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Review

Treatment and Control Methods of Bovine Mastitis: A Review

Isayas A. Kebede, DVM[1*]; Gelan D. Dahesa, DVM[2]

[1]*School of Veterinary Medicine, Ambo University, P. O. Box. 19, Guder, Ethiopia*
[2]*School of Veterinary Medicine, Wolaita Sodo University, P. O. Box. 138, Wolaita*

[*]***Corresponding author***
Isayas A. Kebede, DVM

School of Veterinary Medicine, Ambo University, P. O. Box. 19, Guder, Ethiopia; E-mail: isayasasefa@ambou.edu.et

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ABSTRACT

The goal of this review is to summarize various approaches to treat and control bovine mastitis. Bovine mastitis, often known as udder inflammation, has various causes. The primary treatment for mastitis is intramammary infusion. However, antibiotic resistance mechanisms have emerged, posing a risk to global health today. Given the broad rise of antibiotic resistance, novel drugs to treat and prevent the disease are urgently required. As a result, novel treatment and control methods arose, including the use of animal-derived compounds, bacteriophage therapy, probiotics, herbal therapy, immunotherapy, nanoparticle-based therapy, and sonic pulse therapy. Control measures include immunization, hygiene, feeding management, and dry cow therapy. Bee products have recently replaced animal-derived compounds as a treatment for cattle mastitis. Probiotics, on the other hand, may work by modifying gut flora, with evidence supporting their direct influence on mastitis in dairy cows. In contrast, a proprietary Acoustic Pulse Therapy (APT) device was designed specifically for treating dairy cows. However, its usefulness in veterinary medicine is limited. Vaccines can help prevent mastitis, alleviate clinical symptoms, and accelerate the healing process. Vaccination boosts acquired immunity to a specific pathogen and has few side effects; nevertheless, because to the wide range of mastitis-causing organisms, particularly emerging environmental infections, vaccine treatment of mastitis presents significant challenges. A proper milking hygiene program that meets all of the dairy cow's biological and hygienic requirements has a significant impact on udder health. Vitamins, probiotics, and other feed additives can help improve udder health, cow immunity, and general body condition. Dry cow therapy is an intramammary or systemic antibiotic treatment for the udder administered during the dry season. Cows with clinical or subclinical illnesses should be treated with non-antibiotic antimicrobial agents.

Keywords
Bovine; Control; Methods; Treatment; Mastitis.

INTRODUCTION

Mastitis is the most frequent and costly disease affecting dairy cattle worldwide. Mastitis can be caused by invasive germs, other diseases, or physical gland injury.[1,2]

Mastitis is caused by several illnesses and can be classed as infectious or environmental.[3] Contagious pathogens are those that live mostly in infected cow udders. They transfer from cow to cow, especially during milking, and induce chronic subclinical infections accompanied by clinical episodes. Contagious pathogens include *Staphylococcus aureus*, *Streptococcus agalactiae*, *Mycoplasmas* and *Corynebacterium bovis*.[4]

Mastitis pathogens reported in cow habitats include environmental streptococci (streptococci other than *S. agalactiae*, such as *Streptococcus uberis*; enterococci), enterobacteriaceae, and coagulase-negative staphylococci (CNS). Mastitis-causing microorganisms with zoonotic potential may endanger human populations through the food chain.[2]

Mastitis is an example of a complex disease caused by interactions among three biosystems: the causal agent (pathogen), the animal (host), and the environment in which the animal lives. Breed, mammary gland physiology, teat canal shape, sphincter tone, and the presence of a teat lesion are all considered host factors. The agent's features include the capacity to live in the animal's surroundings, colonize the teat duct, and cling to the mammary epithelium without being washed away by milk flow. Milking techniques, lodging, and bedding are examples of environmental elements.[4]

Mastitis is divided into two categories depending on clinical findings. Mastitis can be symptomatic or asymptomatic. Clinical mastitis creates noticeable udder inflammation. These signs can appear in either the animal or the milk. Subclinical type of mastitis causes no visible changes to the milk or udder, but milk production decreases, bacteria are present in the secretion, and milk composition changes.[5] The California mastitis test, somatic cell counts, and bacterial milk culture can all be used to identify subclinical mastitis. Subclinical mastitis remains the most common type of mastitis, which is economically disastrous and poses a zoonotic risk to the dairy industry and consumers worldwide. Subclinical mastitis outnumbers clinical mastitis 20-40.[6]

Bovine mastitis causes a variety of economic losses, including decreased milk production, replacement costs for culled cows, additional labor, treatment costs, and control measures. Mastitis has a zoonotic effect because it causes food poisoning and disrupts the industrial process. It is also linked to several zoonotic diseases that spread through milk.[7]

The main treatments are intramammary antibiotic therapy, parenteral antimicrobial therapy, and supportive and dry cow therapies. Mastitis control measures include raising public awareness of management procedures like milking and housing hygiene, as well as eradicating current infections, preventing future infections, and monitoring udder health.[1]

Antibiotics are ineffective in treating mastitis in comparison to many other illnesses, and antibiotic residues in milk may constitute a health risk to adults. The increasing prevalence of multidrug resistance among bacterial species is a major concern for public health, and antibiotic usage in dairy production has been closely monitored.[8] Hence, the objectives of this review are to review non-antimicrobial therapy and control methods of bovine mastitis.

TREATMENT METHODS

Antibiotic Therapy

During the dry season, cows are often given antibiotics to avoid mastitis. Dry cow therapy with antimicrobials is authorized as a prophylactic measure in livestock. Antibiotics for clinical mastitis should be chosen based on the history, etiology, antibiotic sensitivity profile, and, most importantly, indicated therapeutic principles.[9] Antibiotics remain the principal treatment method, but their efficacy is limited, and the development of antibiotic-resistant pathogen strains has emerged as a major worry in antibiotic treatment.[10] Furthermore, the growing public concern about antibiotic resistance is causing the milk business to reduce its usage of antimicrobial drugs. As a result, alternative antibiotic medicines are required, particularly those derived from natural products like plants and animals.[10,11]

Mastitis is treated primarily with antibiotics such as penicillin, ampicillin, tetracycline, and gentamicin, which can be delivered intra-mammary, intramuscularly, or intravenously.[10,12] However, due to the increasing growth of antibiotic-resistant organisms, the therapy is predicted to become ineffective in the near future. Microorganisms isolated from mastitis milk have been proven to be resistant to a wide variety of drugs. A study conducted in Bosnia and Herzegovina's Zenica region reported the highest antimicrobial resistance to benzylpenicillin (56.3%) and oxytetracycline (46.2%).[9,13]

Bacteriological cures are the consequence of a combination of the host immune response (spontaneous cure) and treatment effect (treatment cure), and antimicrobial therapy is most effective for infections with a low spontaneous cure rate and a high treatment cure rate. Mastitis pathogens have very different predicted rates of spontaneous bacteriological cures. The greatest disparity exists between expectations of spontaneous bacteriological healing of intramammary infection (IMI) produced by *S. aureus* (about zero) and *Escherichia coli* (about 90%).[14-16]

The pathogens most commonly isolated were *Staphylococcus spp*. (42.55%), *E. coli* (21.28%), *Streptococcus spp*. (6.38%), *Proteus spp.* (8.51%), *Candida spp.* (2.88%), and mixed infection (18.26%). Gentamicin was the most effective antibiotic (64.96%), followed by enrofloxacin (63.83%), cefotaxime+clavulanic acid (52.13%), amoxicillin+sulbactum (42.55%), ciprofloxacin (41.49%), colistin (41.49%), chloramphenicol (39.36%), and ampicillin+sulbactum (38.29%). Oxytetracycline and streptomycin had the lowest efficacy (22.34% and 25.53%, respectively), whereas amoxiclav and ampicillin/cloxacillin had the highest resistance.[17]

Animal-Derived Compounds

Bee products have recently replaced animal-derived compounds as a treatment for cattle mastitis. Bee venom, which contains the active component melittin, was administered to lipopolysaccharide (LPS)-induced mammary epithelial cells (MAC-T) cells to study its anti-inflammatory properties.[18] Bee venom has been found to inhibit LPS-induced cyclooxygenase 2 (COX2) protein expression and messenger ribonucleic acid (mRNA) expression of pro-inflammatory cytokines tumour necrosis factor-alpha (TNF-α) and interleukin 6 (IL-6) *via* down-regulating ERK1/2 phosphorylation and nuclear translocation of nuclear factor kappa B (NF-κB).[10,18]

Mammals naturally produce immunomodulators, such as lactoferrin, which have been discovered as potential non-antibiotic antimicrobial agents for the treatment and prevention of cow mastitis. Lactoferrin is a glycoprotein found in a variety of body fluids, including saliva, tears, bronchial mucus, and milk. This chemical possesses antibacterial properties against numerous mastitis-causing organisms, including *E. coli*, *S. aureus*, coagulase-negative staphylococci, *Pseudomonas aeruginosa* and *K. pneumonia*.[19] Another study isolated lactoferrin from bovine milk whey and tested its antibacterial activity against *S. aureus*, *E. coli*, *S. agalactiae* and *P. aeruginosa*. Lactoferrin effectively inhibited all isolates tested, with higher efficacy against *E. coli* and lower efficacy against *S. aureus*.

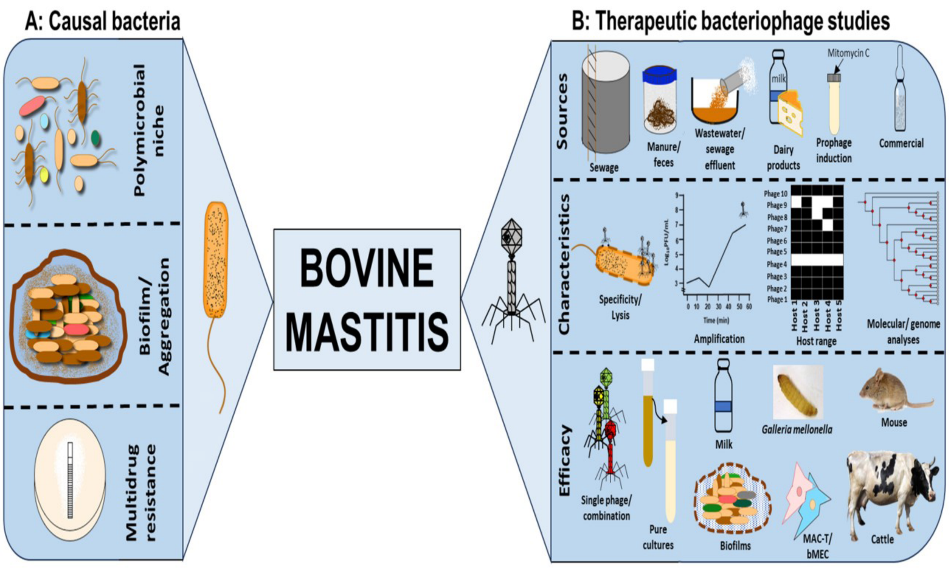
Another study suggests that lactoferrin could be employed as an antibacterial and immunomodulator. β-Lactoglobulin is a protein found in most mammals' whey. When tested against a variety of mastitis-causing bacteria, this protein inhibited both *S. aureus* and *S. uberis*. When coupled with lactoferrin, there was an additional effect against *S. aureus*. In addition to the enhanced combined action of these two proteins, their individual actions on different bacteria can broaden/complement the spectrum of antimicrobial activity.[19,20]

Bacteriophage Therapy

Biofilm-forming bacteria are difficult to treat since they are antibiotic-resistant. In such circumstances, additional therapies are required to effectively eradicate the etiological cause. Bacteriophages are viruses capable of infecting and destroying bacteria. Phages infect bacteria and produce bacterial lysis/killing (lytic or virulent phages) or lysogeny—the integration of phage genetic material into the host bacterial chromosome (temperate phages).[21]

Bacteriophages and endolysins could be used to treat bacterial mastitis.[21] Phage therapy is becoming increasingly common for mastitis. Various phage therapy outcomes showed success against a variety of mastitis-causing bacteria. The majority of studies focused on treating mastitis caused by *S. aureus* bacteria. Because this bacterium is frequently identified from mastitis and causes severe infection (Figure 1).[22]

Figure 1. *Bacteriophage Therapy to Control Bovine Mastitis*[22]



Probiotics

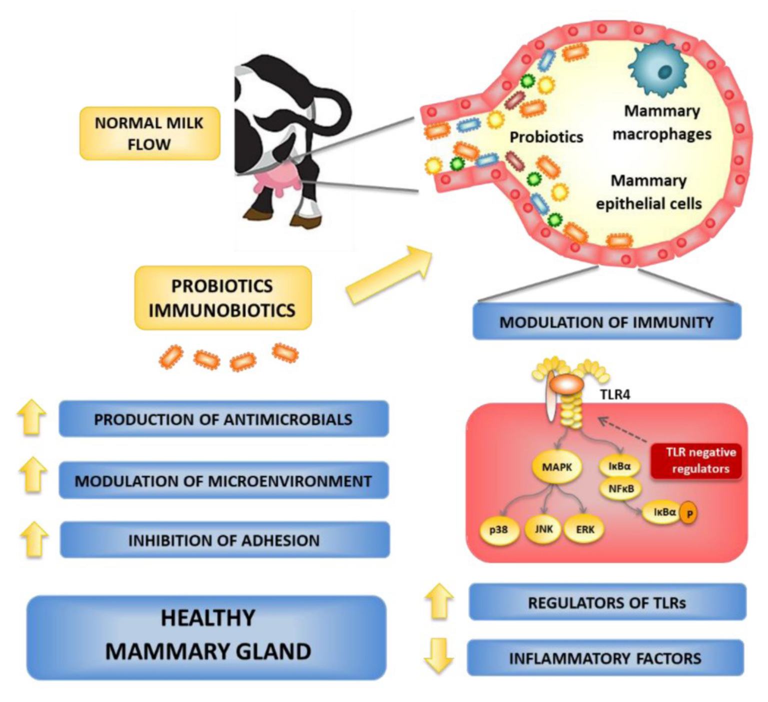
Probiotic bacteria have been intensively investigated as a novel method of preventing infections in animals, notably in the gastrointestinal and vaginal tracts, but few research have focused on their use in the mammary gland.[23] Probiotics can be sold with or without health claims. Probiotics are typically associated with two major advantages: a healthy digestive tract and a healthy immune system. "*Supporting a healthy immune system*" is a broad benefit that must be reported and shown at the strain level, as is expanding probiotic use beyond the digestive tract to include the reproductive tract, oral cavity, lungs, skin, and gut-brain axis. A probiotic medicine is one that has a specific prescription for treating or preventing sickness.

As a result, probiotics that promise to prevent or treat mastitis are classified as probiotic drugs and must be properly tested to meet drug regulatory requirements. A significant difficulty is determining the right level of evidence for demonstrating probiotics' health benefits. According to the consensus group, some of the requirements for a causal relationship between probiotic use and the claimed health benefit include a temporal relationship, dose-response, replication of findings, specificity of association, cessation of exposure, consideration of alternative explanations, biological plausibility, and consistency with other knowledge (Figure 2).

Herbal Therapy

Plant-based ethno-veterinary herbal medicine is a sustainable alternative that includes traditional beliefs, medicinal plants, knowledge, skills, methods and practices in animal health care, production, and breeding.[25,26] The use of ethno-veterinary preparations, such as herbs and herbal medications, is becoming more common in the treatment, prevention, and management of clinical and subclinical

Figure 2. *Probiotic Therapy of Mastitis*[24]



mastitis. Furthermore, the majority of these plants are relatively harmless and do not have the same side effects as allopathic drugs. Herbs with antibacterial and antiviral properties may be effective in treating the condition. In general, both pharmaceuticals and herbs can help treat mild to moderate bacterial infections, while herbs are far more effective than drugs in treating specific diseases.[27]

As a result, the study concluded that animals with subclinical mastitis are divided into two groups: I and II. The udders of Group I cows were topically treated with a paste composed from fresh *Moringa oleifera* leaves, turmeric powder, and common salt. Group II animals received oral medication in the form of a bolus containing *Ocimum sanctum* dry powder, honey, and lemon juice, which was given twice daily for seven days. Out of 10 animals and 16 affected quarters in each group, 9 animals (90.00%) and 14 quarters (87.50%) in group I and 9 animals (90.00%) and 15 quarters (93.75%) in group II were completely recovered.[27]

Immunotherapy

Immunotherapy is a biological based treatment for mastitis. In comparison to treatments with sulfadiazine+trimethoprim or procaine penicillin+streptomycin (BA) (8 cows) or a non-steroidal anti-inflammatory drug (NSAID) (19 cows), Leitner et al[28] used microbeads carrying specific antibodies to the mastitis-causing bacteria as well as the Y-complex, a phagocytosis enhancer. In terms of germ-killing, the Y-complex outperformed antibiotics and non-steroidal anti-inflammatory medications. However, combining NSAIDs like meloxicam with antibiotics improved cow fertility.[9,29]

Nanoparticle-Based Therapy

Nanomaterials have been used to diagnose and treat diseases in humans, but their usage in veterinary medicine and animal agriculture is still in its early stages. However, nanotechnology is a fast-expanding field that allows for the production of new materials at the nanoscale level, with the potential to alter the agri-food industry by providing novel treatment options for common and expensive diseases such as bovine mastitis. Because present treatments are increasingly ineffectual against resistant bacteria, the development of new nanotechnology-based solutions is crucial.[9,30]

Copper nanoparticles, according to Kalinska et al,[31] could be used to treat cow mastitis. The study discovered that commercially available nanoparticles are of high quality and have no negative effects on mammary gland tissue. Copper nanoparticles also influenced or reduced pathogen viability. Copper oxide nanoparticles have been found to diminish the presence of harmful bacteria such as *S. aureus* and methicillin-resistant *Escherichia coli*. Copper oxide and silver nanoparticles were used to eradicate harmful germs.[32,33]

Acoustic Pulse Therapy

Acoustic pulse treatment (APT), also known as shockwave therapy, generates pulsating pressure pulses using a handheld device. Such waves penetrate deeper tissues and can break down scar tissue in chronic wounds, causing revascularization. In studies using APT in subclinical mastitis, a statistically significant proportion of mastitis animals (70.5%) were able to return to normal milk supply, compared to the control group (18.4%). The percentage of cows with log somatic cell counts (SCC) of milk less than 5.6 cells/mL was significantly higher in APT-treated cows than in the control. APT considerably healed cows sick with isolated bacterial kinds, with cure rates varying according on the bacteria involved. A trial of clinical mastitis found that APT treated 76.9% of sick cows (n=13), while the gold standard antibiotic therapy only cured 18.7%.[28] This therapy is promising, but further extensive trials with the associated infectious agent types are required to standardize the treatment. Class IV laser and interferential therapy can also be used in conjunction with APT to measure healing potential.[9]

Acoustic pulse therapy is superior to antibiotics or no intervention in treating clinical and subclinical mastitis in dairy cows. In contrast to typical subclinical mastitis treatment approaches, which necessitate early identification, APT offers a simple targeted treatment for cow udders. It is not necessary to identify bacteria or discard milk during or after treatment. As a result, it is recommended that any cow suspected of having mastitis be treated with APT equipment to refill the reduced milk supply.[28]

CONTROL METHODS

Mastitis control programs developed in the 1960s that included vaccination, teat disinfection, antibiotic dry cow therapy, and culling of chronically infected cows have resulted in significant progress in controlling contagious mastitis pathogens such as *Streptococcus agalactiae* and *Staphylococcus aureus*. However, these treatments are far less effective against environmental infections, particularly *S. uberis* and *E. coli*, which cause a considerable amount of subclinical and clinical mastitis in lactating and non-lactating cows and heifers.[34]

Vaccination

Vaccination boosts acquired immunity to a specific pathogen while producing few side effects. The bulk of these experimental and commercial vaccines are bacterins, which are inactivated entire organisms; however, others contain organism subunits such as surface proteins, toxins, or polysaccharides.[35] However, immunization has limited efficacy against BM due to the variety of microorganisms involved in its proliferation.[24,36] As a result, the clinical and subclinical signs of mastitis were used to determine the efficacy of the polyvalent vaccine. Among 600 vaccinated cows, 9 (1.5%) and 13 (2.3%) developed subclinical and clinical mastitis, respectively. Vaccination is an effective strategy for controlling infectious diseases. The efficacy of vaccine prevention is based on vaccine quality and timely vaccination of vulnerable populations. Modern immunology and vaccination prevention have reviewed the theoretical foundations and described techniques to developing new, safe, and effective vaccinations.[37]

Hygienic Control Measures

A proper milking hygiene program that meets the dairy cow's biological and sanitary needs has a substantial impact on udder health maintenance. The goal of milk hygiene is to ensure that the milk sold is safe for human consumption, not merely to control mastitis in cattle. This necessitates milking sanitation and bulk tank storage.[38,39]

The following practice will reduce the number of infected cows and clinical mastitis at every milking: Good cow management techniques are required for building a mastitis control regimen. Reduce pathogen exposure by thoroughly cleaning all milking equipment, maintaining milkers hygiene, avoiding housing cattle in filthy conditions, changing organic bedding materials regularly, washing dirty udders before milking with clean water, preferably by hand, a disposable paper towel, or a disinfected cloth, and thoroughly drying.

It is recommended to wash udders with a sanitizing solution prior to milking to remove dirt and organic waste, reduce mastitis germs, boost milk let-downs, and improve milk quality. Modern udder cleaning procedures are sterilizing, which creates serious problems, and washing may not be justified as a method of preventing IMI. Udder washing techniques, if not done appropriately, have the potential to spread germs rather than eradicate them. Washing filthy udders with clean water and thoroughly drying them before milking, washing and disinfecting hands before milking each cow, and fore milking all teats in a strip cup are all good hygiene and milking methods. When milking by hand, use proper milking hygiene, such as wearing milking gloves and cleaning your hands and equipment. When milking equipment is used, it must be built, operated, and maintained properly. Even if germs penetrate the teat canal, maintaining cow health, such as boosting udder immune function, will avoid mastitis.[40]

Quorum Sensing

It is the regulation of gene expression in response to changes in cell population density, based on the hypothesis that bacteria make auto-inducers that increase in concentration as cell density rises. Several of them have been extensively investigated in *S. aureus*, and when they engage with certain receptors, they trigger the transcriptional regulatory system, which contains genetic components. Similar studies in *S. uberis* have found the presence of quorum sensing (QS) genes implicated in group behavior, such as luxS and comEA. Because these two bacteria may grow in afflicted tissues and biofilms, they develop inherent resistance to practically all therapeutic drugs. The difficulties in treating recurrent infections may be related to the pathogen's ability, and increased use of quorum sensing will eventually allow for more effective and appropriate treatment processes.[41,42]

Feeding Management

Vitamins and probiotics can help improve udder health, cow immunity, and general body condition. Nutrition can affect udder immunity in a variety of ways, including (a) providing the raw materials for the synthesis of immune components; a lack of these elements leads the immune system to function improperly; and (b) providing the ingredients required for milk production. Among the major nutritional elements required for udder health and milk production are (a) antioxidants such as ascorbic acid, which traps free radicals and prevents Cu and Fe from participating in oxidative reactions, (b) Cu, Zn, and Mn for the superoxide dismutase enzyme, which converts superoxide to hydrogen peroxide to protect the tissues, and (c) selenium and iron for glutathione peroxidase and catalase enzymes, respectively. These enzymes are necessary for the conversion of hydrogen peroxide to water (d) and the modification of udder immunity in dairy cows.[43-45] Selenium and vitamin E help to preserve individual antioxidant levels of cellular structures from the number of free radicals produced, resulting in low tissue concentrations of reactive oxygen species, which are helpful to the body in many conditions. They are also employed in disease etiology and pathological processes.[39]

Dry Cow Therapy

Dry cow therapy is an intramammary udder or systemic antibiotic treatment given during the dry season. Mastitis has typically been treated with antibiotic dry cow therapy and intramammary infections while drying off. Dry cow therapy reduces existing IMIs and prevents future IMIs, making it an essential component of any successful mastitis control program.[46] During the dry phase, antibiotic therapy is more hopeful and simpler to clear and control infection than during lactation because the medicine is not ejected with milk and a higher and more uniform concentration of antibiotics is kept in the udder. Furthermore, there are no cost implications to discarding antibiotic-containing milk.[47]

CONCLUSION

Mastitis is regarded as the most expensive diseases in the dairy industry. Several therapeutic strategies for treating mastitis have been tested, including antibiotic therapy, animal-derived therapy, probiotics, herbal therapy, immunotherapy, nanoparticle technology, and acoustic pulse therapy, but no single technique is effective in controlling or treating the disease due to the variable response of etiological agents to the therapeutic techniques. Antibiotic therapy is thus used most regularly, although antimicrobial resistance is a major concern. It is advised to use non-antibiotic therapy and control methods. Herbal remedies have undeniable advantages, but developing commercially viable drugs takes a tremendous amount of effort. Phages are well-known for their selective actions on specific bacteria, making them the most viable alternative to antibiotics for bovine mastitis. They have already contributed to the saving of countless lives from human infection. However, additional study is required to make them practical and useful in veterinary medicine. Finally, alternative investigations into bovine mastitis therapy and control are recommended.

DECLARATIONS

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Materials

All the datasets generated or analyzed during this study are included in this manuscript.

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Authors' Contributions

GD contributed to the conception of the study idea, study design, data collection, references search, manuscript draft, and writing; IAK contributed to manuscript editing and revisions. All authors have approved the submission of the final manuscript.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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