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A Comprehensive Review on the Role of Mastitis in Dairy Ruminants and Associated Factors

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ABSTRACT

Mastitis in small ruminants is a complex disease that causes financial losses in the dairy sheep and goat sectors due to decreased productivity. Animal care, cleanliness and management are all critical aspects of this economically significant dairy cow disease. The biofilm formation is considered a selective advantage for pathogens causing mastitis, facilitating bacterial persistence in the udder. The pathogenic agents include a variety of gram-bacteria (gram-positive and gram-negative) that can be either contagious pathogens named *Staphylococcus aureus*, *Streptococcus agalactiae*, *Mycoplasma* spp. or environmental (e.g., *Escherichia coli*, *Streptococcus uberis*). The review highlights knowledge and understanding of pathogen, strain-specific and different natural and synthetic methods used for the controls, treatment and emergency measures in the control of bovine mastitis.

Keywords: Bovine mastitis; Bacteria; Antibiotic; Natural products

INTRODUCTION

Mastitis is a major economic challenge in the dairy sector all over. Mastitis is one of the most financially destructive illnesses in dairy cattle. It is also regarded as one of the most serious illnesses affecting the welfare of farm animals. It is an endemic infection of dairy cows that causes inflammation of the mammary organs and udder tissue. It is caused by bacteria (or bugs), poor milking methods, milking equipment failures, teat injuries and direct exposure to bacteria in the environment are all examples of ways bacteria might be introduced. It is the most prevalent disease that causes financial loss in the dairy industry due to decreased milk yield and poor quality. A change in the milk, such as clotting, looking, composition, watery and/or bloody, is the most evident indicator of mastitis. Warm, swollen and painful to the touch udders are also common, as are fever, sadness and a lack of appetite. The Somatic Cell Count (SCC) will rise in all mastitis-affected cows. Furthermore, antibiotics in milk have an impact on human intestinal bacterial flora and may contribute to the formation of antibiotic-resistant bacteria. Mastitis eradication in dairy cows has been a long-term goal that has yet to be realized. This article provides an overview of the risk factors that have been linked to the occurrence and severity of bovine mastitis [1-4].

LITERATURE REVIEW

Several Classifications of Mastitis

Clinical, sub-clinical and chronic mastitis are the three types of bovine mastitis as shown in **Table 1**.

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Table 1: Different clinical stages based on barn observations murphy 1956.

Pathogen	Mild-clinical	Severe-clinical; also swelling or general illness	Non-clinical
Streptococcal, *Strep. agalactiae*	Yes	Yes	Yes
Streptococcal, other	Yes	Yes	Yes
Staphylococcal	Yes	Yes	Yes
Bacillary	Yes	Yes	Yes

Depending on the severity of the inflammation, clinical mastitis can be classified as per-acute, acute or sub-acute as shown in **Table 2**.

Table 2: Types of mastitis based on severity system.

Type of mastitis	
Mild mastitis	Abnormal milk production (e.g., clots, flakes, watery)
Moderate mastitis	Under inflammation and abnormal milk production
Severe mastitis	Systemic illness (e.g., dehydration, weakness)

Genetic Basis of Mastitis Resistance

Mastitis resistance is a diverse feature that is influenced by both genetic and physiological and environmental variables, including infection pressure. Several independent studies on different breeds of dairy cattle have established the genetic variability of mastitis resistance. Clinical mastitis causes hormonal changes such as decreased Luteinizing Hormone (LH) pulsatile secretion, decreased estradiol production and ovulation failure, revealing a scientific basis for a link between mastitis and infertility in cattle. Antibody response and neutrophil functionality were the key immune features investigated, as neutrophil recruitment and activity are critical in the innate defense against udder infection. TLR 4 (Toll-Like Receptor 4) is one such potential gene that is responsible for revealing a scientific basis for a link between mastitis and infertility in cattle [5-7].

Lactoferrin and Lysozyme

External secretions, polymorphonuclear leukocytes and macrophages all contain lysozyme, a bacteriolytic enzyme. The Lysozyme gene was found to have a substantial relationship with the Somatic Cell Score (SCS) and the 305-day milk output. Lactoferrin differs from iron-binding transferrin in blood, particularly in its ability to bind iron at low pH, so lactoferrin in milk would not be the result of vascular leakage. Two genes encoding proteins found in milk and involved in the udder's innate defense mechanisms: Lactoferrin (BTA22), an iron-binding protein with bacteriostatic properties primarily in the involuted mammary gland and lysozyme (BTA5), a protein that can specifically cleave bacterial cell walls. At the time of neutrophil degranulation, Leffel and Spitznagel 1975 discovered that almost 80% of the lactoferrin present was discharged into the extracellular fluid.

Causes of Mastitis

The most common cause of bovine mastitis is bacterial Inter Mammary Infection (IMI). Several host factors influence the severity and outcome of IMI, including innate host resistance, energy balance, immunological condition, parity and lactation stage. Mastitis is caused by a variety of infections and is divided into pathogenic and environmental mastitis epidemiologically. In pathogenic mastitis, the etiological agents include a huge spectrum of gram-positive and gram-negative bacteria that can be contagious e.g., *Staphylococcus aureus, Streptococcus agalactiae, Mycoplasma* spp. On another hand, environmental negative *Staphylococcus*, *Streptococcus uberis*, *Strept. dysgalactiae*. A wide range of mastitis is a broad term that refers to intra-mammary infections caused by microorganisms whose major reservoir is the cow's environment e.g., *Escherichia coli*, *Enterococcus* spp, coagulaselence factors have been evolved by pathogens to infect tissue in the mammary gland. Contagious pathogens have their primary reservoir in the udders of diseased cows. Environmental pathogens were less common than infectious infections. They transfer from cow to cow, especially during milking and are known to cause chronic sub-clinical infections with clinical episode flare-ups. Mastitis reduces milk productivity in both quantity and quality, resulting in significant financial losses. The application of various well-characterized infection control techniques, such as those listed in the National Mastitis Council's "5-point" plan, later extended to a "10-point" strategy and is essential for the prevention and management of infectious mastitis [8-10].

Different Bacterial Strains of Bovine Mastitis-Contagious Mastitis Pathogen

Staphylococcus aureus: *Staphylococcus aureus* is a gram-positive bacteria with a spherical shape. It colonizes the nipple skin and penetrates the mammary gland canal. It's more difficult to get rid of *S. aureus*. Infections reduce milk production by 45% per quarter or 15% per infected animal. *S. aureus* virulence factors and surface proteins have been studied for their ability to act as antigens, eliciting a protective immune response. Because it does not elicit the same robust immune response in cows as *E. coli* or endotoxin, the infection is always milder, resulting in chronic mastitis lasting a few months. The glycocalyx is an exopolysaccharide produced by *Staphylococcus aureus*. It aids *S. aureus* in adhering to mammary epithelial cells and acquiring nutrients, allowing it to persist in a high-shear environment while also protecting it against antibiotics, disinfectants and phagocytosis. Because the antibiotic does not reach the target location at minimum inhibitory concentration, gram-positive bacteria are difficult to treat with antibiotics [11-13].

Streptococcus agalactiae: *Streptococcus agalactiae* is a gram-positive coccus (round bacteria) that tends to chain formation. It is a major cause of contagious mastitis. an obligate infection of the mammary gland that is spread directly between cows during milking with a low global prevalence. Low production rates and a high SCC are, however, normal. It can live permanently in cow mammary glands by building a biofilm that allows it to cling and remain in the mammary gland, increasing resistance to host factors and food shortage at the same time [14].

***Mycoplasma* spp:** *Mycoplasma* spp. cause gland fibrosis, abscesses and lymphatic nodule fibrosis by damaging secretory tissue. *M. californicum*, *M. canadense* and *M. bovigenitalium* are three other important species. Mycoplasmosis is usually linked to the beginning of mastitis outbreaks, the introduction of new animals into a herd, past bronchial or arthritic disease and herds with antibiotic-resistant mastitis. Animals of all ages, as well as those in the middle of lactation, are vulnerable. *Mycoplasma* infection is more common in early lactation and it can be isolated from high-production animals without causing any symptoms. The infection is commonly endogenous during outbreaks of respiratory disease in heifers or cows and the onset is quick [15].

Environmental Mastitis Pathogens

Environmental spp. are common in dairy herds, producing clinical and subclinical mastitis. Their presence has been increased as management techniques against infectious bacteria such as *Staphylococcus aureus* have become more widely implemented. Environmental infections are infrequent and persistent enough to induce mastitis or a considerable increase in Somatic Cell Counts (SCC) in bulk milk (values greater than 400,000 cells/ml). Opportunistic infections, such as coagulase-negative staphylococci, cause moderate forms of mastitis. Many other microbes, including yeasts, could be to blame for causing mastitis, but they are less common and only occur when certain conditions exist. Changes in the environment are increasing exposure to these contaminants. *Pseudomonas aeruginosa* mastitis is frequently linked to contaminated water sources and it causes endotoxemia in the same way that coliform mastitis infections do. Quinn et al. found that *Nocardia asteroides* produce severe mastitis with fibrosis and lasting damage to mammary tissues [16].

Escherichia coli: The bacteria *Escherichia coli* can infect the mammary gland by entering the udder through the teat canal. It is the most common gram-negative pathogen discovered. It's present in the environment around dairy cows, such as the herd's bedding, especially when it's moist. Because its pathogenicity is not mediated by a single and particular virulence factor, *E. coli* was categorized as an opportunistic pathogen with many virulence factors. The severity of mastitis caused by this bacteria is linked to factors other than strain characteristics, such as host factors. In most cases, host defenses eliminate intramammary *E. coli* infections on their own. *E. coli* mastitis isolates could generate biofilm, albeit at varying intensities Fernandes *E. coli* causes an inflammatory response in the host very quickly. The endotoxin lipopolysaccharide, which is present on the outer membrane of *E. coli*, is the virulence factor well known for triggering the inflammatory response of Lipo Poly Saccharide (LPS). When LPS binds to the Toll Like Receptor (TLR4) in combination with LPS-binding protein and cluster of differentiation 14, several signaling cascades are triggered. When TLR4 is activated, it recruits members of the Interleukin-1 (IL-1) receptor-associated kinase family and Tumor Necrosis Factor (TNF) receptor-associated factor 6, which then activates the Transforming Growth Factor-Activated Kinase 1 (TAK1) complex. The activated TAK1 complex serves as an inhibitor of the nuclear factor-B kinase (IKK) complex. The state of the host's defenses is crucial in deciding the fate of infections. As a result, rather than *E. coli* pathogenicity, the severity of *E. coli* mastitis is mostly dictated by the host factor.

Streptococcus uberis: *Strep. uberis* is a bacterial pathogen that causes persistent mastitis and is linked to both clinical and subclinical infections Abureema. Proteins play a major role in the production of *Streptococcus uberis* biofilms. Several *S. uberis* strains isolated from mastitis were able to form biofilms, indicating that milk components are potent biofilm inducers. It has been detected in different parts of animals including lips, tonsils, skin, oral cavity, rumen, respiratory tract, rectum, teat orifice, teat canals, infected udders, feces and wounds.

Biofilms and Mastitis

Biofilms are organized colonies of bacteria that are adhered to an inert or living surface and encased in a self-produced polymeric matrix. Biofilm production can be damaging to host tissues because it encourages the release of lysosomal enzymes, reactive oxygen and nitrogen species by phagocytes. Biofilm production is a dynamic process and any biofilm will eventually shed planktonic cells that reproduce quickly and inhabit adjacent surfaces. The initial adhesion and subsequent aggregation into multicellular structures are the first steps in the creation of biofilms. The role of biofilm in human infections has been an expanding research field since bacterial aggregates were observed in 1977 in the lungs of patients with cystic fibrosis. One of the distinguishing properties of biofilms is the formation of an exopolysaccharide matrix. Biofilm production is accompanied by considerable genetic and physiological changes in the microbes, resulting in a loss of sensitivity to almost all antibiotic classes, among other things. The existence of biofilm in the udders of dairy cows was studied in another investigation by collecting swabs from the udders of killed dairy cows with *S. aureus* infection. Swabs were taken from the teat cistern, Biofilms are seen in the majority of chronic wounds in humans and are thought to play a role in the pathophysiology of poor wound healing. Gland cistern, parenchyma and immunofluorescence labeling of Polysaccharide Intercellular Adhesions (PIA), a component of the *S. aureus* biofilm matrix, were used to stain them. Studies proved the presence of biofilms in bovines with mastitis. Swabs were taken from the teat cistern, gland cistern and parenchyma and immunofluorescence labeling of Polysaccharide Intercellular Adhesions (PIA), a component of the *S. aureus* biofilm matrix, was used to stain them. This shows the mastitis-causing pathogens and their biofilm formation ability. Fluorescence microscopy was used to examine the samples. Biofilms are seen in the majority of chronic wounds in humans and are thought to play a role in the pathophysiology of poor wound healing [17] (**Table 3**).

Table 3: Main mastitis-causing pathogens and their biofilm formation ability.

Pathogenic agents	Biofilm formation	Mastitis type
S. aureus	Positive	Subclinical mastitis
CNS: Coagulase Negative *Staphylococci*	Positive	Subclinical mastitis
E. coli	Positive	Clinical mastitis
S. uberis	Positive	Clinical mastitis
S. dysgalactiae	Positive	Clinical mastitis
S. agalactiae	Positive	Mastitis

Bovine Mastitis Control and Treatment: Natural Compounds

Plant derived anti-microbials: Plants represent a promising source of novel physiologically active antibacterial drugs. The low toxicity of plant derived substances is another advantage. In LPS induced mastitis in mice, baicalein, a flavone isolated from *Scutellaria baicalensis* and *Scutellaria lateriflora*, was claimed to inhibit inflammatory response by reducing TLR4 mediated NF-B and MAP signaling pathways Turmeric's main ingredient, curcumin, has been touted as one of the finest prospective therapeutic agents for treating bovine mastitis He et al. The researchers tested 10 commercial essential oils on mastitis-causing pathogens in livestock (*Staphylococcu S. aureus*, Staphylococcus. *chromogenes, Staphylococcus. siuri, Staphylococcus. warneri, Staphylococcus. xylosus* and *E. coli*) and three of them, *Satureja montana* L., *Thymus vulgaris* L. *ct. thymol* and *Origanum majorana* L., were able to inhibit the tested pathogens as shown in **Table 4**. Doss also evaluated extracts from twenty medicinal plants against a variety of pathogenic pathogens that cause bovine mastitis.

Table 4: Role of different plant extracts in bovine mastitis.

Plant/Extract	Role
Baicalein	Attenuate inflammation by suppressing activation of TLR_2, TLR_4, NF-κB and MAPK signaling pathway
Baicalin	Inhibits apoptosis by regulating TLR2, BCL-2, BAX and caspase-3
Thymol	Inhibiting NF-κB activation
Citral and *linalool*	Inhibits *Staph. aureus* growth and biofilm formation
Baicalin	Antimicrobial action against *E. coli*, damage bacteria cell wall
Limonene	Antimicrobial activity
Liquidambar orientalis	Antimicrobial activity against Staph. *aureus* and *Coagulase* Negative *Stapylococci*

Thalictrum minus root extract	Antimicrobial activity against *Staph. xylosus*, *Staph. lentus*, *Staph. equorum*, *Enterococcus faecalis* and *Pantoea agglomerans*
Terminalia chebula fruit extracts	Antimicrobial activity against *E. coli*, *Pseudomonas aeruginosa* and *Bacillus megaterium*
Poncirus trifoliate fruit extract	Antimicrobial activity against *Clostridium perfringens* and *Pantoea agglomerans*
Eucalyptus globulus	Inhibits *Staph. aureus* growth and biofilm formation
Cinnamon cassia	Antimicrobial activity
Valencia orange	Inhibits *Staph. aureus* growth and biofilm formation
The mixture of *Satureja montana* L., *Thymus vulgaris* L. *and Origanum majorana* L.	Antimicrobial activity against *Staph. aureus*
Minthostachys verticillata	*Phagocytosis* and modulating an innate immune response
Cedar, *Thyme* and *Manuka*	Antimicrobial activity against *Staph. epidermidis* and *Staph. xylosus*

Animal Derived Compounds

Lactoferrin, a naturally occurring immunomodulatory generated by animals, was chosen as a viable non-antibiotic antimicrobial agent for the treatment and prevention of bovine mastitis Gomes. Furthermore, marine sponges have been identified as a potential source of novel antibacterial compounds. Several species of Coagulase-Negative *Staphylococci* (CNS) identified from bovine mastitis cases were inhibited by extracts from these sessile aquatic creatures. When MAC-T cells were challenged with various pathogenic agents such as LPS, lipoteichoic acid, TNF-1 and IL-6, pre-treatment with Chinese propolis (15 g/mL) was able to prevent a decrease in cell viability as well as a drop in pro-inflammatory cytokines mRNA levels such as TNF-1 and IL-6 Wang [18-20].

Measures to Ensure Hygiene Practices

Controlling these four pathogens (*Staphylococcus aureus, Streptococcus agalactiae, Streptococcus dysgalactiae* and *Streptococcus uberis*) should be the top goal. Pathogens infect the mammary gland and the team's streak canal in Mastiffs, although the exact procedure is unknown. Smooth rubber gloves were placed before handling each cow and the gloves were then soaked in an acceptable disinfectant. The most common way has been to immerse teat cups in a cleaning solution for a few seconds. Although this strategy lowered disease transmission from cow to cow, it did not eliminate it. To eliminate dirt and organic debris, kill mastiff organisms, encourage milk let-downs and increase milk quality, udders should be cleansed with a sanitizing solution before milking. Antimicrobial therapy aims to eliminate germs. Antimicrobial therapy aims to kill germs while causing no harm to the host. Pathogen elimination is contingent on obtaining the required concentration of the suitable antimicrobial. Dipping teats after milking and treating each quarter at the end of lactation are the most effective hygiene and therapeutic techniques. Mastitis degrades the quality and content of milk, rendering it unfit for human consumption. Finally, after dry cow therapy with long-acting antibiotics, culling chronically unwell animals to reduce the duration of existing infection and avoid new intramammary infections.

Vaccination

Some of the reasons for their ineffectiveness include inappropriate immunization schedules, ineffective adjuvant formulation and a narrow range of protection. Since many strains can exist within a herd and a single cow, finding a vaccination that can protect against a wide range of strains is critical. Vaccination resulted in an increase in specific IgG1, IgG2 and IgM, however, there was no indication for greater opsonic activity leading to increased phagocytic uptake there are no vaccines available to prevent K. pneumonia-induced mastitis. In the case of environmental mastitis, *E. coli* vaccination resulted in a higher annual benefit per cow when compared to a non-vaccine approach. The property of these bacterins to induce the development of antibodies directed against common core antigens shared by Gram-negative bacteria is their basis. Violacein was thought to be an effective antibacterial agent and its nanoparticles were much more effective against *S. aureus*. Vaccinated cows are just as likely as control animals to become infected with Gram-negative mastitis bacteria, but they have a lower risk of clinical mastitis. This shows the target pathogens of a different mastitis vaccines in dairy cows.

Commercial Vaccines

Commercially marketed polyvalent vaccine including *E. coli* J5 and *S. aureus* strain SP 140 (Startvac, Hipra, Spain) Freick. The effect of vaccines on the incidence of clinical mastitis, milk production and cow culling or death was studied using a commercial vaccine containing *E. coli* rough mutant O111:B4 bacterium (**Table 5**).

Table 5: Target pathogens, of different mastitis vaccine studies in dairy cows.

Target pathogens	Results/Recommendations
S. aureus, E. coli	There is no effect on the health of the udders.
S. aureus, E. coli	The incidence of mastitis has decreased moderately.
S. aureus	No significant differences in mastitis incidence No significant differences in cure rate.
S. aureus	Significantly lower SCC Less *S. aureus* isolated.
S. aureus	Serum immunoglobulin levels have increased significantly. Milk production has increased significantly.
S. aureus	60% reduction in *S. aureus* in milk.
S. aureus	No significant effect of mastitis on clinical signs.
S. aureus	Mastitis rates have dropped significantly.

DISCUSSION

Cytokines

Small proteins called cytokines play a vital role in cell signaling. The chemokine IL-8 is secreted during infection by neutrophils and other/scells in response to invading pathogens. Following IL-8 binding to CXCR1 or CXCR2, migration is induced, cytokine production is altered, phagocytosis is increased and reactive oxygen species are produced. Chemotactic neutrophil migration from blood could be impaired due to decreased proportion of cells expressing the adhesion receptor CD62L. β-defensin antimicrobial peptides are a key component of Polymorphonuclear (PMN) cells' oxygen-independent microbicidal system. When combined with antibiotics, there was an additive effect possible their use as adjuvant mastitis therapy Alluwaimi. CACNA2D1 (calcium channel, voltage-dependent, alpha-2/delta subunit 1) is a non-cytokine candidate gene that influences mastitis. BPI (Bactericidal/Permeability-Increasing protein) is a Bacterial/Permeability-Increasing protein (BPI) that is largely expressed by neutrophils in the inflammatory response. Variation in the bovine BPI gene and the Somatic Cell Score (SCS), a marker of clinical mastitis in Holstein cattle is substantially associated (0.80-0.90).

Antibiotic Therapy

Without the necessity for segregation, eradication of *Streptococcus agatactiae* infection was now a viable possibility. These were mainly based on "blitz therapy," in which all diseased cows in a herd were treated at the same time. The optimum time to treat mastitis is during the dry cow period; because no milk is produced at this time, the risk of antibiotics entering the food chain is reduced. *Staphylococcal* infection was also growing more prevalent, presumably as a result of the switch to machine milking, which had a low cure rate with antibiotics. Mastitis has been linked to "nearly every conceivable factor of management and environment and nearly everyone appears to overlook the fact that mastitis exists and can be a serious problem even when management and environment meet reasonable standards "Murphy 1956.

Nanotechnology

Researchers have been able to create nanosized particles (less than 100 nm) using nanotechnology, which can be used in a variety of applications, including medicine delivery. When compared to typical microparticles, nanoparticles have a larger surface area and so have more interactions with biological targets (such as bacteria). Furthermore, nanoparticles are far more likely than micron particles to infiltrate cells. Because nanoparticles may be taken up by phagocytes, they could be used as delivery methods in the treatment of cow mastitis.

Bacteriophages

Phage therapy may be effective in the treatment of *E. coli* and *S.aureus* induced mastitis. However, more research is needed to determine the therapeutic potential of bacteriophages in the treatment of clinical and subclinical bacterial infections associated with mastitis.

Economic Losses from Mastitis

Mastitis in dairy cattle was once regarded as one of the most serious economic diseases, causing the country to lose a significant amount of money. Mastitis accounts for approximately 38% of the overall direct costs of common industrial illnesses globally. Mastitis-related economic losses in India have increased 115-fold in the last five decades NAAS 2013. The losses in Mastitis were either due to temporary or permanent loss of milk production, poor milk quality, discarding of milk from affected animals before or after antibiotic treatment and pre-mature culling of the cow or reduced productive life of animals resulting in more expensive replacement, veterinary fees, cost of medicines and payment for extra labor hours.

Losses in Milk Yield

Total milk production from abnormal quarters, as diagnosed by the bromthymol blue test made on foremilk samples had fewer solids not fat than that of normal quarters. Milk yield can be considered only as a possible factor affecting individual susceptibility to mastitis.

CONCLUSION

Bovine mastitis is a disease that affects millions of cows around the world, making it one of the most important bovine pathologies and the most expensive for the dairy industry. A huge range of natural products derived from plants, animals and bacteria have been studied and found to be effective in the treatment of bovine mastitis. With the presence of biofilms, the infection, in this case, is more difficult to treat and remove, making this a more important concern. The significance of biofilms in mastitis infections is critical for determining and studying the optimal control options for use in veterinary practice to reduce dairy industry losses and assure milk safety and quality. Field studies should be considered to ensure the success of alternative therapies before commercial applications.

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DECLARATION

Sehajpal Singh Dhillon and Simarjeet Kaur designed the outline and material and wrote the article. Both authors proof-reading the manuscript. The authors read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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