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Review Article

Nutrition, gastrointestinal microorganisms and metabolites in mastitis occurrence and control

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ABSTRACT

Mastitis affects almost all mammals including humans and dairy cows. In the dairy industry, bovine mastitis is a disease with a persistently high incidence, causing serious losses to the health of cows, the quality of dairy products, and the economy of dairy farms. Although local udder infection caused by the invasion of exogenous pathogens into the mammary gland was considered the main cause of mastitis, evidence has been established and continues to grow, showing that nutrition factors and gastrointestinal microbiome (GM) as well as their metabolites are also involved in the development of mammary inflammatory response. Suboptimal nutrition is recognized as a risk factor for increased susceptibility to mastitis in cattle, in particular the negative energy balance. The majority of data regarding nutrition and bovine mastitis involves micronutrients. In addition, the dysbiotic GM can directly trigger or aggravate mastitis through entero-mammary gland pathway. The decreased beneficial commensal bacteria, lowered bacterial diversity, and increased pathogens as well as proinflammatory metabolites are found in both the milk and gastrointestinal tract of mastitic dairy cows. This review discussed the relationship between the nutrition (energy and micronutrient levels) and mastitis, summarized the role of GM and metabolites in regulating mastitis. Meanwhile, several non-antibiotics strategies were provided for the prevention and alleviation of mastitis, including micronutrients, probiotics, short-chain fatty acids, high-fiber diet, inulin, and aryl hydrocarbon receptor.

1. Introduction

Mastitis is an inflammatory response that occurs in the parenchyma or mesenchyme of the mammary gland. It leads to abnormalities in milk composition and udder appearance (redness, warmth, and pain), and systemic symptoms, such as fever. In the dairy industry, bovine mastitis accounts for 38% of the total direct cost associated with common production diseases (Das et al., 2018). A series of losses caused by mastitis, including decreased milk yield, milk quality and fertility, increased mortality, and treatment costs, are a severe blow to the dairy farm (Sharun et al., 2021).

Traditionally, mastitis has been ascribed to the invasion of exogenous pathogens from the cow's living environment. Actually, nutrition and gastrointestinal microbiome (GM), as well as their metabolites, can also affect the occurrence and development of mastitis (Fig. 1) (Hu et al., 2020; Ma et al., 2018; O'Rourke, 2009; Rodríguez, 2014). The main effect of nutrition on mammary health lies in its ability to suppress the immune system. Cows experiencing negative energy balance (NEB) have a higher risk of ketosis, resulting in impaired leukocyte function and an increased risk of mastitis (Bouvier-Muller et al., 2016; Heinrichs et al., 2009;

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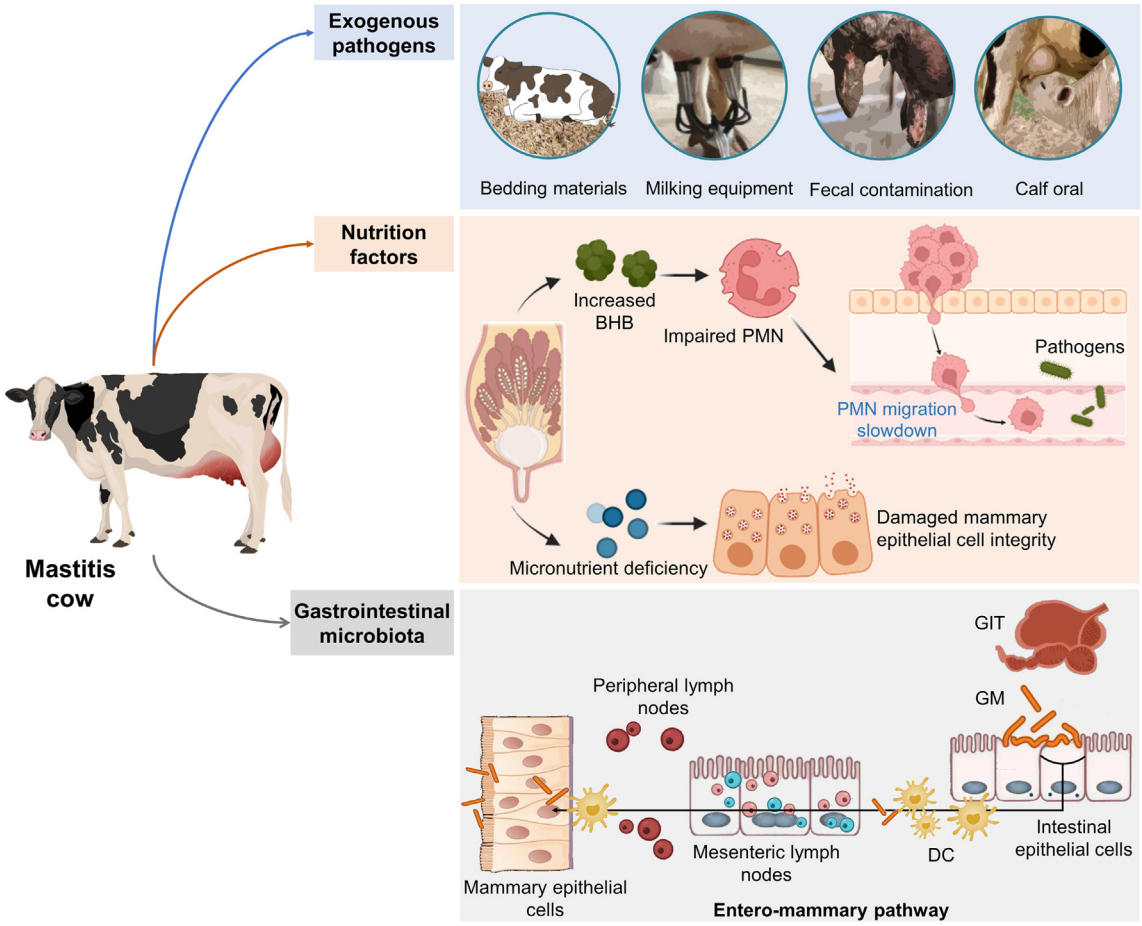


Fig. 1. Predisposing factors of mastitis in dairy cows. BHB = β-hydroxybutyrate; PMN = polymorphonuclear neutrophils; GIT = gastrointestinal tract; GM = gastrointestinal microbiome; DC = dendritic cell.

O'Rourke, 2009). The GM also plays a role in the development of the host immune system and resistance to pathogens invasion (Pickard et al., 2017). Recent data suggested that the dysbiosis of GM could directly induce or aggravate mastitis, exhibiting inflammatory cell infiltration and elevated myeloperoxidase activity in mammary gland tissues, especially an increase in blood-milk barrier permeability (Hu et al., 2020; Ma et al., 2018). The GM can be sampled and carried by mononuclear immune cells, mainly dendritic cells or macrophages, which are transferred to the mammary gland through hematogenous and lymphatic translocations (Rescigno et al., 2002; Rodríguez, 2014).

Currently, antibiotics intervention is still the mainstay of clinical mastitis (CM) treatment. However, the widespread use of antibiotics causes microbial dysbiosis in milk, and the increase of antibiotics residue in milk poses a further threat to human health (Anika et al., 2019). Dietary supplementation with trace minerals and vitamins (Cope et al., 2009; Moghimi-Kandelousi et al., 2020; Scaletti et al., 2003; Xiao et al., 2021), probiotics (Jiménez et al., 2008; Ma et al., 2018), and key GM metabolites, such as short-chain fatty acids (SCFA) (Hu et al., 2020) and activation of aryl hydrocarbon receptors (AhR) (Zhao et al., 2021), or intake of a high dietary fiber diet (Shively et al., 2018), could all alleviate mastitis. Our previous studies have shown ameliorated effects of inulin on cow subclinical mastitis (SCM) by modulating GM and metabolites (Wang et al., 2021a, 2022b, 2022c). As livestock practices aim to reduce the use of antibiotics in farm animals, there is a growing need to better understand the relationship between nutrients and infectious disease. Our data may provide a novel insight into the pathogenesis of mastitis and potential strategies for mastitis control.

2. Nutrition and mastitis

The decrease in dry mater intake and the increase in nutrients required for milk synthesis after parturition may result in NEB. Cows in NEB are likely to suffer from impaired mammary defense mechanisms (Bouvier-Muller et al., 2016; O'Rourke, 2009). The NEB and elevated serum β-hydroxybutyric acid were associated with the decreased leukocyte function, increasing the risk of intramammary infection in cows (Heinrichs et al., 2009; Suriyasathaporn et al., 2000). Polymorphonuclear neutrophils (PMN) and macrophages have attenuated phagocytosis due to energy deficiency, and the production of chemokines for blood leukocyte migration to infected glands is reduced. Essentially, high serum β-hydroxybutyric acid limits the ability of leukocytes to migrate to the infected udder. Polymorphonuclear neutrophils in cows with high serum β-hydroxybutyric acid levels (under NEB) cannot be recruited faster to the infected udder. Thus, these cells are out competed by bacteria, causing mastitis (Pérez-Báez et al., 2019; Suriyasathaporn et al., 2000; Zadoks, 2006). Studies have reported that cows with pre-partum ketosis are more likely to develop CM (Berge and Vertenten, 2014; Pérez-Báez et al., 2019). Ketosis is considered a gateway condition for other metabolic and infectious disorders, including mastitis. In addition to the influence

of energy status, micronutrient deficiencies also contribute to damaging the resistance of cows to mastitis (Heinrichs et al., 2009). Micronutrient deficiency can weaken primary defense of the mammary gland by altering keratin plug or impairing the integrity of mammary epithelial cells (Sordillo, 2016). The vitamin and mineral requirements of dairy cows are influenced by various factors, including age, pregnancy, production levels, and growth rate (NRC, 2001). It is generally believed that the amount of certain vitamins and minerals that animals need to maintain optimal immune function is greater than the amount they need to grow and reproduce. Lactation and growth performance may have been impaired before deficient symptoms become apparent (NRC, 2001).

3. Characteristics of microbiota and metabolites in milk, rumen and feces of mastitic dairy cows

Several studies reported reduced activity, lying behavior, feed intake, eating time, and cud chewing following mastitis (Fig. 2A) (Bareille et al., 2003; Yeiser et al., 2012; Zimov et al., 2011). Compared with healthy cows, lower diversity, richness and abundance of GM were found in mastitic dairy cows (Wang et al., 2021b), which might be attributed to the decreased feed intake (Yeiser et al., 2012) and lower dietary variety (Huang et al., 2022). Our previous investigations revealed a higher abundance of potentially pathogenic bacteria and proinflammatory compounds, but a lower abundance of potentially beneficial bacteria, in both the milk and gastrointestinal tract (GIT) of mastitic dairy cows (Wang et al., 2020a, 2020b; Wang et al., 2021b, 2022a). Therefore, we summarized our findings and other related studies in Fig. 2B.

3.1. Milk

Typical mastitis pathogens are classified into the following three categories. (1) Infectious pathogens (e.g., *Staphylococcus aureus*, *Streptococcus dysgalactiae*, *Streptococcus agalactiae* and *Mycoplasma* spp.), which are usually transmitted among herds during milking (Sharun et al., 2021). They generally colonize the epithelial surface, causing chronic infection, or invade the deep layers of mammary gland, causing fibrosis and abscesses. (2) Environmental pathogens (*Escherichia coli Serratia* spp., *Klebsiella pneumoniae Serratia* spp., *Enterobacter aerogenes Serratia* spp., *Serratia* spp., *Proteus Serratia* spp., and *Corynebacterium Serratia* spp., etc.), which elicit an inflammatory response by invading the mammary gland, are then partially eliminated by the host's innate immunity (Klaas and Zadoks, 2018). (3) Opportunistic pathogens (e.g., *Coagulase-negative Staphylococcus Serratia* spp. and *Pseudomonas Serratia* spp.), which are the most common bacteria on the teat apex, teat canal, and udder skin. They can transition from commensal bacteria to pathogenic bacteria when there is ecological dysbiosis between the microbiota and the host (Derakhshani et al., 2018).

Our previous study found a high level of ceramide (d18:1/22:0), a known pro-inflammatory mediator, in CM milk with *Staphylococcus* and *Streptococcus* as the main pathogens (Wang et al., 2020a, 2020b). Ceramide mediates the internalization of *Staphylococcus Serratia* spp. and *Streptococcus Serratia* spp. into mammalian cells and is involved in the activation of intracellular inflammatory signaling pathways and the release of cytokines (Grassmé and Becker, 2013). In SCM milk infected with *Acinetobacter* spp. and *Corynebacterium* spp., an enrichment of testosterone glucuronide was shown (Wang et al., 2020a, 2020b). Testosterone glucuronide can inhibit host antibody responses and interfere with lymphocyte transformation, resulting in increased susceptibility to infection (Tamimi et al., 2006). Moreover, upregulated arachidonic acid (prostaglandin F2α) was observed in mastitic milk, which is a key proinflammatory mediator during acute inflammation (Thomas et al., 2016). These findings suggest an enrichment of proinflammatory metabolites in milk during mastitis. In addition, more short peptides were observed in CM and SCM milk than in healthy ones (Xi et al., 2017). The elevated levels of free amino acids in milk may be ascribed to pathogen-specific fermentation or protein degradation (Xi et al., 2017; Eckersall, 2019).

However, the decrease in *Bifidobacterium* spp., *Dietzia* spp., *Alistipes* spp. and *Sphingobacterium* spp. is accompanied by the downregulation of metabolites involved in thiamine metabolism (thiamine and 5-aminoimidazole ribonucleotides), purine metabolism (xanthine), pyrimidine metabolism (urea and uridine) (Wang et al., 2020a, 2020b), phenylalanine metabolites (hippuric acid and benzoic acid), and tyrosine metabolite (4-hydroxyphenyl lactate) (Xi et al., 2017) in the milk of mastitic dairy cows. Thiamine and xanthine play important roles in inhibiting inflammatory signaling pathways (Crane et al., 2013; Pan et al., 2016). The decrease in urea may be attributed to the accumulation of bacteria and fungi in infected quarters, which can produce urease to degrade urea (Kananub et al., 2018). Benzoic acid, a precursor of hippuric acid, can inhibit the growth of *E. coli* (Knarreborg et al., 2002). 4-hydroxyphenyllactic acid is a tyrosine analog, which can be abundantly produced by *Bifidobacterium* spp. and *Lactobacillus* spp. The decreased of 4-hydroxyphenyllactate in mastitic milk may be related to the reduction of the above two genera (Ma et al., 2016; Wang et al., 2020a, 2020b). Furthermore, metabolites involved in energy metabolism (citric acid, (S)-malate, cis-aconitate, oxalate glutarate and L-carnitine) are reduced at the peak of infection (Eckersall, 2019; Xi et al., 2017), indicating energy expenditure during mastitis.

3.2. Rumen

Our previous study observed high abundance of bacteria associated with gut and oral inflammation, such as *Moraxella* spp., *Pasteurellaceae* spp., *Gastranaerophilales* spp. and *Neisseria* spp., in the rumen of CM cows (Wang et al., 2021b). *Moraxella* is a major pathogen causing respiratory tract infections and enteritis, with a strong association with rumen wall damage (Nagaraja, 2016). *Pasteurellaceae* spp., *Neisseriaceae* spp. and *Gastranaerophilales* spp. are known to be enriched in enteritis patients (Gevers et al., 2014; van Ulsen and Tommassen, 2006; Zhang et al., 2017). In addition, a great level of *Enterorhabdus* spp., a common opportunistic pathogen that causes intestinal infections, was observed in the rumen of SCM cows (Wang et al., 2021b). Hu et al. (2022) reported that in the rumen of cows with mastitis caused by subacute ruminal acidosis (SARA), the abundance of *Stenotrophomonas* spp. significantly increased, suggesting that the occurrence of mastitis in SARA cows may result from endogenous pathogens such as *Stenotrophomonas* spp.

A reduction in ruminal bacteria during mastitis was observed, including *Prevotella_1* spp., *Lachnospiraceae* spp., *Bifidobacterium* spp., *Romboutsia* spp., *Coprococcus* spp., *Eubacterium_ruminantium_group* spp., *Succinivibrionaceae* spp. and *Butyrivibrio* spp. (Wang et al., 2021b; Zhong et al., 2018). These are mainly SCFA-producing (especially propionate and butyrate) bacteria. Propionate and butyrate can limit the growth of pathogenic *Enterobacteriaceae* (Hippe et al., 2015), inhibit the production of pro-inflammatory cytokines and neutrophil migration by neutrophils, thereby improving the inflammatory response (Nakamura et al., 2018). The dysbiosis in the rumen microbiota resulted in decreased concentrations of SCFA in the rumen of mastitis cows (Wang et al., 2021b; Zhong et al., 2018).

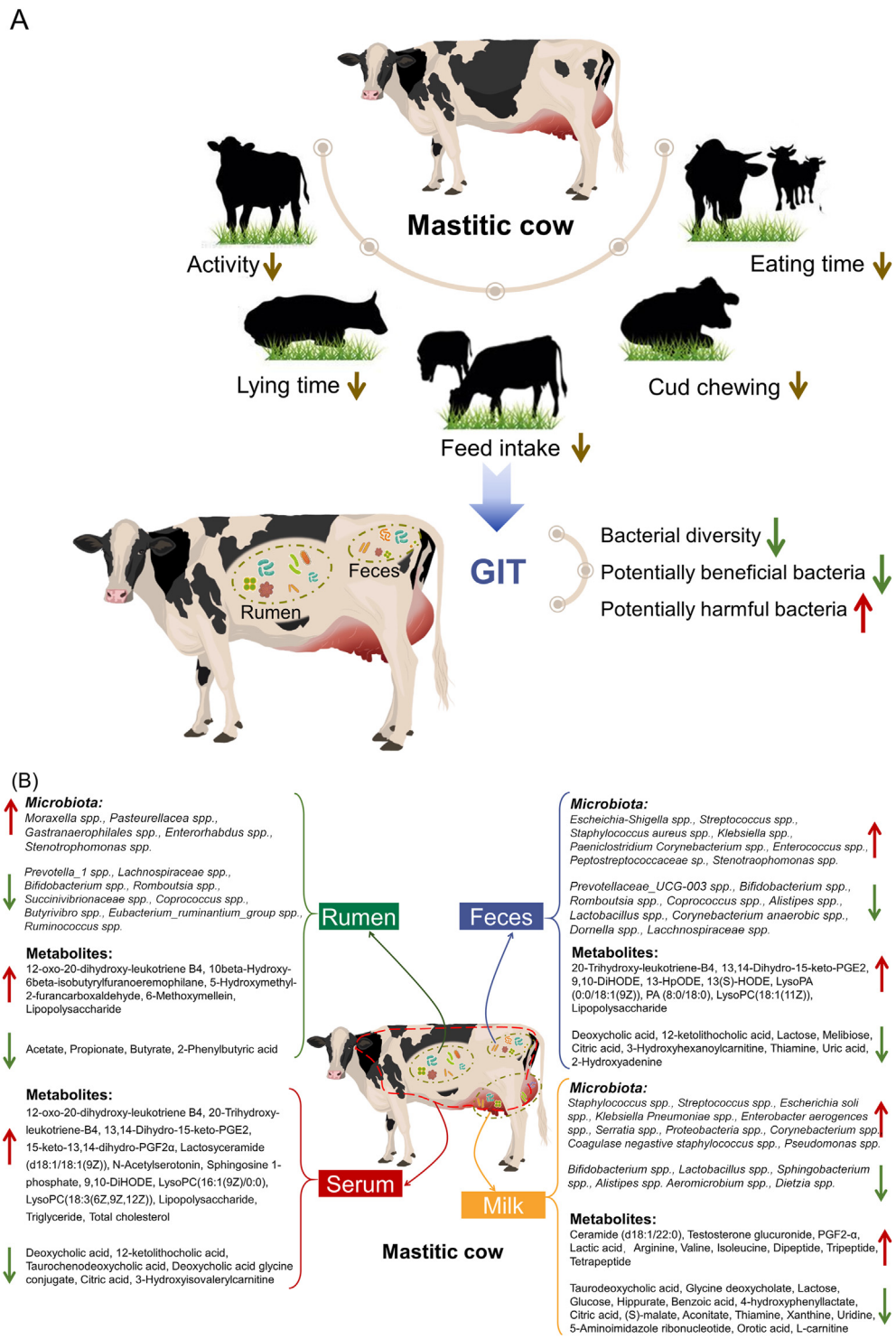


Fig. 2. Feed intake, activity behavior, and characteristics of gastrointestinal microbiome in mastitic dairy cows. (A) Characteristics of feeding and activity behavior in mastic cows. (B) The profile of microbiome and metabolites in rumen, feces, serum, and milk of mastitic dairy cows. GIT = gastrointestinal tract.

3.3. Feces

Greater abundances of *Escherichia-Shigella*, *Enterococcus*, *Streptococcus*, *Staphylococcus* (Wang et al., 2022a), *Ruminococcus* and *Oscillobacter* (Ma et al., 2018) were detected in the feces of CM cows. *Klebsiella*, *Paeniclostridium*, *Corynebacterium*, *Enterococcus*, and *Peptostreptococcaceae* were enriched in the feces of SCM cows (Scarsella et al., 2021); In which, *Escherichia-Shigella*, *Klebsiella*, *Corynebacterium* and *Enterococcus* are common mastitis pathogens (Pang et al., 2018). *Paeniclostridium* is a pathogen associated with intestinal inflammation (Kim et al., 2017). In addition, a decrease in *Prevotellaceae_UCG-003*, *Lachnospiraceae_NK3A20_group*, *Bifidobacterium*, *Romboutsia*, *Coprococcus*, *Alistipes*, *Lactobacillus* (Scarsella et al., 2021; Wang et al., 2022a), *Corynebacterium*

anaerobic, *Dornella*, *Lachnospiraceae* and *Rothia* (Ma et al., 2018) was reported in mastitic dairy cows. The deprivation of *Lactobacillus* and *Bifidobacterium* has been observed in both feces and milk of mastitic dairy cows (Ma et al., 2016; Wang et al., 2020a, 2020b). *Lactobacillus* produces bacteriocins, which plays an active role in controlling mastitis pathogens (Ma et al., 2016). *Bifidobacterium* in both milk and the GIT can induce an influx of PMN that enhance innate immunity in the bovine mammary gland, which plays a vital role in the elimination of secondary pathogens of mastitis (Nagahata et al., 2020). Deficiency of beneficial commensal microbes in the GIT and mammary gland may increase mastitis susceptibility (Ma et al., 2016). An epidemiological study suggested that the occurrence of bovine prototheca mastitis was correlated with persistent intestinal infection, with the source of infection being feces (Kurumisawa et al., 2018). These findings confirm the possibility of crosstalk between the bacteria in the GIT and the mammary gland.

Interestingly, our previous study found an increase in proinflammatory metabolites involved in arachidonic acids (20-trihydroxyleukotriene B4, 13,14-dihydro-15-keto-PGE2 and 12-oxo-20-dihydroxyleukotriene B4) and linoleic acids (9, 10-DiHODE, 13-HPODE and 13(S)-HODE), and a decrease in secondary bile acids (SBA) metabolites (i.e., taurochenodeoxycholic acid, 7α-ketodeoxycholic acid and glycocholic acid) in the feces of mastitic dairy cows (Wang et al., 2022a). The SBA with extensive anti-inflammatory effects have the capacity to suppress the expressions of proinflammatory cytokines and chemokines, relying on bile acid signaling receptors such as farnesoid X receptor and Takeda G-protein-coupled receptor 5 (Sinha et al., 2020). It is reported that the GM involved in the conversion of primary bile acids to SBA mainly include *Bifidobacterium* spp., *Lactobacillus* spp., *Lacetospiraceae* spp. and *Bacteroides* spp. (Jia et al., 2018). Thus, the reduction of the above GM may account for the decreased SBA levels. In addition, down-regulation of the citric acid cycle, carnitine, and purine metabolism was also observed in the feces of mastitic dairy cows (Wang et al., 2022a), which is consistent with the observations in milk (Wang et al., 2020a, 2020b; Xi et al., 2017). Other depleted metabolic pathways in feces, including lysine biosynthesis, purine and pyrimidine metabolism, and selenium (Se) metabolism, may be involved in intestinal mucosal protection (Ma et al., 2018).

Collectively, in mastitic dairy cows, the GIT shares similarities with milk in terms of microbiota and metabolites, characterized by a general increase in potential pathogens and pro-inflammatory metabolites involved in arachidonic acid, linoleic acid, and sphingomyelin metabolism, along with a reduction in beneficial commensal bacteria and compounds involved in carbohydrate, purines, vitamins, and energy metabolism.

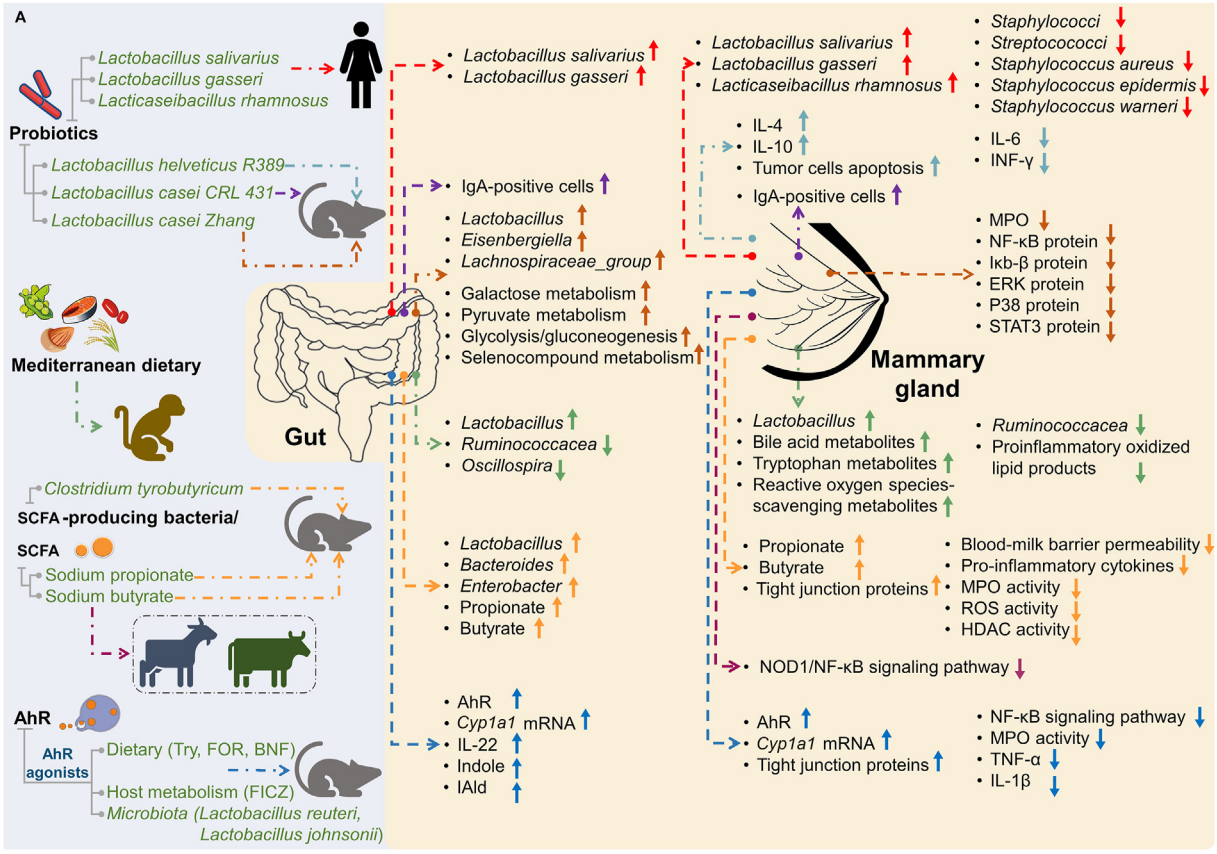
4. The role of gastrointestinal microbiome in regulating mastitis

4.1. Gastrointestinal microbiome-derived lipopolysaccharides (LPS) induced mastitis

Rumen commensal bacteria are involved in host immune protection and resistance to pathogens. The rumen epithelial-vascular barrier allows the absorption of fermentation products and also acts as a selective barrier against translocation and systemic spread of pathogens and toxins. The dysbiosis of ruminal microbiota increases rumen acidity and permeability, even leads to disruption of rumen and vascular endothelial barrier integrity, which promotes the translocation and systemic spread of pathogens and harmful metabolites, such as LPS, causing chronic low-grade inflammation (Nagaraja, 2016). During lactation, increased milk yield increases blood flow and allows more LPS into the mammary gland (Hu et al., 2022). In SARA cows, rumen-derived LPS is transferred into the blood and accumulates in the mammary gland by disrupting the integrity of the blood-milk barrier (Hu et al., 2022), and increases the levels of mammary pro-inflammatory factors (tumor necrosis factor [TNF]-α, interleukin [IL]-1β, IL-6, and IL-8) (Jin et al., 2016; Zhang et al., 2015). Dysbiosis in the GM increases GIT permeability, resulting in elevated levels of circulating GM-derived LPS, which are considered to be an inducer of mastitis.

4.2. Gastrointestinal microbiome triggers or aggravates mastitis through entero-mammary axis

Intramammary microbial dysbiosis is a visible indicator of mastitis (Patel et al., 2017; Wang et al., 2020a, 2020b). Currently, microorganisms found in the mammary gland are classified to be exogenous (from the external environment) and endogenous (from the host itself) (Fig. 1). Exogenous microorganisms entering the cow's mammary gland are from the environment and the oral cavity of the calf (Derakhshani et al., 2018). However, host GM may transfer into the mammary gland through endogenous pathways (Fig. 1). Previous studies support the notion that certain GM can migrate to the mammary gland through a mechanism involving mononuclear immune cells. These mononuclear phagocytes are mainly derived from peripheral blood and can differentiate into dendritic cells, which can capture GM and transport them to the mammary gland (Rescigno et al., 2002; Rodríguez, 2014). This process has been described as an entero-mammary pathway (Rescigno et al., 2002; Rodríguez, 2014; Young et al., 2015). The translocation of viable bacteria through the intact intestinal mucosa to distal tissues surface is called bacterial translocation (Nagpal and Yadav, 2017). An increased frequency of bacterial translocation from the gut across the mesenteric lymph nodes to the mammary gland during pregnancy and lactation in mice has been reported (Donnet-Hughes et al., 2010). Parallel phenomena were observed in dairy cows. Young et al. (2015) investigated the microbial composition and diversity in milk, blood, and fecal samples from healthy dairy cows and found that *Ruminococcus* spp., *Peptostreptococcus* spp. and *Bifidobacterium* spp. were present in all three sample types. It is speculated that these bacteria may be transferred from the gut to the mammary gland via circulating leukocytes. Recent studies further revealed that the dysbiotic GM could trigger or aggravate mastitis. Fecal microbiota transplantation (FMT) from mastitic dairy cows to the gut of sterile mice induced mastitis symptoms, as well as inflammation in serum, spleen, and colon. However, FMT from healthy hosts had no such effect (Ma et al., 2018). To investigated whether GM dysbiosis causes the translocation of pathogens on the entero-mammary axis, green fluorescent protein (GFP) labeled *E. coli* (GFP-*E. coli*) was orally administered on day 25 of FMT. Interestingly, significant GFP signals were detected in the mammary glands of mastitic mice (Zhao et al., 2023). These findings suggested that dysbiotic GM facilitated pathobiont translocation from the GIT to the mammary gland, ultimately causing mastitis. A subsequent study found that antibiotic-induced GM dysbiosis in *S. aureus*-infected mastitic mice resulted in increased blood-milk barrier permeability and mastitis severity. Fecal microbiota transplantation from healthy mice reversed these effects (Hu et al., 2020). To date, knowledge regarding the functions of ruminal microbiota and metabolites in dairy cow mastitis remains limited. Collectively, the endogenous entero-mammary axis provides evidence for the microbial connection between the GIT and the mammary gland of dairy cows.


A
Probiotics
Lactobacillus salivarius
Lactobacillus gasseri
Lacticaseibacillus rhamnosus
Lactobacillus helveticus R389
Lactobacillus casei CRL 431
Lactobacillus casei Zhang
Mediterranean dietary
Gut
SCFA-producing bacteria/
Clostridium tyrobutyricum
SCFA
Sodium propionate
Sodium butyrate
AhR
AhR agonists
Dietary (Try, FOR, BNF)
Host metabolism (FICZ)
Microbiota (Lactobacillus reuteri, Lactobacillus johnsonii)
Lactobacillus salivarius
Lactobacillus gasseri
IgA-positive cells
Lactobacillus
Eisenbergiella
Lachnospiraceae_group
Galactose metabolism
Pyruvate metabolism
Glycolysis/gluconeogenesis
Selenocompound metabolism
Lactobacillus
Ruminococcacea
Oscillospira
Lactobacillus
Bacteroides
Enterobacter
Propionate
Butyrate
AhR
Cyp1a1 mRNA
IL-22
Indole
IAld
Lactobacillus salivarius
Lactobacillus gasseri
Lacticaseibacillus rhamnosus
IL-4
IL-10
Tumor cells apoptosis
IgA-positive cells
Mammary gland
Lactobacillus
Bile acid metabolites
Tryptophan metabolites
Reactive oxygen species-scavenging metabolites
Propionate
Butyrate
Tight junction proteins
NOD1/NF-κB signaling pathway
AhR
Cyp1a1 mRNA
Tight junction proteins
Staphylococci
Streptococcaceae
Staphylococcus aureus
Staphylococcus epidermis
Staphylococcus warneri
IL-6
INF-γ
MPO
NF-κB protein
Ikb-β protein
ERK protein
P38 protein
STAT3 protein
Ruminococcacea
Proinflammatory oxidized lipid products
Blood-milk barrier permeability
Pro-inflammatory cytokines
MPO activity
ROS activity
HDAC activity
NF-κB signaling pathway
MPO activity
TNF-α
IL-1β
B
Rumen
Streptococcus
Staphylococcus
Escherichia-Shigella
Clostridia
Arachidonic acid metabolism
Linoleic acid metabolism
Sphingolipid metabolism
Glycerophospholipid metabolism
Butyrivibrio
Lachnospiraceae_NK3A20_group
Lactobacillus
Bifidobacterium
Eubacterium_ruminantium_group
Prevotella
Bacteroidales_BS11_gut_group
Bacteroidales_RF16_group
Galactose metabolism
Glycolytic pathway
Glutathione metabolism
Thiamine metabolism
Phenylalanine metabolism
Butyrate
Propionate
Hindgut (Feces)
Inulin
Subclinical mastitic cows
Paeniclostridium
Peptostreptococcus
Arachidonic acid metabolism
Linoleic acids metabolism
Sphingolipid metabolism
Alistipes
Bacteroidales
Bifidobacterium
Lachnospiraceae_AC2044_grou
Lachnospiraceae_NK3A20_group
Secondary bile acid biosynthesis
Bile acid biosynthesis
Galactose metabolism
Serum
Arachidonic acid metabolism
Linoleic acids metabolism
IL-6 LPS
IL-8 TNF-α
TC
TG LDL
Secondary bile acid metabolism
Bile secretion
Phenylalanine metabolism
Tryptophan metabolism
Escherichia-Shigella
Enterobacteriaceae
Klebsiella
Staphylococcus
Enterococcus
Streptococcus
Arachidonic acid metabolism
Linoleic acid metabolism
Phospholipid metabolism
Milk SCC
Bifidobacterium
Lactobacillus
Prevotellaceae_UCG-003
Muribaculaceae
Phenylalanine metabolism
Tryptophan metabolism
TCA cycle
Galactose metabolism
Mammary gland

5. Potential non-antibiotics strategy for mastitis control

Dietary supplementation with trace minerals (i.e., Cu, Zn and Se) and vitamins (i.e., vitamins E, A and β-carotene), probiotics, GM-derived metabolites, such as SCFA and AhR, or the consumption of a high dietary fiber diet play a remarkable role in the prevention of mastitis (Fig. 3A). Our previous studies have shown the amelioration effects of inulin supplementation on SCM in dairy cows (Fig. 3B).

5.1. Trace minerals and vitamins

The role of micronutrients in specific and non-specific immune defense is the key to the resistance to mammary infection (Heinrichs et al., 2009; O'Rourke, 2009). Vitamin E, being a component of lipid membranes, plays a vital role in protecting lipid membranes from attacks by tissue reactive oxygen species (Xiao et al., 2021). Selenium is a component of glutathione peroxidase, which acts in the cytoplasm. Vitamin E deficiency is often observed in perinatal cows, and many dairy cows are also found to have limited or marginal Se (Mehdi and Dufrasne, 2016). Vitamin E and Se deficiencies results in impaired PMN activity (Vasiĺ et al., 2022). Dietary supplementation of Se and vitamin E in dairy cows facilitates the faster flow of PMN into milk after bacterial attack in mammary glands, and increases the intracellular killing effect of PMN to pathogens (Xiao et al., 2021). Zinc is essential for maintaining skin integrity and is involved in the development and normal function of innate immune cells such as neutrophils. Studies reported that dietary supplementation with 5 mg/kg of Zn hydroxychloride and 40 mg/kg of Zn–Met complex could improve integrity of mammary gland epithelium (Weng et al., 2018). Meanwhile, receiving 32.5 and 36.0 kg/d Zn for 12 weeks could reduce somatic cell counts (SCC) and amyloid A levels in milk of dairy cows (Cope et al., 2009). Reyes-Jara et al. (2016) found that a concentration as low as 250 mg/kg Cu was able to inhibit the great majority of microorganisms isolated from bovine mastitic milk samples. Dietary supplementation with (20 mg/kg) with copper sulfate beginning 60 d prepartum through 42 d of lactation has been shown to reduce clinical response (Scaletti et al., 2003) and morbidity in the *E. coli*-infected mastitic dairy cows. The antibacterial properties of Cu can be explained by oxidative destruction of bacterial lipids, proteins, and DNA (Willing et al., 2018). Vitamin A is required for the morphogenesis and development of mammary glands, as well as during weaning, when epithelial cell death is combined with tissue remodeling. It is essential to maintain the integrity and stability of the mammary epithelial mucosa (Cabezuelo et al., 2019). Beta-carotene can reduce the formation of superoxides within phagocytes. Phagocytosis and internal killing of bacteria is the primary mechanism by which phagocytes destroy pathogens (Sordillo et al., 1997). Moreover, β-carotene possesses anti-inflammatory properties, inhibiting nuclear factor-κ-gene binding (NF-κB) activation by decreasing STIM1/ORAI1 expression, and thus alleviating LPS-induced inflammation in bovine mammary epithelial cells (Meng et al., 2022).

Micronutrient deficiencies may cause immunosuppression, a decline in immune cell activity or dysfunction of the innate defense mechanism in the nipple, thereby contributing to the development of mastitis. Micronutrients should be considered when implementing mastitis prevention or nutritional regulation in dairy farms.

5.2. Probiotics

The extraintestinal translocation of GM may have a beneficial impact on immune regulation (Rodríguez, 2014; Young et al., 2015). The use of probiotics in treating mastitis is an inspiring example. Probiotics are live and metabolically active bacteria that exert beneficial effects by interacting with GM to restore microbial homeostasis or correct dysbiosis (Rainard and Foucras, 2018). Lactic acid bacteria isolated from human milk have shown therapeutic potential for mastitis. In *staphylococcal* mastitis, oral administration of *Lactobacillus salivarius* spp. (1×10^9 CFU), *L. salivarius* spp. and *Lactobacillus gasseri* spp. (1×10^{10} CFU) are able to reduce the mean *Staphylococcus* counts in milk, and relieve mastitic symptoms (Arroyo et al., 2010; Jiménez et al., 2008). *L. salivarius* spp. and *L. gasseri* spp. exhibit high survival rates and strong adhesion to intestinal cells in the GIT. Their antibacterial properties rely on the production of antibacterial compounds (lactic acid, acetic acid, and hydrogen peroxide) (Martín et al., 2005). On the other hand, lactic acid bacteria have been demonstrated to enhance immunity in the mammary gland. de Moreno de LeBlanc et al. (2005) observed elevated IL-4 and IL-10 and reduced INF-γ and IL-6 in the serum and mammary gland of mice with breast cancer after feeding milk fermented by *Lactobacillus helveticus R389* spp. for 7 d. As mentioned above, dysbiotic GM can trigger mastitis (Hu et al., 2020; Ma et al., 2018). However, supplementation with probiotics appears to reverse this phenomenon. Fecal microbiota transplantation from mastitic dairy cows to germ-free mice induced inflammatory responses in the mammary gland and gut of mice. Subsequent supplementation with *Lactobacillus casei Zhang* at a dose of 5×10^8 CFU per day for 25 d alleviates the inflammatory reaction in the gut and blood. The damages to mammary acinar cells and neutrophil infiltration were also attenuated. The myeloperoxidase concentration and expression levels of inflammation-related proteins (NF-κB, Iκb-β, ERK, p38, and STAT3) in the mammary gland were significantly decreased (Ma et al., 2018). In ruminants, a probiotic mix at 50 g/d (containing 1.3×10^9 CFU/g of a mixture probiotics; *L. casei Zhang* spp. and *Lactobacillus plantarum P-8* spp. with the proportion of each strain 1:1) administration significantly decreased milk SCC in dairy cows, and reduced their susceptibility to mastitis by increasing the contents of milk immunoglobulin G, lactoferrin, lysozyme, and lactoperoxidase (Xu et al., 2017). The beneficial effects might be attributed to the improved ruminal microbiota after probiotics treatment. The reduction of certain pathogens, especially *Bacillus cereus* spp., a predisposing factor for developing CM (Jones and Turnbull, 1981), upon probiotics supplementation facilitate the ruminal microbiota to a balance and healthy state that potentially lowers the risk of diseases of lactating cows. Similarly, Li et al. (2021) reported that marine-derived *Bacillus amyloliquefaciens-9* (GB-9) spp. could be a helpful probiotic to control SCM in lactating goats. The supplementation with 0.3% GB-9 (wt/wt) for 7 weeks in decreasing the SCC was associated with the altered abundance of *Bacteroides* spp., which was correlated with the concentrations of immunoglobulins and chemokines.

Possible mechanisms of probiotics in mastitis control include: (1) direct antagonism through the production of metabolites (lactic acid, SCFA, and hydrogen peroxide) or bacteriocins, as well as competitive exclusion through competition for nutrients (Sanders et al., 2018); (2) enhancement of the epithelial barrier function by maintaining effective concentrations of IgA and antimicrobial

Fig. 3. Potential non-antibiotics strategy for mastitis control. (A) The role of trace minerals and vitamins, probiotics, high dietary fiber diet, short-chain fatty acids (SCFA), and activation of aryl hydrocarbon receptors (AhR) in the prevention of mastitis. (B) Alleviation of subclinical mastitis by inulin supplementation. FOR = formononetin; BNF = β-naphthoflavone; FICZ = 6-formylindolo[3,2-b] carbazole; IAld = indole-3-aldehyde; INF-γ = interferon-γ; MPO = myeloperoxidase; ROS = reactive oxygen species; HDAC = histone deacetylase; SCM = subclinical mastitis; TC = total cholesterol; TG = triglyceride; LPS = lipopolysaccharide; LDL = low density lipoprotein; SCC = somatic cell counts.

peptides secreted on the surface of epithelial cells through the reinforcement of tight junctions (TJ) (Ohland and Macnaughton, 2010); and (3) interaction with monocytes, macrophages and dendritic cells in innate immune responses, and regulation of T helper cells in adaptive immune responses (Klaenhammer et al., 2012).

Although oral administration of probiotics can be used as modulators to prevent and control the development of mastitis and enhance the host's immune system, its clinical effects remain partially controversial. More clinical and prospective studies are needed to validate the therapy effects of probiotics in mastitis.

5.3. Short-chain fatty acids

Dysbiosis in GM may cause deprivation of SCFA (Hu et al., 2020; Wang et al., 2021b). Our previous study found lower concentrations of acetate, propionate and butyrate in the rumen of mastitic dairy cows compared with healthy ones (Wang et al., 2021b), which may be partly related to the decrease in feed intake and feeding behavior during mastitis (Yeiser et al., 2012; Zimov et al., 2011). Similarly, Zhong et al. (2018) observed reduced propionate concentration in the rumen of cows with high SCC (>1,000,000 cells/mL) compared to those with low SCC (<200,000 cells/mL). Hu et al. (2020) observed increased permeability of the blood-milk barrier and *S. aureus*-induced mastitis severity in GM dysbiosis mice. Moreover, dysbiotic GM decreased SCFA level. Treatments with propionate, butyrate and butyrate-producing bacteria such as *Clostridium tyrobutyricum* spp., increased the relative abundances of *Lactobacillus* spp. and *Bacteroides* spp. and decreased the abundance of *Enterobacter* spp. in the gut. The concentrations of propionate and butyrate in the feces and mammary gland were elevated. Meanwhile, blood-milk barrier permeability, inflammatory cell infiltration, and myeloperoxidase activity were significantly reduced. In LPS-induced murine mastitis, propionate treatment increased the expressions of TJ proteins (occludin and claudin-3) in the mammary epithelial barrier, and decreased the levels of inflammatory factors (TNF-α, IL-6, and IL-1β), as well as the expressions of phosphorylated (p)-p65, p-IκB proteins in mice mammary epithelial cells (Wang et al., 2017). Sodium butyrate could also diminish the abundances of p-IκBα/IκBα and p-p65/p65 proteins and the nuclear localization of NF-κB p65 protein induced in LPS-induced inflammation in bovine mammary epithelial cells (BMECs) (Sun et al., 2020). Moreover, propionate and butyrate have capacity to reduce inflammatory gene expression in BMECs by inhibiting histone deacetylase activity and increasing histone H3 acetylation (Ali et al., 2021; Chen et al., 2019; Silva et al., 2018). Oral sodium butyrate was found to be effective against mastitis in ruminants. High-concentrate feeding-induced SARA could increase the concentration of γ-D-glutamyl-meso-diaminopimelic acid (iE-DAP) in the rumen, which activated nucleotide-binding oligomerization domain protein 1 (NOD1)-NF-κB signaling pathway-dependent inflammation in the mammary glands of dairy cows and dairy goats (Wang et al., 2019, 2021). The iE-DAP is a component of bacterial peptidoglycan, which triggered inflammation by activation of NOD1 signaling pathway (Chandra Roy et al., 2018). Sodium butyrate supplementation abated the inflammation in the mammary gland through inhibiting the decrease in ruminal pH and decreasing the concentrations of LPS, TNF-α, IL-1β and IL-6 and plasma iE-DAP. This, in turn, suppressed the expressions of NOD1, phosphorylated inhibitor of kappa B alpha (p-IκBα) and NF-κB p65, ultimately inhibiting the NOD1/NF-κB inflammatory pathway.

These data reveal that the protective effects of propionate and butyrate against mastitis are primarily achieved by regulating the permeability of the blood-milk barrier, enhancing epithelial-cell TJ, restoring the blood-milk barrier, and inactivating NF-κB signaling and histone deacetylase activity.

5.4. Aryl hydrocarbon receptors

The AhR is widely recognized as a ligand-dependent transcription factor with prominent contributions to immunity, inflammation resolution and resistance to host infection (Lawrence and Vorderstrasse, 2013). Compounds derived from the diet, microorganisms, microbial derivatives and host metabolism are potent agonists of AhR (Shinde and McGaha, 2018). The activated AhR can reduce intestinal epithelial permeability by inhibiting NF-κB activation (Scott et al., 2020). Moreover, AhR promoted intestinal epithelial cell proliferation and produced antimicrobial peptides through the generation of IL-22, which is essential for clearance of gut pathogens (Sonnenberg et al., 2011).

Interestingly, recent studies further revealed the role of AhR in mastitis. Zhao et al. (2021) activated AhR using 6-formylindolo[3,2-b] carbazole (FICZ, an AhR agonist), which ameliorated mastitis symptoms by limiting NF-κB activation and enhancing barrier function. The GM of mastitic mice was further disrupted with antibiotics, which aggravated the mastitis response and impaired mammary AhR activation and intestinal barrier integrity. However, dietary supplementation with tryptophan or *Lactobacillus reuteri* decreased histological scores, myeloperoxidase activity, and TNF-α and IL-1β concentrations in the mammary gland. The inhibition of *E. coli*-infected mastitis by activated AhR is related to the improvement of barrier integrity and suppression of inflammatory signaling. Aryl hydrocarbon receptor activation increased the expression of occludin and claudin-3, improved the integrity of the blood-milk barrier, reduced p-p65 and p-IκB expressions, and inhibited the phosphorylation level of NF-κB. Dietary tryptophan can be metabolized to various indole derivatives by GM. Aryl hydrocarbon receptor activation by *L. reuteri* and tryptophan metabolism are mainly ascribed to the production of indole-3-aldehyde and indole (Zhang et al., 2021; Zhao et al., 2021). Aryl hydrocarbon receptor activated by indole could inhibit the infiltration of inflammatory T cells (Hezaveh et al., 2022). Furthermore, flavonoid is also a potent AhR agonist. Beta-naphthoflavone (BNF)-mediated AhR activation increases *Cyp1a1* expression in mammary gland tissue of pregnant mice (Belton et al., 2018). In addition, formononetin (FOR), a natural flavonoid, was reported to improve blood-milk barrier integrity by activating AhR-induced sarcoma (Src) inactivation (Xiang et al., 2022). Sarcoma is a component of AhR cytoplasmic complex. Aryl hydrocarbon receptor deficiency causes enhanced Src phosphorylation (Gutiérrez-Vázquez and Quintana, 2018). In LPS-induced mastitic mice, FOR pretreatment increased *AhR* expression in a concentration-dependent manner, which increased the expressions of TJ proteins (claudin-3, occludin, and zonula occludens-1) in mammary gland and downregulated LPS-induced Src phosphorylation to mitigate inflammation (Xiang et al., 2022).

The AhR profoundly affects inflammatory diseases (Shinde and McGaha, 2018) and resistance to host infection (Lawrence and Vorderstrasse, 2013; Wang et al., 2012). The remarkable regulatory capacity of activated AhR in mastitis warrants further investigation to explore its potential role in treating mastitis.

5.5. Diet patterns

Diet can shape and affect the composition of GM. Recent studies have suggested that dietary patterns could also modulate the profiles of the mammary gland microbiota and metabolites (Shively et al., 2018). In one study, two groups of female monkeys were offered either a Mediterranean diet (higher plant-derived protein

and fat, fish and dairy products, monounsaturated fatty acids (MUFA), fiber, and lower sodium and refined sugar) or a Western diet (higher saturated fat and sodium, and lower MUFA and n-3 fatty acids) for 31 months. The results showed an increase in *Lactobacillus* spp. and a decrease in *Ruminococcus* spp. in both the mammary glands and feces of monkeys on the Mediterranean diet, suggesting several similarities in the effects of diet on the microbiome in gut and mammary gland (Shively et al., 2018). Elevated *Lactobacillus* spp. in the mammary gland was conductive to resist mammary infection (Jiménez et al., 2008; Ma et al., 2016). In addition, the Mediterranean diet increased the levels of bile acids (e.g., cholate, glycocholate, and taurocholate) and tryptophan metabolites (mainly indoles) in the mammary gland (Shively et al., 2018), all of which have general anti-inflammatory activities. Tryptophan-derived bacterial metabolites, mainly indoles, could decrease the levels of LPS-induced IL-1β and IL-8, inhibit the TNF-alpha-mediated activation of NF-κB (Beaumont et al., 2018), and enhance epithelial-cell TJ (Bansal et al., 2010; Shimada et al., 2013). The consumers of the Mediterranean diet showed a reduction in proinflammatory lipid oxidation products in mammary tissue, suggesting the modulation of oxidative stress in the mammary gland by the Mediterranean diet (Shively et al., 2018). Conversely, a high-fat diet induced changes in GM and metabolites, as well as the infiltration of pro-inflammatory macrophages (Kawano et al., 2016; Wang et al., 2020a, 2020b). Meanwhile, it decreased the expression of intestinal TJ-related genes and promoted the translocation of LPS to the mammary gland, thereby increasing mammary barrier permeability. Supplementation with fish oil could reverse this phenomenon (Soto-Pantoja et al., 2021).

In ruminants, interestingly, our latest research found that supplementation with a water-soluble dietary fiber, inulin, was an effective nutritional strategy in cow mastitis control (Wang et al., 2021a, 2022b, 2022c). Our results showed that inulin intake might affect the profile of microbiota and metabolites in the mammary gland of SCM cows, which might be ascribed to an improved GM. Inulin is composed of 31 β-D-fructofuranose and contains one terminal glucose moiety [$\alpha(1 \rightarrow 2)$ linkage] per molecule (Ahmed and Rashid, 2019). As the anomeric carbon of fructose residues is in the β-configuration, inulin cannot be broken down by digestive enzymes in the GIT, but it can be used by GM (García-Peris et al., 2012; Wang et al., 2021a, 2022b). Inulin has prebiotic activity by promoting the proliferation of probiotics, such as *Bifidobacterium* spp. and *Lactobacillus* spp., and inhibiting the growth of pathogens (García-Peris et al., 2012). Our preliminary study found that inulin supplementation increased the abundances of propionate- (*Prevotella* spp., *Bacteroidales_BS11_gut_group* spp. and *Bacteroidales_RF16_group* spp. etc.) and butyrate-producing bacteria (*Butyrivibrio* spp., *Lactobacillus* spp. and *Bifidobacterium* spp. etc.) in the rumen and feces of SCM cows, which further increased propionate and butyrate concentrations in the GIT (Poulsen et al., 2012; Tian et al., 2019; Wang et al., 2021a, 2022b). In addition, *Bifidobacterium* spp., *Lachnospiraceae* spp., *Lactobacillus* spp., *Ruminococcus* spp. and *Bacteroidetes* spp. participant in the conversion of primary bile acids to SBA in the GIT (Jia et al., 2018). These SCFA and SBA metabolites have widely anti-inflammatory properties as mentioned earlier (Tedelind et al., 2007; Hu et al., 2020). The changes in the GM after inulin intake may further affect the microbiota structure in the mammary gland of SCM cows. The increased levels of *Lactobacillus* and *Bifidobacterium* were also found in milk after inulin supplementation (Wang et al., 2022c). On the other hand, decreased *Escherichia-Shigella* spp., *Staphylococcus* spp., *Streptococcus* spp. and *Corynebacterium* spp. accompanied with lower lipid pro-inflammatory metabolites (arachidonic acid, linoleic acid, and sphingomyelin metabolites) were also observed in milk (Wang et al., 2022c). The changes in the composition of microbiome and metabolites in milk showed a similar trend to those observed in the GIT after inulin supplementation, suggesting that some co-regulated microbiota and compounds exist between the two niches.

Current data suggested that dietary interventions have the potential to affect the internal environment of the mammary gland and the development of breast-related diseases. This further supports the connection between the gut and mammary gland. Thus, varying dietary patterns could be considered as an alternative strategy for mastitis control and other breast-related conditions.

6. Conclusion

Mastitis is a significant concern for mammary gland health and milk quality in mammals. However, exogenous pathogens are no longer considered the only major threat. The nutritional level and host's gastrointestinal microbiome can also affect the occurrence and development of mastitis. Negative energy balance and micronutrient deficiencies can increase susceptibility to mastitis by weakening the functionality of immune cells in the mammary gland. Simultaneously, dysbiosis in the GM could directly induce or aggravate mastitis, potentially through the entero-mammary gland axis. Ensuring adequate energy, minerals and vitamins, and maintaining GM diversity and homeostasis are essential for sustaining udder health and immune status. These strategies help to control mastitis by a non-antibiotic approach. However, it should be noted that the management of dairy farms plays a key role in mastitis control, such as providing a clean and dry environment for cows. The greatest significance of nutritional intervention is to prevent the occurrence of the disease, or to delay the development of disease in the early stages, such as SCM. Therefore, a holistic approach should be taken, with nutritional management as an integral component of the control program.

Author contributions

Yue Wang: Writing – original draft; Conceptualization. **Yiguang Zhao**, **Xuemei Nan**, **Liang Yang:** Writing – reviewing & editing. **Hui Wang**, **Jun Liu:** Visualization. **Benhai Xiong**, **Junhu Yao**, **Xiangfang Tang** and **Linshu Jiang:** Project administration; Supervision; Validation.

Declaration of competing interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, and there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the content of this paper.

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