 2001). In addition, advances in ruminant nutrition demand new strategies for nutritional manipulation to improve performance (Chiquette, 2009, Arcuri et al., 2016). Over the last decade, there has been a significant increase in the number of studies based on the replacement of chemical feed additives for potential natural substitutes (Qiao et al., 2010; Sallam et al., 2019). Following a tendency to reduce the use of antibiotics in animal production, as well as to improve efficiency and health, supplementation feed additive performance improvers are used as a strategy of nutritional manipulation in dairy cows. Therefore, prebiotics and probiotics are an alternative to the use of antibiotics in dairy cows feeding (Bidarkar et al., 2014).

Probiotics are living microorganisms that have beneficial effects on the host, improving microbial balance. Prebiotics serve as nutrients that stimulate the growth and development of beneficial microflora in the digestive tract (Gibson et al., 1997). Live yeasts are the most commonly used probiotic to supplement dairy cows, while the products of yeast fermentation are the most commonly used prebiotics (Uyeno et al, 2015). Some studies show positive effects in milk yields and composition (Adams et al., 1995; Harrison et al., 1988; Ramsing et al., 2009), while others do not observe these benefits (Robinson, 1997; Schingoethe et al., 2004). In this way, the results observed are still distinct and controversial, and the literature is still unclear as to the mode of action of these additives. Several mechanisms are suggested to explain the effects on animal performance, especially changes in ruminal microbiota, which mainly reflect the feed intake, production and milk composition (Desnoyers et al., 2009). Thus, the purpose of this study was to evaluate the effect of feed additives supplementation for dairy cows and to identify which is the best one to be used.

## **2. Materials and Methods**

The searches for this meta-analysis were carried out in the following websites: Elsevier, Scientific Electronic Library Online - Scielo, Science Direct, Scopus, PubMed, Wiley, Cambridge Core, AGRÍCOLA and Google Scholar. The search terms used were “live yeast”,

“yeasts culture”, “prebiotics”, “probiotics”, “direct feed microbials”, “dairy cattle” and “dairy cows” in various combinations, from April to October 2019.

It was included in the dataset full articles and short communications from peer-reviewed journals as well as theses and dissertations. Only studies reporting *in vivo* experiments were included in the dataset. To be included in the dataset the additives should be provided in feed. Studies which the additive could not be identified were not included in the dataset. To identify the treatment used in the experiments, the manufacturer of the additive was contacted to establish if the additive was live or not. Yet, studies needed to contain information at least about milk production or milk composition, dry matter intake, or ruminal and digestibility parameters to be included in the dataset,. Studies that did not contain information about dispersion measures and only one observation for each treatment were not included in the dataset.

Data were extracted and type on an excel spreadsheet, where each line represented an average of analyzed variable and treatments were organized in columns. After dataset was completed, we defined the treatments according to the additive used, as live yeasts of genus *Saccharomyces cerevisiae* (LY), *Aspergillus oryzae* (AO), prebiotics (SCFP), and control. SCFP treatment considered yeast culture, yeast cell wall,  $\beta$ -glucans, mannanooligosaccharides and, mandatorily, should be provided by *Saccharomyces cerevisiae* fermentation products.

Studies in which the means of VFA were expressed in mmol were transformed into percentage of VFA from the following equation (Equation 1):

$$x = a*100/b \quad (1)$$

where x = percentage of VFA, a = mean of VFA in mmol, b = total VFA. The acetate:propionate ratio was calculated by dividing the acetate mean by the propionate mean when the means were not available in the study. Yet, productive efficiency was obtained by dividing milk yield by dry matter intake. Data were analyzed as mixed models regressing the variables against additives in the diet using the SAS MIXED procedure (v. 9.4; SAS Institute Inc., Cary, NC). The RANDOM command (St-Pierre, 2001) was used to include the fixed effects of the additive type and the random effects of the studies in the model. To account for the variation in accuracy between studies, the inverse of the standard error squared of the mean of each treatment or the inverse of the number of observations in each study (when the standard error squared was absent in the articles) was used as a factor in the WEIGHT model declaration (St-Pierre, 2001). The REML estimation method (SAS Institute Inc., 2008) was used to ascertain

the maximum restricted likelihood, assuming the distribution of random effects as normal. Outliers were identified and excluded if the absolute values of studentized residues exceeded  $\pm 3$  (Sauvant et al., 2008). Based on Fisher's least significant difference test, the P-DIFF option of the LSMEANS instruction was used to determine the differences between the means.

Initially the purpose of this study was to evaluate the effect of prebiotics and probiotics supplementation on the early (until 100 DIM), medium (101 to 200 DIM) and late lactation (more than 201 DIM) of dairy cows separately, however, it was not possible due to the limited number of observations in each phase, mainly late lactation. Thus, the DIM, rumen pH, milk yield and diet chemical composition (i.e. NDF, CP content) were tested as covariates. However, if the random covariance was not significant ( $P > 0.05$ ), they were removed from the model (St-Pierre, 2001). When covariates were significant, regression equations were developed to investigate the effect of additives supplementation on a given variable using the MIXED procedure in SAS software (v. 9.4; SAS Inst. Inc., Cary, NC, USA). For each equation, the CONTRAST statement was used to test whether regression parameters differed among additives. The slopes and intercepts of each equation were estimated using the ESTIMATE statement of the MIXED procedure in SAS.

### 3. Results

#### *3.1 Description of the dataset, treatments, animals and diet*

In total, 114 studies were pooled in the dataset, comprising 332 observations, which are listed in the Appendix. The summary of dataset with descriptive analysis is shown in Table 1.

In this meta-analysis, 42.8% of treatments corresponded to the control, 31.3% to the use of LY, 18.7% to the use of SCFP, and 7.23% to the use of AO. Except for the control, the average additive dose used was 17.8 ( $\pm 8.32$ ) grams per animal per day of AO, 89.5 ( $\pm 19.1$ ) grams per animal per day of SCFP and 12.6 ( $\pm 1.80$ ) during an average period of 58.1 ( $\pm 2.52$ ) days. The dataset includes publications from 1989 to 2019, of which 36.8% were conducted in the United States of America, followed by Poland and France (4.29%), and Japan and Iran (3.37%).

The lactating cows (96.6 days in milk  $\pm$  3.99) weighed 614 kg ( $\pm$  7.03) and were 85.6% Holstein, 5.41% Crossbred, 3.61% Jersey and 5.42% other dairy breeds. All data associated with diet composition by additive type are shown in Table 2.

### 3.2 Milk variables, dry matter intake and body condition score

Comparing with the control, LY promoted the highest performance, increasing milk yield by 7.08%, followed by SCFP, which increased milk yield by 2.46% ( $P < 0.0001$ ; Table 3). Among the covariates used, only the DIM effect was dependent of additive supplementation, therefore, regression equations were developed to show its effects (Equations 2 and 3). DIM had a negative relationship with milk yield according to the additive supplementation. LY reduced milk yield losses by 44.54% according to the lactation advance compared to the other additives and the control (Equations 2 and 3;  $P < 0.05$ ). Whereas NDF had a negative relationship with milk production, irrespective of additive supplementation, decreasing milk production by 0.164 kg for each increase of NDF percentage unit (Equations 2 and 3).

$$\text{Milk yield with LY} = 41.1 (\pm 2.09 \text{ kg}) - 0.0300 (\pm 0.0086) \times \text{DIM} - 0.164 (\pm 0.0522) \times \text{NDF} \\ \text{RMSE} = 0.6650 \quad (2)$$

$$\text{Milk yield with other treatments} = 41.1 (\pm 2.09 \text{ kg}) - 0.0541 (\pm 0.0237) \times \text{DIM} - 0.164 (\pm 0.0522) \\ \times \text{NDF} \text{ RMSE} = 0.6650 \quad (3)$$

Milk fat was increased by 1.37% with LY in relation to the control, followed by SCFP, which increased it by 0.55%, whereas; that additive AO did not influence milk fat ( $P = 0.0497$ ; Table 3). Regarding to the control, the SCC was reduced by 39.8% with LY ( $P < 0.0001$ ) and TS were increased by 3.67% and 1.22% with LY and SCFP respectively ( $P < 0.0001$ ). Moreover, LY increased, in relation to the control, milk lactose in 0.84% ( $P = 0.0024$ ) and SNF in 2.16% ( $P = 0.0025$ ). Milk protein and MUN were not affected by additive supplementation (Table 3).

Compared with the control, the DMI was increased by 1.07% when cows were supplemented with AO ( $P = 0.0314$ ), while the other treatments had no positive effects. Productive efficiency (average milk yield/average DMI) was therefore, 1.62 for LY, 1.56 for SCFP, 1.51 for AO and 1.50 for the control. The body condition score (BCS) was the highest when the additive SCFP ( $P = 0.0096$ ; Table 3) was consumed; however, the control and LY maintained the BCS at acceptable values.

### 3.3 Digestion parameters

LY supplementation increased rumen pH ( $P < 0.0001$ ) and apparent total tract NDF and CP digestibility ( $P < 0.0001$ ; Table 4). As a covariate, diet NDF had significant positive relationships with rumen pH ( $P = < 0.0001$ ), showing different slopes between LY and other additives and control (Equations 4 and 5;  $P < 0.05$ ).

$$\text{Rumen pH with LY} = 1.55 (\pm 0.0483) + 0.00352 (\pm 0.00535) \times \text{NDF RMSE} = 0.0670 \quad (4)$$

$$\text{Rumen pH with other additives} = 4.16 (\pm 0.101) + 0.0585 (\pm 0.0112) \times \text{NDF RMSE} = 0.0670 \quad (5)$$

Rumen concentrations of VFA, acetate, propionate, butyrate, isovalerate, valerate, acetate – propionate ratio and ammonia were not affected by additive supplementation. However, the rumen concentration of isobutyrate was decreased by 4.43% with LY ( $P < 0.05$ ; Table 4) compared to SCFP supplementation. The additive supplementation also did not influence the apparent total tract digestibility of DM, OM and ADF ( $P > 0.05$ ) (Table 4).

## 4. Discussion

The present meta-analysis confirmed that LY supplementation improves the performance of dairy cows, increasing milk yield and keeping the dry matter intake equal to of the control group. In general, LY managed to decrease the loss of milk yield during lactation compared to other additives tested (Equations 1 and 2). For dairy cows, LY have shown the most reliable effects to improve milk yield (Moallem et al., 2009; Schingoethe et al., 2004). In addition, Wholt et al. (1991) observed that cows supplemented with live yeasts had peak lactation earlier and was greater than unsupplemented cows. However, how higher is the peak of milk production, the faster there is a sharp decline of milk production, when compared to cows with lower productions, in the first phase of lactation (Lean et al., 1989). Thus, to our knowledge, our results are the first to show that LY supplementation is able to keep milk production higher through lactation than supplementation with other additives or not supplementation. The positive effect of LY supplementation on milk yield is better explained by the greater rumen pH in cows receiving LY, suggesting greater activity of the microbial population and consequently increased NDF and CP digestibilities. In addition, probably as a result of improvement of animal performance, the BCS of cows supplemented with LY was lower than those supplemented with

others additives or control, but still within the expected values for dairy cows in early lactation (2.5 to 3.5 on a scale of 1 to 5) (Edmonson et al., 1989).

In this study, rumen pH was increased when dairy cows were supplemented with LY. This high pH seems to be due to stimulus for the growth of beneficial microorganisms. *In vitro* studies showed improvement in the population of lactate-utilizing bacteria, such as *Megasphaera elsdenii* or *Selenomonas ruminantium* in the presence of LY (Nisbet and Martin, 1990; Rossi et al., 2004). Moreover, LY compete with lactic acid-producing bacteria for growth substrates, which consequently limited the amount of lactate produced by this bacterial species (Chaucheyras et al., 1996). Thus the results of this meta-analysis indicate the ability of LY to avoid pH drops in the rumen probably by limiting the accumulation of lactate in the rumen. In the other hand, lactate is accumulated in the rumen only at low levels because it is less absorbable than the VFA, and the pH decrease motivated by high concentrations of VFA, has been toxic for bacteria (Brossard et al., 2004; Kozloski, 2019). In addition, the NDF digestibility may be improved by LY utilization due the greater pH, since ruminal pH decrease can reduce microbial population, mainly species that degrade fiber, particularly sensitive to low pH, as *Fibrobacter succinogenes*, *Ruminococcus albus* and *R. flavfaciens* (Russell and Wilson, 1996). Therefore, we expected an increase in the VFA concentrations, but, controversially, we observed that concentrations of total VFA and individual concentration of VFA's were not affected by the additive supplementation, which is in accordance with what has been reported by Marden et al. (2008), Desnoyers et al. (2009) and Lascano and Heinrichs (2009). The VFA concentrations in the rumen is the product between produced and absorbed VFA, and this measurement is hard to perform in an experiment and we do not have this information from the papers to use in this meta-analysis; however, more studies to better understand rumen metabolism with LY supplementation are still needed. In this meta-analysis were observed that milk yield and milk lactose increased. Thus, we suggest that LY would probably increase VFA production and absorption. The number of studies that generated the results for rumen fermentation and nutrient digestibility are lower than those that generated the results of milking performance, and this could make it more difficult to better detect differences in rumen fermentation with the use of LY supplementation. Thus, this reinforces that more studies are still needed to better understand rumen fermentation dynamics in dairy cows receiving LY supplementation.

As LY increased ruminal pH, CP digestibility, without increasing the total and individual ruminal concentration of VFA, there was probably an input of substrates for gluconeogenesis, mainly propionate and gluconeogenic amino acids, supplying the glucose demands by the mammary gland for lactose synthesis, which increased with LY supplementation. Increases in milk fat, TS and SNF can also be assigned to this statement, where supplementation with LY improve the digestive processes that occur in the rumen, and subsequently increase the nutrients available for absorption by mammary gland for synthesis of milk components. Another possible explanation for the increase of milk lactose concentration is the decrease of SCC with LY supplementation, which maintains udder health, because when there is a reduction in milk lactose concentration due to mastitis, there is a compensatory increase in the concentration of soluble minerals in milk (Na and Cl) and an increase in SCC (Fox and Mcsweeney, 2015). The SCC is a set of defense cells and epithelial cells of the mammary gland, being a parameter to evaluate mammary gland health. In healthy conditions, normal SCC values should be less than 200.000 cells/ml of milk, however, when infections occur this value increases due to the migration of defense cells to the udder (Santos and Fonseca, 2019). Mannooligosaccharides and  $\beta$ - glucans present in the yeast cell wall can activate the immune system, triggering a defense response in other mucous membranes, in addition to those in which the initial stimulus occurred (Korolenko et al., 2019). This mechanism of cell migration to other tissues is known as the common mucosal immune system and would be a plausible explanation for the lower SCC in the milk produced by cows supplemented with LY.

On the other hand, LY can remove oxygen from freshly eaten food to maintain the rumen in a better anaerobic condition and maintain metabolic activity (Newbold et al. 1996). This can also explain the higher pH in the rumen of cows fed with LY, which may provide favorable rumen environment to the microorganisms by decreasing O<sub>2</sub> and consequently increase feed fermentation and utilization. Increase in the number of rumen bacterial cells (Dawson et al., 1990; Newbold et al., 1998), especially cellulolytic bacteria (Harrison et al., 1988; Newbold et al., 1998) is one of the most consistent results observed with live yeasts supplementation in ruminants. When the bacterial population increases, the requirement for available nitrogen (N) in the rumen also increases (Bach et al, 2005). In this study, LY increased the total tract CP digestibility. If the amino-N was used for cellulolytic bacteria in the rumen, it is logical to expect that an increased proportion of amino acid carbon skeletons available for fermentation and VFA

production would be diverted to microbial protein synthesis, minimizing the increase in ruminal VFA concentrations, consequently avoiding a decrease in ruminal pH (Bach et al, 2005). In addition, in this current study, ruminal ammonia concentration was not affected by any of the additive supplementation, contrary to Erasmus et al. (1992), who found lower values of ruminal ammonia with LY supplementation. Therefore, we suggest that lower ruminal ammonia concentrations and increases in CP digestibility are reflexes of higher concentrations of bacteria in the rumen, especially cellulolytic bacteria, that use ammonia to produce microbial protein, increasing the flow of microbial protein to the small intestine that reaches the mammary gland and reflect increase of milk yields (Erasmus et al, 1992; Dann et al., 2000). Furthermore, although supplementation with LY increased CP digestibility, it was expected that milk protein content would also be increased due to the increased supply of protein to the mammary gland. However, MUN was not influenced by LY supplementation, accentuating that the dietary protein was used to produce more milk, and therefore more protein secretion, which may lead milk protein to suffer a dilutive effect.

This study observed more positive effects in dairy cows using LY as additive probably because yeasts were live organisms, having greater activity in rumen, while AO and SCFP were not. The mode of action of AO is still unclear and there is little information about it; still, its effects seem to be connected to amylolytic enzymes production by this fungus, which work within hours into the rumen, and then are degraded by proteolysis by microorganisms, being inactivated. This can be main cause of AO not having been superimposed on other additives. In addition, AO also can favor fiber degradation, facilitating the adherence of cellulolytic bacteria to the fiber, through the chemostatic attraction caused by the release of soluble sugars or by alteration of the fiber surface (Newbold, 1997), however, LY supplementation may have provided more stimulatory factors than AO, such as B vitamins, for cellulolytic bacteria, improving the NDF digestibility and milk fat content. Yet, LY probably provided stimulating factors for proteolytic bacteria, increasing CP digestibility, and consequently producing more microbial protein and milk yield, while the AO supplement was actively proteolytic (Wiedmeier et al., 1987).

Lastly, the response of LY to improve productive efficiency could be influenced by supplementation dose (Ferraretto et al., 2012). Analyzing effects of different doses of live LYs by *Saccharomyces cerevisiae*, Jiang et al. (2017) verified increases in milk yield of dairy cows

receiving a low dose of live yeast ( $5.7 \times 10^7$  cfu/d) compared to a high dose ( $6.0 \times 10^8$  cfu/d). In this study, dose was tested as covariate in the model for all variables of the additive in which there was significant effect; however, it did not remain in the model because none of them showed a significant difference. In this way, more studies comparing different dosages of yeasts can be useful to establish which is the best one to improve food and productive efficiency of dairy cows.

## 5. Conclusions

This meta-analysis showed that LY is the best option of feed additive to be used in dairy cows because it improves their performance, increasing milk yield and decreasing DMI. The main factor of the positive response is the action of LYS in the rumen pH and nutrients digestibility, as well as improvement in milk composition and the health of dairy cows.

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## Declaration of competing interests

The authors declare that they have no competing interests.

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Table 1. Descriptive analysis of the variables used in the dataset to evaluate the effects of additive supplementation on milk yield and composition, intake, digestibility, and ruminal parameters in dairy cows.

| Variable <sup>1</sup> | n   | Mean | Median | Minimum | Maximum | SEM    |
|-----------------------|-----|------|--------|---------|---------|--------|
| Milk Yield kg/d       | 290 | 31.2 | 31.0   | 7.29    | 48.9    | 0.495  |
| CP %                  | 273 | 3.2  | 3.15   | 2.59    | 3.79    | 0.013  |
| Fat %                 | 287 | 3.7  | 3.69   | 2.71    | 5.62    | 0.028  |
| Total Solids %        | 64  | 12.5 | 12.5   | 11.25   | 14.9    | 0.098  |
| SNF %                 | 79  | 8.8  | 8.83   | 7.59    | 9.87    | 0.048  |
| Lactose               | 183 | 4.8  | 4.78   | 4.255   | 5.49    | 0.0159 |
| SCC                   | 61  | 271  | 254    | 21.63   | 713     | 23.1   |
| MUN                   | 103 | 13.9 | 13.8   | 6.85    | 20.9    | 0.312  |
| DMI kg/d              | 228 | 21.6 | 21.6   | 11.2    | 29.6    | 0.246  |
| BCS                   | 80  | 2.9  | 3      | 2.12    | 3.59    | 0.039  |
| pH                    | 101 | 6.3  | 6.27   | 5.41    | 7.08    | 0.0317 |
| VFA mmol              | 104 | 107  | 104    | 60.3    | 180     | 2.49   |
| Acet mol/100mol       | 109 | 61.8 | 61.3   | 52.2    | 70.5    | 0.369  |
| Prop mol/100mol       | 111 | 22.9 | 23.1   | 17.5    | 36.1    | 0.337  |
| But mol/100mol        | 103 | 11.7 | 11.2   | 8.69    | 17.2    | 0.166  |
| Isobut mol/100mol     | 58  | 1.0  | 0.974  | 0.05    | 1.71    | 0.0454 |
| Isoval mol/100mol     | 64  | 1.9  | 1.71   | 0.17    | 5.86    | 0.151  |
| Val mol/100mol        | 64  | 1.8  | 1.62   | 0.5     | 3.96    | 0.0883 |
| Acet:Prop             | 111 | 2.8  | 2.82   | 1.69    | 3.83    | 0.0488 |
| Ammonia mg/dL         | 84  | 12.6 | 13.0   | 2.17    | 23.9    | 0.533  |
| ATTD DM %             | 54  | 66.8 | 68.9   | 56.7    | 74.1    | 0.689  |
| ATTD OM %             | 43  | 69.0 | 71.1   | 58.3    | 75.1    | 0.751  |
| ATTD NDF %            | 60  | 47.6 | 48.0   | 29.6    | 69.4    | 1.27   |
| ATTD ADF %            | 37  | 45.8 | 50.2   | 18.1    | 70.0    | 2.12   |
| ATTD CP %             | 47  | 67.8 | 68.7   | 56.9    | 83.1    | 0.854  |

<sup>1</sup> Acet = acetate; Prop = propionate; But = butirate; Isobut = isobutirate; Isoval = isovalerate; Val = valerate; Acet:Prop = ratio acetate propionate; ATTD DM = apparent total tract digestibility of dry matter; ATTD OM = apparent total tract digestibility of organic matter; ATTD NDF = apparent total tract digestibility of neutral detergent fiber; ATTD ADF = apparent total tract digestibility of acid detergent fiber; ATTD CP = apparent total tract digestibility of crude protein.

Table 2. Descriptive analysis of the diet composition used in the dataset by additive supplementation.

| Variable      | Additive             |                  |                 |                  |                   |                  |                 |        |
|---------------|----------------------|------------------|-----------------|------------------|-------------------|------------------|-----------------|--------|
|               | Control <sup>1</sup> |                  | AO <sup>2</sup> |                  | SCFP <sup>3</sup> |                  | LY <sup>4</sup> |        |
|               | Mean                 | SEM <sup>5</sup> | Mean            | SEM <sup>5</sup> | Mean              | SEM <sup>5</sup> | Mean            | SEM    |
| Forage %      | 48.9                 | 0.977            | 42.7            | 1.51             | 48.2              | 1.62             | 51.2            | 1.31   |
| Concentrate % | 51.1                 | 0.977            | 57.4            | 1.51             | 51.8              | 1.62             | 48.8            | 1.31   |
| DM %          | 55.2                 | 1.634            | 55.2            | 5.52             | 50.4              | 0.823            | 53.6            | 2.16   |
| CP % DM       | 17.1                 | 0.361            | 17              | 0.25             | 16.7              | 0.205            | 17              | 0.588  |
| NDF % DM      | 34.2                 | 0.548            | 35.1            | 0.7              | 32.9              | 0.622            | 35.4            | 0.841  |
| ADF % DM      | 21.4                 | 0.414            | 21.9            | 0.538            | 20.6              | 0.445            | 22.3            | 0.612  |
| NFC % DM      | 38.9                 | 0.757            | 37.2            | 1.67             | 39.6              | 0.687            | 38.2            | 1.243  |
| TDN % DM      | 72.4                 | 0.871            | 71.4            | 1.6              | 70.8              | 0                | 73              | 0.8771 |
| ASH % DM      | 7.1                  | 0.214            | 6.9             | 0.767            | 7.06              | 0.313            | 7.02            | 0.2247 |
| Ca % DM       | 0.873                | 0.028            | 0.70            | 0.01             | 0.881             | 0.029            | 0.856           | 0.0441 |
| P % DM        | 0.437                | 0.00817          | 0.50            | 0.02             | 0.417             | 0.009            | 0.44            | 0.0099 |

<sup>1</sup> Control = negative control.

<sup>2</sup> AO = *Aspergillus oryzae*.

<sup>3</sup> SCFP = *Sacharomicces cerevisiae* fermentation products.

<sup>4</sup> LY = live yeasts (*Sacharomicces cerevisiae*).

Table 3. Influence of additives on milk yield, milk composition, DMI and BCS.

| Variable                     | Additive             |        |                    |        |                    |        |                   |        | P - value | Sigma  |          |
|------------------------------|----------------------|--------|--------------------|--------|--------------------|--------|-------------------|--------|-----------|--------|----------|
|                              | Control <sup>1</sup> | SEM    | AO <sup>2</sup>    | SEM    | SCFP <sup>3</sup>  | SEM    | LY <sup>4</sup>   | SEM    | Additive  | Study  | Residual |
| Milk Yield <sup>5</sup> kg/d | 32.5 <sup>c</sup>    | 0.803  | 33.1 <sup>bc</sup> | 0.884  | 33.3 <sup>b</sup>  | 0.823  | 34.8 <sup>a</sup> | 0.806  | <.0001    | 44.0   | 0.511    |
| CP <sup>6</sup> %            | 3.14                 | 0.0221 | 3.11               | 0.0259 | 3.143              | 0.0228 | 3.15              | 0.0229 | 0.2099    | 0.0373 | 0.0017   |
| Fat <sup>5</sup> %           | 3.65 <sup>b</sup>    | 0.0521 | 3.64 <sup>b</sup>  | 0.0571 | 3.67 <sup>ab</sup> | 0.0534 | 3.70 <sup>a</sup> | 0.0533 | 0.0497    | 0.181  | 0.00563  |
| Total Solids %               | 12.25 <sup>b</sup>   | 0.198  | 12.1 <sup>b</sup>  | 0.330  | 12.4 <sup>a</sup>  | 0.243  | 12.7 <sup>a</sup> | 0.205  | <.0001    | 0.5807 | 0.0883   |
| SNF <sup>6</sup> %           | 8.80 <sup>b</sup>    | 0.0757 | 8.80 <sup>b</sup>  | 0.0819 | 8.77 <sup>b</sup>  | 0.0814 | 8.99 <sup>a</sup> | 0.0808 | 0.0025    | 0.0985 | 0.00586  |
| Lactose                      | 4.74 <sup>b</sup>    | 0.0236 | 4.77 <sup>ab</sup> | 0.0279 | 4.75 <sup>b</sup>  | 0.0242 | 4.78 <sup>a</sup> | 0.0245 | 0.0024    | 0.0311 | 0.00117  |
| SCC                          | 318 <sup>a</sup>     | 32.0   | 319 <sup>a</sup>   | 35.0   | 332 <sup>a</sup>   | 33.4   | 191 <sup>b</sup>  | 33.1   | <.0001    | 18483  | 960      |
| MUN <sup>7</sup>             | 13.7                 | 0.515  | 13.7               | 0.614  | 13.8               | 0.521  | 13.8              | 0.520  | 0.404     | 9.495  | 0.126    |
| DMI <sup>6,8</sup> kg/d      | 21.6 <sup>ab</sup>   | 0.3011 | 21.9 <sup>a</sup>  | 0.328  | 21.4 <sup>b</sup>  | 0.318  | 21.5 <sup>b</sup> | 0.3060 | 0.0314    | 5.93   | 0.2390   |
| BCS                          | 2.93 <sup>b</sup>    | 0.062  |                    |        | 2.96 <sup>a</sup>  | 0.0623 | 2.89 <sup>b</sup> | 0.0644 | 0.0096    | 0.104  | 0.00185  |

<sup>a-b</sup> Means in the same row with different superscripts differed significantly (Fisher's test  $P < 0.05$ ).

<sup>1</sup> Control = negative control.

<sup>2</sup> AO = *Aspergillus oryzae*.

<sup>3</sup> SCFP = *Sacharomicces cerevisiae* fermentation products.

<sup>4</sup> LY = live yeasts (*Sacharomicces cerevisiae*).

<sup>5</sup> Days in milk and diet NDF were considered covariates in the model.

<sup>6</sup> Days in milk were considered as covariates in the model.

<sup>7</sup> Diet CP was considered a covariate in the model.

<sup>8</sup> Milk yield was considered a covariate in the model.

Table 4. Influence of additives on ruminal parameters and apparent total tract digestibility.

| Variable <sup>1</sup>          | Additives            |        |                   |        |                    |        |                    |        | P-value | Sigma  |          |
|--------------------------------|----------------------|--------|-------------------|--------|--------------------|--------|--------------------|--------|---------|--------|----------|
|                                | Control <sup>2</sup> | SEM    | AO <sup>3</sup>   | SEM    | SCFP <sup>4</sup>  | SEM    | LY <sup>5</sup>    | SEM    | Treat   | Study  | Residual |
| Ph <sup>6</sup>                | 6.17 <sup>b</sup>    | 0.0543 | 6.22 <sup>b</sup> | 0.0594 | 6.19 <sup>b</sup>  | 0.0604 | 6.32 <sup>a</sup>  | 0.0555 | <.0001  | 0.0852 | 0.00477  |
| VFA mmol                       | 107                  | 4.29   | 110               | 4.79   | 109                | 4.69   | 108                | 4.32   | 0.467   | 583    | 14.7     |
| Acet <sup>7</sup> mol/100mol   | 62.7                 | 0.650  | 62.5              | 0.699  | 62.5               | 0.691  | 62.7               | 0.697  | 0.891   | 10.1   | 0.688    |
| Prop <sup>8</sup> mol/100mol   | 22.6                 | 0.694  | 22.7              | 0.704  | 22.9               | 0.740  | 22.7               | 0.718  | 0.465   | 7.39   | 0.232    |
| But <sup>8</sup> mol/100mol    | 11.1                 | 0.339  | 11.1              | 0.358  | 10.9               | 0.350  | 11.1               | 0.366  | 0.698   | 1.56   | 0.110    |
| Isobut mol/100mol              | 0.975 <sup>a</sup>   | 0.0731 |                   |        | 0.994 <sup>a</sup> | 0.0738 | 0.922 <sup>b</sup> | 0.0746 | 0.0408  | 0.0907 | 0.00225  |
| Isoval <sup>9</sup> mol/100mol | 1.76                 | 0.218  | 1.77              | 0.22   | 1.77               | 0.218  | 1.75               | 0.218  | 0.960   | 0.888  | 0.00377  |
| Val mol/100mol                 | 1.79                 | 0.145  | 1.75              | 0.153  | 1.8                | 0.146  | 1.77               | 0.147  | 0.738   | 0.412  | 0.00555  |
| Acet:Prop                      | 2.86                 | 0.0783 | 2.87              | 0.0798 | 2.81               | 0.0872 | 2.80               | 0.08   | 0.121   | 0.202  | 0.00514  |
| Ammonia <sup>10</sup> mg/dL    | 12.9                 | 0.9187 | 13.1              | 1.29   | 12.8               | 0.941  | 12.30              | 0.957  | 0.369   | 18.7   | 0.913    |
| ATTD DM%                       | 67.3                 | 1.03   | 66.8              | 1.45   | 67.3               | 1.67   | 66.9               | 1.04   | 0.440   | 19.4   | 0.758    |
| ATTD OM%                       | 69.2                 | 1.26   | 68.4              | 1.93   | 69.3               | 1.69   | 68.7               | 1.27   | 0.483   | 21.5   | 0.965    |
| ATTD NDF <sup>11</sup> %       | 47.2 <sup>a</sup>    | 2.63   | 45.5 <sup>a</sup> | 3.17   | 44.6 <sup>b</sup>  | 2.64   | 48.0 <sup>a</sup>  | 2.66   | <.0001  | 76.1   | 0.0419   |
| ATTD ADF <sup>11</sup> %       | 42.3                 | 4.1    | 39.8              | 4.42   |                    |        | 43.3               | 4.11   | 0.220   | 95.4   | 1.14     |
| ATTD CP <sup>7</sup> %         | 66.6 <sup>b</sup>    | 1.33   | 66.1 <sup>b</sup> | 1.99   | 68.6 <sup>ab</sup> | 2.93   | 72.1 <sup>a</sup>  | 1.37   | <.0001  | 17.9   | 6.07     |

<sup>a-b</sup> Means in the same row with different superscripts differed significantly (Fisher's test  $P < 0.05$ ).

<sup>1</sup> Acet = acetate; Prop = propionate; But = butirate; Isobut = isobutirate; Isoval = isovalerate; Val = valerate; Acet:Prop = ratio acetate propionate; ATTD DM = apparent total tract digestibility of dry matter; ATTD OM = apparent total tract digestibility of organic

matter; ATTD NDF = apparent total tract digestibility of neutral detergent fiber; ATTD ADF = apparent total tract digestibility of acid detergent fiber; ATTD CP = apparent total tract digestibility of crude protein.

<sup>2</sup> Control = negative control.

<sup>3</sup> AO = *Aspergillus oryzae*.

<sup>4</sup> SCFP = *Sacharomicces cerevisiae* fermentation products.

<sup>5</sup> LY= live yeasts (*Sacharomicces cerevisiae*).

<sup>6</sup> Diet NDF was considered a covariate in the model.

<sup>7</sup> Diet NDF and pH were considered covariates in the model.

<sup>8</sup> Diet NFC was considered a covariate in the model.

<sup>9</sup> DIM were considered as covariates in the model.

<sup>10</sup> Diet CP was considered a covariate in the model.

<sup>11</sup> pH was considered as a covariate in the model.

## Appendix

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