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Immunostimulation and Novel Therapeutic Properties of Probiotic Bacteria in The Prevention of Mammary Gland Inflammation: A Review Article

Article Info.

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Abstract

The most prevalent and financially important inflammatory disease of the mammary gland is mastitis, which affects both humans and animals, especially those involved in dairy manufacturing. Mastitis increases the chance of culling the affected animals, decreases milk production, and poor quality of milk. In general, infections caused by bacteria that penetrate the mammary epithelial cells and interfere with the mechanical barrier, as well as produce severe inflammation, are the main cause of the infection and disease. Conventional antibiotics are still the standard of treatment, but their extensive usage raises significant concerns about recurring infections, milk residual contamination, and antimicrobial resistance (AMR). Recently, there has been increasing interest in investigating non-antibiotic alternatives and potential treatment methods such as immunobiotics, or probiotics (lactic acid bacteria and Bifidobacterium spp.), which have immunomodulatory properties along with their bioactive compound antimicrobial, antibiofilm, anti-inflammatory, and immune stimulation. This is one novel preventive method for the treatment and avoidance of bovine mastitis.

Key words: Bovine mastitis, Mammary gland inflammation,

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Introduction

One of the most common conditions affecting dairy cattle globally is bovine mastitis (BM). The term "BM" refers to mammary gland inflammation (MG), which has a significant impact on milk production and quality, animal welfare, the dairy industry's financial success, and public health .Many pathogens, such as bacteria, viruses, and fungi, can cause a range of clinical signs, from acute MG inflammation to silent subclinical infection (1). One of the main clinical signs of an MG infection is an acute inflammation, which is caused by the activation of immune cells by the synthesis of cytokines and chemokines. Mastitis cure rates are influenced by the type of infections that cause the disease, the effectiveness of the administered antibiotics, and the immune status of hosts (2). Antimicrobial resistance (AMR) poses a major threat to dairy cattle's health, which is often due to the overuse of antibiotics. Furthermore, the distribution AMR bacterial infections and drug residues through the consumption of raw milk from cows treated previously with antibiotics, AMR caused by Bovine mastitis (BM) may pose serious health hazards to the public (3).

Also, milk containing antibiotic residues may interfere with fermentation. It is necessary to review the traditional antibiotics-based strategy and try innovative and long-lasting therapeutic solutions. In addition, the AMR genes can be transferred to bacteria by antibiotic therapy,hence the probiotics, genetic selection, herbal therapies, and vaccination could be reasonable alternatives to antibiotic substitutes in the management and/or avoidance of mastitis. It was considered that probiotics might be a more cost-efficient and effective tool than herbal therapy and immunization. Furthermore, using probiotics may reduce the incidence of AMR, and it is also an environmentally safe material (5). Therefore, probiotics, especially those with immunomodulatory properties or immunobiotics, may be a viable substitute for managing and/ or treating BM (6).

Immunobiotics are thought to be safe for both human and healthy livestock production, and they improve the health of both humans and animals by modifying the host immunological responses (7). Recent research indicates that certain probiotic strains have a remarkable ability to modulate MG's response to Toll-like receptor (TLR)-mediated inflammation, even though the majority of research has shown that these strains can suppress mammary pathogens through competitive exclusion or the production of antimicrobial compounds. In this respect, our research showed that immunobiotic lactic acid bacteria (LAB) strains might be employed to prevent BM by modulating mammary epithelium immune responses utilizing an initially developed bovine mammary epithelial (BME) cell line (8).

A new emerging approach in the field of MG immunobiology is the use of immunobiotics. Probiotics in dairy cows have allegedly sparked claims of their potential for preventing or curing mastitis, according to a number of research studies, but even with all of the studies being done on this subject (9-10).

The review presents a summary of the importance of probiotic bacteria and their relationship to anti-inflammatory immune stimulation and effective control of mastitis and treatment of disease also in dairy cows, as well as the establishment of numerous strategies to enhance the treatment and control of these conditions.

Bovine mastitis

Inflammation of the bovine mammary gland is one of the most serious diseases affecting dairy herds globally because of its significant financial impact, which is seen in both decreased production and culling rates. The primary classification of bovine mastitis is based on its etiology (infectious and non-infectious) and clinical (or subclinical) characteristics. The most frequent causes are infectious ones, and bacterial infections are frequently the most common manifestation in herds. Additionally, bacterial pathogens are divided into several groups: Environmental, opportunistic, and contagious bacteria (11-13).

Numerous studies indicate that *Staphylococcus aureus*, *Streptococcus agalactiae*, *Streptococcus uberis*, *Escherichia coli*, and *Klebsiella pneumoniae* are the most common etiological agents in mastitis. Furthermore, as resistance mechanisms spread worldwide, bacterial resistance has emerged as a growing problem. As of right now, resistant strains are easily created by conventional antibiotic treatments. There have been numerous reports of resistance to antimicrobials such as erythromycin, gentamicin, amoxicillin, tetracycline, amikacin, and penicillin. However, recent research has shown that resistance to novel antibiotics has increased; bacterial profiles have demonstrated resistance to vancomycin, colistin, tigecycline, ceftazidime, cefquinome, and piperacillin. Moreover, the issues of drug residues and human consumption are of high priority in public health (14-16).

Classification of Bovine Mastitis

Bovine mastitis is classified to :a) Clinical features factors: Which are indicated by clinical mastitis characterized by the presence of clots, flakes, or watery discharges in milk, and subclinical mastitis is increasingly difficult to diagnose, since there are no obvious symptoms in milk or animals (17).

b) Noninfectious factors: Machine milking-related mechanical injuries can seriously harm quarters, increasing their susceptibility to infections as a result of keratin or mucous membrane damage lining the teat sinus (12).

c) Infectious disease factors: The exact etiology of mastitis is unknown; currently, about 200 microorganisms are linked to the disease, and novel pathogens, including as bacteria, viruses, fungi, and yeast, are constantly being found and reported (12-18).

Influence of Bovine Mastitis on Financial Losses

The dairy industry suffers significant financial losses as a result of bovine mastitis, treatment, lost output, altered product quality, wasted milk, additional work, culling, subpar animal welfare, and the possibility of other illnesses It was reported that financial impacts of mastitis on animal production in countries such as India was estimated~0.8 about billion USD, in Japan ~ 0.77 billion USD, in the USA 2 billion USD , in Canada 0.31 billion USD, 0.8 billion USD in Colombia, in Bangladesh ~0.002 billion USD, and in Australia USD 1.3 (19-20-21-22-23). In summary, BM raises the possibility of financial losses for both the agricultural companies and individual farmers. It was found that 31% milk production, 24% treatment expenses, 18% milk waste, 4% excess labor demand, and 23% early culling are all associated with the expected losses to BM. The worldwide dairy industry has calculated that BM costs them between USD 19.7 and USD 32 billion annually (24-25). Hence, the above statistics data indicate that the yield of dairy cattle is significantly affected economically by mastitis.

Conventional, alternative, and new potential Strategies for Preventing of Bovine Mastitis

Most bovine mastitis management practices today focus on preventing problems during milking by using a good milking system and hygienic milking practices. Conventional and alternative mastitis control and treatment techniques, such as antibiotics, immunotherapy, bacteriophages, antimicrobial peptides, stem cell therapy, natural secretion factors, diet, dry cow and lactation therapy, genetic selection, botanical therapy, nanoparticle therapy and vaccination, are not always successful or efficient in controlling and fully protecting cattle against bovine mastitis due to the diversity of microbial pathogens (26). According to recent research, probiotics and their bioactive compound-producing could be a potential treatment or prevention approach to bovine mastitis that also treats the problem of developing antimicrobial resistance (27-28-29). The use of immunobiotics, or probiotics with immunomodulatory properties, is one novel preventive method for the treatment of bovine mastitis (BM)

Probiotic mechanism, a new potential control method against bovine mastitis

1- Indirect and direct effects of probiotics on microbial pathogens:

The most widely used probiotic formulations are lyophilized or fresh products of fermentation that are taken orally, the most widely utilized and researched bacteria are those belonging to the genera *Lactobacillus* spp. and *Bifidobacterium* spp. , which are found in a healthy human intestine, especially healthy infant stool. Numerous benefits of probiotics involve the body's indigenous microbiota. Oral probiotics are living, metabolically active bacteria that act in concert with the microbiota of the digestive tract to re-establish microbial balance or repair symbiosis, among other therapeutic benefits (30). Researchers who discovered bacterial DNA in milk are casting doubts on the long-held belief that the mammary gland is a sterile organ. This result was taken as proof that beneficial bacterial communities are formed in the mammary gland of dairy cows or breastfeeding mothers (31- 32).

To prevent or cure bovine mastitis, probiotics are becoming more popular as an intriguing substitute (33). Other finding showed that lactic acid bacteria, as part of the indigenous microbiota of the teat canal, might be used as candidates in bovine mastitis prevention(34). As well as Klostermann *et al.* (35). indicated that intra-mammary administration of a live culture of *Lactococcus lactis* may be as effective as antibiotic treatment in certain cases, given their demonstrated promise in this area, researchers from all around the world are collaborating to develop probiotic-based formulations for both the avoidance and treatment of bovine mastitis (36).

Staphylococcal mastitis has been treated with oral probiotics made from specific strains of *Lactobacillus* spp. that were obtained from human breast milk. Also, Lactic acid, short-chain fatty acids, hydrogen peroxide, nitric oxide, and bacteriocins are among the antimicrobial substances produced by a number of probiotic bacteria that may be able to suppress microbial infections. Just because a substance works well in a lab (in vitro) doesn't mean it will work the same way in a living organism (in vivo) to have a significant impact, so an antimicrobial compound that is effective in vitro might not be effective in vivo. This is another crucial factor to take into account. Therefore, bacteriocins could be more efficient when administered directly than probiotics (32)

2- Enhancing the Mechanical Barrier

The physical protection provided by the epithelial barrier is one of the main ways the mammary gland (MG) defends itself. Below summarizes the basic steps of these defense mechanisms as described by Zubareva *et al.* (37) and Mubarik *et al.* (38). The following are some ways that probiotics support or strengthen this barrier:

a- Protection of Tight Junctions: Studies have demonstrated that probiotics strengthen the tight connections among epithelial cells, halting the spread of pathogens. For instance, strains such as *Lacticaseibacillus rhamnosus* can upregulate proteins that are essential for tight junction function, such as claudins and occludin.
b- Mucin Secretion and production: Some probiotic strains increase the production and secretion of mucins, as well as glycoproteins, which reduce adhesion and invasion by capturing or excluding microbial pathogens at the surface of epithelial layers.
c- Exclusion of Competition: Probiotics and microbial pathogens vie for mammary gland epithelial cells' attachment sites. It limits the ability of infections to colonize the gland and inhibits the formation of biofilms via filling these niches.

3- Effect on Immunomodulation and stimulation

According to previous research (39, -41) Probiotics actively modulate the host's immune stimulation and response in addition to providing physical protection as display in figure (1), assisting in establishing a balance between restricted tissue damage and efficient clearance of pathogens via:

a- TLR Stimulation and Modulation: To decrease excessive pro-inflammatory signals, several probiotics, such as *Limosilactobacillus reuteri* and *Bifidobacterium longum* interact with Toll-like receptors (TLR2 and TLR4); this modification may preserve the immune system sufficiently activated to defend against infections while preventing the overproduction of cytokines (minimizing hyper-inflammations) that are pro-inflammatory.

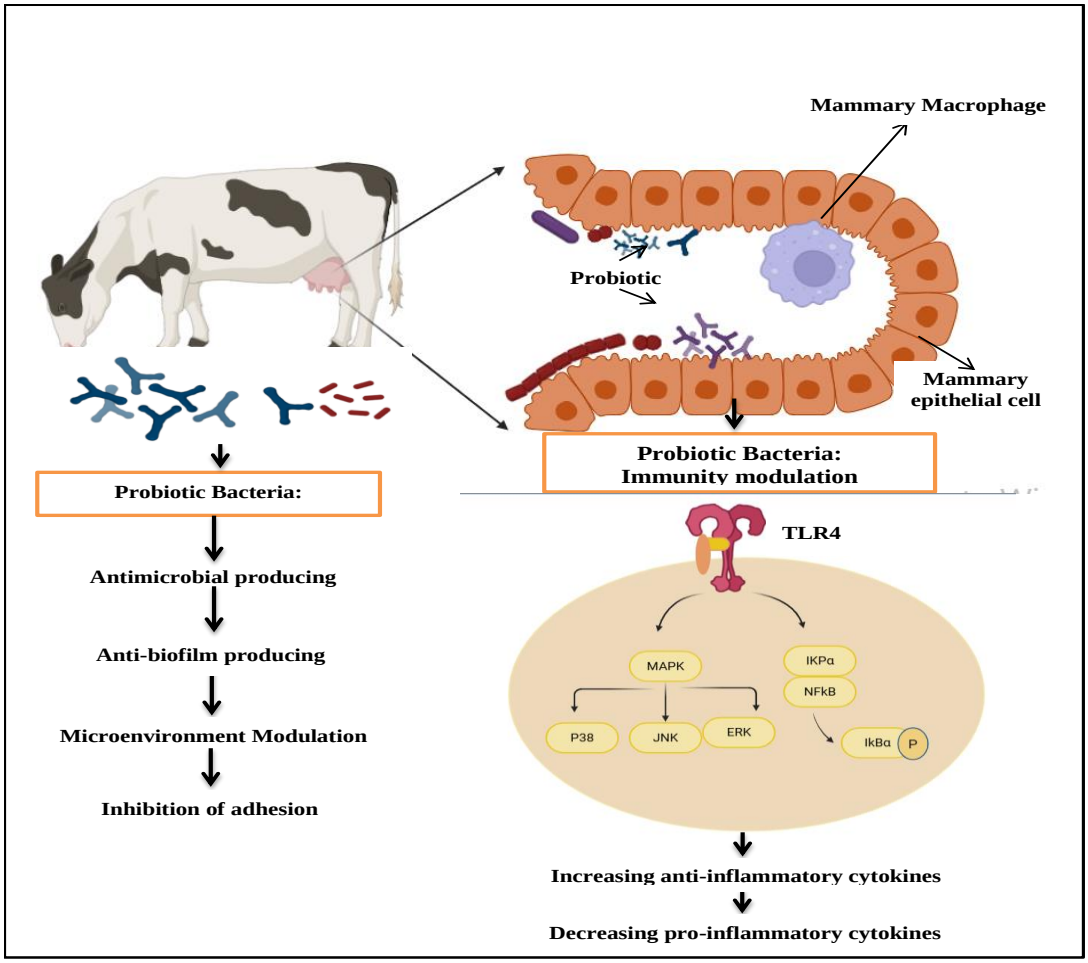

Figure 1: Effect of probiotics on immunostimulation and normal milk flow from cows (Created by Bio Render)

b- Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) Suppression: The decreased activity of the NF-κB signaling pathway is a major way that probiotics as *Lacticaseibacillus rhamnosus* and *Lacticaseibacillus casei*, lower pro-inflammation, This reduces tissue inflammation and damage by lowering the transcription of inflammatory cytokines, such Tumor necrosis factor-α (TNF-α), Interleukin-6 (IL-6) , and Interleukin-1β (IL-1β).

c- Cytokine Regulation: It has been discovered that some probiotic strains as *Lacticaseibacillus paracasei and Bifidobacterium breve* reduce pro-inflammatory cytokines while increasing the production of anti-inflammatory cytokines, such as interlukin -10(IL-10). The alteration in cytokines leads to the recovery of tissue quickly and decreases the level of inflammation.

d- Immune Cell Attraction*Limosilactobacillus fermentum* and *Ligilactobacillus salivarius* may have a beneficial effect on the activation and attraction of immune cells, including dendritic cells (DC), neutrophils(Neo), and macrophages, improving the host's capacity to eradicate infections without stimulating chronic- inflammation.

4-Antimicrobial and antibiofilm action

Additionally, Researchers proved probiotics have direct antibacterial properties that prevent or eradicate the microorganisms that cause mastitis, and without inducing resistance to antibiotics, the antibacterial activities can be especially helpful in decreasing pathogen challenges, such as the following below (32-42-43):

a- Production of Bacteriocins: Numerous LAB strains, such as *Lactobacillus acidophilus* and *Enterococcus faecium* secrete bacteriocins, which are short antimicrobial peptides that specifically inhibit or suppress similar species of bacteria, such as *Escherichia coli* and *Staphylococcus. aureus.*

b- Production of organic acid from *Lactiplantibacillus plantarum*, *Lactobacillus delbrueckii* and *Bifidobacterium bifidum* lead to block virulent pathogens that develop and adhere to host tissues when their pH level for their environment is acidic due to producing organic acids via fermentation of lactic acid along with its metabolites.

c- Bio-surfactants and Hydrogen Peroxide: the reactive oxygen molecules and bio-surfactants, which are produced by certain probiotics as *Lactobacillus johnsonii*, *L. gasseri*, can damage the cell membranes of microbial pathogens or prevent the formation of biofilms.

Limitations and Clinical Uses Application

In light of the increasing rate of antibiotic resistance, probiotics indicate a potential supplement and/or substitute for conventional antibiotics to reduce the incidence of mastitis and also for treatment; however, when using probiotics in therapeutic settings, it is crucial to thoroughly evaluate a number of criteria:

1-Applications and Advantages in Clinical Practice:

a- Decrease in Antibiotic Use: Research has demonstrated that certain probiotic strains may decrease bacterial populations and mastitis indicators via minimizing consumption of antibiotics and the potential risks associated from using them randomly (42).

b- Side Effect Description: In general, all probiotics are extremely safe and have a slight possibility of side effects. Because they may improve the physical condition and health of both dams and infants by modifying the dam's milk microbiota via their application during breastfeeding or lactation is especially promising. (44).

c- Simplified Administration: Probiotics can be taken orally or via intramammary medication, providing a variety of treatment methods that can be adapted to various clinical contexts (39).

2- The limitations and Complications:

Strain-Specific benefits and probiotic efficacy greatly depend on the strain; not every strain may offer identical advantages, making trial standardization more difficult to achieve (45). As well as the dosage and administration for optimal probiotic viability and efficacy in the mammary gland (MG) , appropriate dosage schedules, formulations, and administration techniques still need to be established (46).

Furthermore, challenges regarding consistency and clinical reliability are raised by the broad variations in probiotic product integrity and oversight by regulations, and finally, the restricted massive amounts of experimental trials—although the experimental data are strong, larger randomized controlled trials are required to verify permanent safety as well as effectiveness within the diversity of populations (47).

Methods of Administering Probiotic Bacteria to Treat Mastitis

Probiotic bacteria are a promising new strategy for preventing and treating mastitis, especially in dairy cows, according to other researchers (48-49). The administered probiotics can be taken in several main ways, the most important of which are:

1. **Oral administration:** Probiotics are administered via feed or water. They work to modify the intestinal microbiome and strengthen systemic immunity, reducing the likelihood of pathogens being transferred to the mammary gland.

2**. Intramammary infus**ion: Probiotic bacteria are introduced directly into the teat canal after milking. This is an effective method for displacing pathogenic microbes from the site of infection and enhancing the local immune response.

3. **Topical/Teat application**: Probiotics are applied to the surface of the teat to prevent the adhesion of pathogenic bacteria and form a protective layer that reduces the penetration of pathogens.

Studies have shown that the use of probiotics such as *Lactobacillus* spp. and *Bifidobacterium* spp. has reduced mastitis rates, enhanced the natural immune response, and reduced the need for

antibiotics. Therefore, the choice of administration method depends on the goal (preventive or therapeutic) and the health and production conditions of the herd (35).

Prospects for the Future

Including probiotic strains in mastitis treatment protocols in addition to traditional therapies, as well as the creation of specialized probiotic strain supplements with improved antibacterial, antibiofilm, immunomodulatory, and immunostimulation agents and adhesion properties, and bioactive compounds along with prebiotics produced from probiotic strains during their metabolism have an active function against mammalian glandular mastitis.

Conclusion

Probiotic bacteria's diverse involvement in preventing and treating mastitis through immunological modulation, mechanical barrier strengthening, and direct antibacterial activity is highlighted by the growing body of research. Probiotics provide a viable, long-term substitute or supplement to antibiotics, tackling important issues including resistance to antimicrobial and infection recurrence.

Important probiotic strains, including *Lactobacillus plantarum*, *Lactobacillus casei*, *Lactobacillus rhamnosus*, and *Lactiplantibacillus paraplantarum*, great potential in blocking the colonization of pathogens, enhancing mammary epithelial authenticity, and regulating pathways of inflammation (e.g., TLR/NF-κB). More standardized trials are needed to enhance strain selection, dosage, as well as administration before these results can possibly be applied in medical applications.

Future studies should emphasize customized probiotic treatments based on each patient's unique microbiota composition, integrating probiotics along with prebiotics together with other bioactive compound, as well as utilizing developments in metabolomics and genetics to increase effectiveness. For probiotic-based therapeutics in mastitis to be widely accepted in medical applications, cooperation between microbiologists, veterinarians, physicians, and regulatory agencies becomes important.

Conflicts Of Interest

The authors declare that there is no conflict of interest.

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التحفيز المناعي والخصائص العلاجية الجديدة للبكتريا الحيويه العلاجيه في الوقاية من التهاب الضرع

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الخلاصة

التهاب الضرع هو أكثر الأمراض الالتهابية شيوعًا وأهمية من الناحية المالية، ويصيب كلًا من البشر والحيوانات، وخاصةً تلك العاملة في مجال تصنيع الألبان. يزيد التهاب الضرع من احتمالية إعدام الحيوانات المصابة، وانخفاض إنتاج الحليب، وسوء جودته. بشكل عام، تُعدّ العدوى التي تسببها البكتيريا التي تخترق الخلايا الظهارية الثدية وتتداخل مع الحاجز الميكانيكي، بالإضافة إلى تسببها في التهاب حاد، السبب الرئيسي للعدوى والمرض. لا تزال المضادات الحيوية التقليدية هي العلاج الأساسي، إلا أن استخدامها المكثف يثير مخاوف كبيرة بشأن تكرار العدوى، وتلوث بقايا الحليب، ومقاومة المضادات الحيوية (AMR). في الآونة الأخيرة، يتزايد الاهتمام بدراسة البدائل غير المضادة للمضادات الحيوية وطرق العلاج المحتملة، مثل المضادات الحيوية المناعية، أو البروبايتيك (بكتيريا حمض اللاكتيك وأنواع البيفيدوباكتيريوم)، التي تتميز بخصائص تعديل المناعة، إلى جانب مركّبها النشط بيولوجيًا، المضاد للميكروبات، والمضاد للأغشية الحيوية، والمضاد للالتهابات، والمحفز المناعي. تُعد هذه إحدى الطرق الوقائية الجديدة لعلاج التهاب الضرع البقري والوقاية منه.

الكلمات المفتاحية: التهاب الضرع البقري, التهاب الغدة الثدية , البكتريا العلاجيه, التحفيز المناعي.