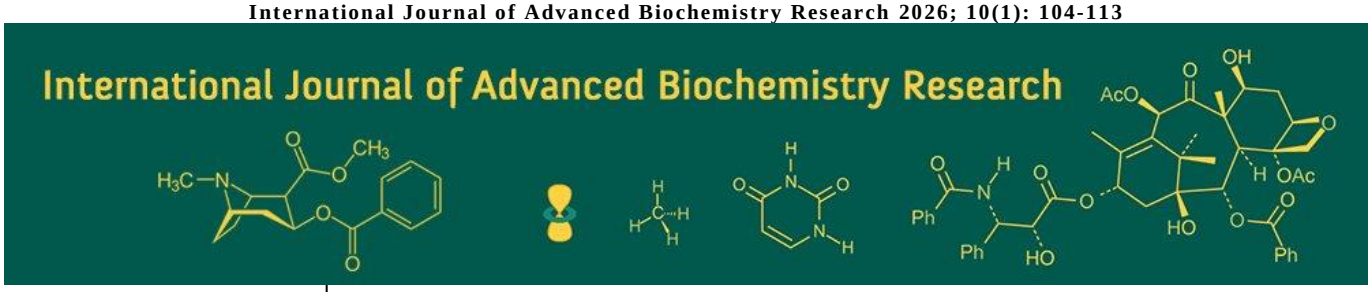

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Bovine mastitis: An economically important dairy problem: A review

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Abstract
Mastitis is one of the very important and devastating disease of dairy animals having multi etiologic i.e. bacteria, fungi, or viruses in animals. On the basis of clinical sign, symptoms and etiology mastitis may be clinical, subclinical, contagious, and environmental mastitis. It harms both animal owner as well as affected dairy animals by three ways- one is due to reduced milk yield, second treatment loss and third is health loss due to blindly use of higher antibiotics often seen in field conditions. In India the annual economic loss recorded due to clinical form of bovine mastitis Rs. 7165.51 crores per annum while due to subclinical form of bovine mastitis was Rs 2646 crores in 2001. For development of suitable diagnostics and preventive measures (Vaccinology) the knowledge of mechanism of mastitis is very essential. Presently there is no commercial mastitis vaccine available in India. Mastitis is a public health concern problem so, before starting treatment AMR, animal as well as public health issues should be kept in mind. Government's One Health Approach (OHA) and AMR 2.0 guidelines should follow during treatment of mastitis in dairy animals. Alternate to antibiotic therapy i.e. Herbal, Homeopathic and phage therapy should be adopted for betterment of animal, human and environment.

Keywords: Antibiotics, AMR, economic, mastitis, one health approach, prevention

Introduction
Since there are more cattle and buffalo in India, the prevalence of Mastitis is relatively higher. According to FAO data, the global cow and buffalo populations were 1,575.8 and 205 million, respectively (FAOSTAT, 2023). With 19.46% of the world's cattle and 59.29% of its buffalo, India is home to the biggest livestock population in the world, significantly contributing food security and the creation of livelihoods (Ahlawat *et al.*, 2025) [2]. India is first in buffalo population and second in cattle population in the world, behind Brazil (193.5 million) (FAOSTAT, 2023). According to the 20th Livestock census, there were 192.5 and 109.8 million cattle and buffalo in India out of a total of 535.8 million livestock (BAHS, 2025) [5]. The combined annual cattle and buffalo milk output in India in 2024-25 was 247.87 million tonnes, a 3.58% rise from previous year, while the per capita availability of milk was reported to be 485 grams per day (BAHS, 2025) [5]. The global production of milk (Cattle and Buffalo milk), accounted for 96 percent of the global milk production (897 million tonnes) in 2022. Asia was the largest milk producing region in 2022 with a 45 percent share of the total. Milk production in Asia went up 150 percent between 2000 and 2022 from 160 million tonnes to 401 million tonnes, mostly due to the increase in India (131 million tonnes) which was the largest producer with a 23 percent share of the global total in 2022 (FAOSTAT, 2023).

Mastitis is one of the very devastating diseases of large and small milking animals. It causes heavy economic loses to the animal owners. The animal owner faces financial losses by three ways-one is due to reduced milk yield, second treatment loss and third is health loss due to blindly use of higher antibiotics often encountered in field conditions (McInerney *et al.*, 1992) [47]. Mastitis is a Multi-etiological disease which is characterized by the inflammation of mammary gland. It is caused by either physical trauma or invasion of microorganisms in the udder. The affected udder becomes red, swelled, hard in consistency and animals feel pain when we touch the affected parts of udder. The physical, chemical and microbiological properties of Mastitis affected udder's milk changed significantly (Constable *et al.*, 2017) [15].

In the present scenario Mastitis is considered as most challenging disease in India next only to Foot and Mouth Disease (Varshney and Mukharjee, 2002) [91]. But according to Sharma *et al.*, 2003 [72], the occurrence of Mastitis in dairy animals was found higher than FMD but in high yielding cows more than 90 per cent prevalence of Mastitis were reported. On an average, the annual financial losses estimated due to Mastitis were 200 US dollar (about 16,521.00 Indian rupees) per cow per year in which milk production loss and culling represents 11 per cent to 18 per cent of the gross margin per cow per year. 70 per cent of the total losses are contributed by decrease in milk production (Costello, 2004) [17]. As per Viguier *et al.* (2009) [93], mastitis accounted for a loss of around $2 billion in the United States of America (USA) in 2009. As reported previously, the projected yearly economic loss in India due to both subclinical and clinical mastitis was $98.228 billion [7165.51 billion Indian Rupees] (Bansal and Gupta, 2009) [6]. In India the annual economic loss due to clinical form of bovine mastitis had increased 135 folds in about almost 5 decades from INR 52.9 crores per annum in 1962 (Dhanda and Sethi, 1962) [22] to INR 7165.51 crores per annum in 2009 (Bansal and Gupta, 2009) [6]. While the subclinical form of bovine mastitis causes more financial loss i.e., upto Rs 2646 crores reported by Dua, 2001 and 2129.72 crores by Sirohi and Sirohi, 2001 [23, 78].

Mastitis in Cattle and Buffalo is an important economic production problem worldwide including India and European countries (Das *et al.*, 2018; Hadrich *et al.*, 2018) [19, 29]. In India, the prevalence of subclinical mastitis ranges from 10 to 50 per cent, although the prevalence of clinical mastitis is just 1 to 10 per cent. In the instance of subclinical mastitis, milk production is reduced by 17.5 per cent. The prevalence of sub-clinical mastitis is 15 to 40 times higher than that of clinical mastitis, making sub-clinical mastitis the most important part of dairy farm management. In addition, subclinical mastitis is difficult to detect (Sheikh *et al.*, 2018) [69]. Cases of subclinical mastitis that go undiagnosed may result in protracted economic loss and clinical mastitis. Approximately 65% of mastitis cases are attributable to unsanitary and unhygienic dairy farm practices (Sinha *et al.*, 2014) [77].

Mastitis has a concern to public health due to the potential for transmission of several zoonotic milk-borne diseases, drug residues, bacterial toxins, and organisms containing numerous virulent and antimicrobial resistance genes. Targeted antimicrobial therapy serves a crucial role in mastitis control by lowering herd infection levels and avoiding new infections. The main objective of this review is to find a suitable preventive measures as well as cost-effective treatment measures of bovine mastitis.

Types of Mastitis

Mastitis can be classified into three categories, namely sub-clinical, clinical and chronic mastitis, depends on etiological microorganisms, animal's breed, age, immunity and lactation stage. Due to the absence of obvious changes in milk and the difficulty of identification, subclinical mastitis (SCM) leads to a significant reduction in milk production. Grossly clinical mastitis (CM) can be identified easily based upon visible symptoms in terms of udder inflammation showing redness in affected part or complete udder, warmth, swelling, pain upon touch, milk clots, watery milk, discolouration and change in consistency of milk. The general symptoms are pyrexia (> 39.5º C) and loss of appetite. In dairy animals, chronic mastitis is a rare condition that causes prolonged inflammation of the mammary gland (Krishnamoorthy *et al.*, 2021) [39].

Mastitis is categorized into environmental mastitis, contagious mastitis, and gangrenous mastitis based on the pathogen's source and mode of transmission. Environmental mastitis is mostly caused by *E. coli*, an opportunistic infection that directly invades the teat when cows are exposed to contaminated environments. In any herd, its prevalence rate is less than 10%. Contagious mastitis is caused by *Staphylococcus aureus*, *Streptococcus dysgalactiae*, and *Streptococcus agalactiae*, which dwells on the surface of the teat. Transmission between mammary glands occurs during lactation. Further subtypes of contagious mastitis include subclinical mastitis, clinical mastitis, and chronic mastitis. The early phase of subclinical mastitis is characterized by the absence of symptoms. This is followed by the mastitic phase, which is characterized by a 10-20% reduction in milk yield. It can develop to clinical mastitis in later stages if left untreated (Sharma *et al.*, 2012) [70]. Clinical mastitis is marked by characteristic inflammatory symptoms and adversely affects early lactation and reproductive performance. Additionally, clinical mastitis that results in severe mastitis is known as per-acute mastitis. Per-acute mastitis is characterized by a decrease in milk production, an alteration in milk constituents, fever (104-106 degrees Fahrenheit), depression, shivering, appetite loss, and weight loss. In severe cases, death is occasionally a consequence; however, such instances are extremely rare. Acute mastitis is characterized by slight swelling in the infected quarter and flakes or clots in milk that is yellowish and runny. Here, there is no discernible alteration to the udder. Chronic mastitis is a sub-clinical form of mastitis that can progress to sub-acute or acute forms. Chronic mastitis last for months, continues from one lactation to the next, and may impair the formation of ovarian follicles in later phases. Gangrenous mastitis is also referred to as "blue bag." Here, the udder becomes cold, and after three to four days, it turns blue, resulting in the death of the animal. It is a severe form of mastitis in which the bacteria cause thrombosis, infarction, and gangrene. *Mannheimia haemolytica* and *Staphylococcus aureus* are etiological agents of Gangrenous mastitis (Krishnamoorthy *et al.*, 2017) [38].

Causative Agents of Mastitis

Mastitis is a disease with more than one causative agent. This means that it can be caused by bacteria, fungi, or viruses in animals. Most cases of clinical, subclinical, contagious, and environmental mastitis are caused by some bacteria. The most common bacteria involved are *Staphylococcus aureus*, *Streptococcus agalactiae*, *Streptococcus pyogenes*, *Trueperella pyogenes*, *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Enterobacter aerogenes*, and Pasteurella spp (Sharma *et al.*, 2012; Abdalhamed *et al.*, 2018; Khan *et al.*, 2021) [70, 1, 36]. *Staphylococcus aureus*, *Streptococcus dysgalactiae, and Streptococcus agalactiae* are all infectious pathogens. S. aureus, especially Methicillin-resistant S. aureus (MRSA), are the most common organisms, while *E. coli* and *Streptococcus uberis* are the most dangerous environmental pathogens. Coagulase-negative staphylococci and their role in causing mastitis should also be seriously considered

(Petersson-Wolfe *et al*., 2010) [57]. Streptococcus agalactiae and S. aureus are the most common Gram-positive bacteria found in clinical mastitis. Klebsiella spp. and E. coli are the most common Gram-negative bacteria found in clinical mastitis (Lakshmi and Jayavardhanan 2016) [41]. *S. agalactiae* and *S. aureus* mostly spread through contact, so herd bio-security preventive measures play a very important role in reducing reservoirs. found that S. aureus, Klebsiella spp., and *E. coli* cause the most milk loss in first-time mothers. Streptococcus spp. (CAMP-negative Streptococcus spp), *T. pyogenes, S. aureus, Klebsiella spp.*, and *E. coli* infections cause big losses in older cows. In general, the pathogens that cause mastitis are S. aureus, S. agalactiae, and S. uberis, while Mycoplasma bovis and Corynebacterium bovis are involved less often. Mastitis in animals has been linked to fungi like Aspergillus spps, Nocardia spps, and Candida spps, and viruses like Adeno virus, Herpes virus, Mammilitis virus, Rota virus, Reo virus, Pseudocowpox virus, and Apthovirus (Sharma *et al*., 2012) [70]. The intramammary microbiota is made up of a large group of different bacteria (Rainard 2017; Andrews *et al*., 2019) [102, 103]. The commensal mammary microbiota in a healthy udder is an important part of keeping the immune system in balance. So, a change in the variety of udder microbiota (called dysbiosis) can affect mastitis. When diagnosing mastitis, it's important to think about the normal microbiome of the udder, since healthy quarters also have bacteria. Ruminococcus, Oscillospira, Roseburia, Dorea, Prevotella, Bacteroides, Paludibacter, and Bifidobacterium are some of the types of bacteria that are often found in the udder (Derakhshani *et al*., 2018) [20]. Any injury or birth defect of the udder or teat, like a teat fistula, teat spider, leaking teat, or udder wound, that exposes the udder to microbes from the outside or keeps milk in the udder tends to cause mastitis (Rambabu *et al*., 2011) [61]. Mastitis is a complicated problem that happens when several things at the host level work together in a bad way. These include pathogens, how they grow in the udder parenchyma, signaling pathways that lead to clinical symptoms, and different molecular mechanisms that are controlled by pathogen-associated molecular patterns (PAMPs). This is made possible by different pattern recognition receptors (PRRs) of the host, such as Toll-like receptors (TLRs), NOD-like receptors (NLRs), and RIG-like receptors (RIGs), which, along with a variety of environmental factors, cause udder inflammation caused by microbial infections. Mastitis disease needs a team-based approach to both diagnose and treat it (Bhattarai *et al*., 2018) [10].

Pathogenesis of Mastitis

Pathogenesis must be understood in order to create a good diagnostic approach. Normally, sphincter muscles securely shut the teat canal, limiting the passage of germs. It is lined with keratin, a waxy material generated from stratified squamous epithelium that prevents bacterial migration and includes antimicrobial compounds, such as long-chain fatty acids, that aid in fighting the infection (Paulrud 2005) [54]. As parturition approaches, fluid builds within the mammary gland, causing increased intramammary pressure and mammary gland vulnerability due to the dilatation of the teat canal and leakage of mammary secretions (Sordillo and Streicher, 2002) [80]. In addition, during milking, the keratin is drained out and the teat canal is dilated (Rainard and Riollet, 2006) [59]. The sphincter requires around 2 hours to restore to its contracted state (Capuco *et al*., 1992) [13]. Giri *et al*., (1984) [28] discovered that once bacteria penetrate the teat canal, they attempt to evade the udder's cellular and humoral defence mechanisms. If they are not eradicated, they will begin to proliferate in the mammary gland. They cause leukocytes and epithelial cells to secrete chemoattractants, such as cytokines such as tumour necrosis factor-a (TNFa), interleukin (IL)-8, IL-1, eicosanoids (such as prostaglandin F2a [PGF2a]), oxygen radicals, and acute phase proteins (APPs) (e.g. haptoglobin [Hp], serum amyloid A [SAA]). This recruits circulating immune effector cells, especially polymorphonuclear neutrophils (PMNs), to the site of infection. PMNs absorb and eliminate invading bacteria through oxygen-dependent and oxygen-independent mechanisms. They have intracellular granules that hold peptides, proteins, enzymes (such as myeloperoxidase), and neutral and acidic proteases that are bactericidal (such as elastase, cathepsin G, cathepsin B and cathepsin D). The released oxidants and proteases damage the bacteria and some epithelial cells, resulting in decreased milk production and the release of enzymes like N-acetyl-b-D-glucosaminidase (NAGase) and lactate dehydrogenase (LDH). Destruction of majority of the PMNs takes place via apoptosis once their mission is fulfilled. Consequently, macrophages consume the leftover PMNs (Viguier *et al*., 2009) [93]. In addition to dead leukocytes, dead and shed mammary epithelial cells are released into the milk, resulting in elevated milk SCCs. The somatic cell count (SCC) in the milk of a healthy cow should be fewer than 200,000 per milliliter. Somatic cells are predominantly white blood cells (WBCs), such as neutrophils and macrophages absorbed into the mammary gland tissue as a result of inflammation (Khan *et al*., 2021) [36]. If the infection persists, internal swelling of the mammary epithelium might ensue. The alveoli of the mammary gland become injured and begin to lose their anatomical integrity. The blood-milk barrier is broken, allowing extracellular fluid components such chloride, sodium, hydrogen, potassium, and hydroxide ions to enter the gland and combine with the milk. When the blood-milk barrier has been severely compromised, blood may be discovered in breast milk. This results in apparent udder alterations, including increased external swelling and reddening of the gland. Additionally, the milk undergoes alterations, including an increase in conductivity, pH, water content, and the appearance of visible clots and flakes (Zhao *et al*., 2008) [101]. This signifies the onset of clinical signs and, in the most severe cases, may ultimately result in the animal's fatality.

Diagnosis of Mastitis in Animals

Mastitis diagnosis is the most important criterion for clean milk production in the dairy business, not just for economic and public health reasons, but also for animal welfare. For mastitis prevention or early detection of mastitis for management or therapeutic purposes, the diagnosis must be prompt, accurate, and quick. This involves the use of both conventional and sophisticated diagnostic tests. Conventional approaches are typically inexpensive, simple, readily accessible, and field-applicable, but lack specificity. The advanced tests are typically precise and specific for the many types of mastitis, despite being expensive and needing technical expertise and sophisticated infrastructure and facilities (Singh *et al*., 2013; Chakraborty *et al*., 2019) [76, 14].

Mastitis can be diagnosed in dairy animals based on clinical signs and symptoms. In subclinical mastitis, as opposed to the clinical variety, there are no obvious symptoms, however a change in milk content can be a sign. Therefore, it is identified and confirmed by laboratory analysis of milk or animal-side tests such as the California mastitis test (CMT), followed by laboratory isolation of the causative agent. Use of culturing techniques for the detection of mastitis-causing bacteria remains the gold standard, despite being labor-intensive and costly. Mastitis can also be identified with 'cow-side' or 'on-site' diagnostics, which both farmers and veterinarians can utilize with minimal training. The California mastitis test is among the oldest and best-known (CMT). The addition of a detergent to a milk sample with a high cell count will lyse the cells, liberate nucleic acids and other contents, and result in the development of a "gel-like" matrix. However, interpretation might be subjective, leading to false positives and negatives (Schalm and Noorlander, 1957) [67]. Changes in conductivity or pH can also be used to indicate mastitis. Although these impacts are simple to evaluate, they lack sensitivity. Thus, there is a critical need for novel biomarkers that are unique for mastitis, easily detectable, arise at an extremely early stage, and can be assessed "on-site" (Khan *et al*., 2021) [36].

Advanced molecular approaches based on phenotyping and genotyping procedures provide swift and specific identification techniques for diagnosing mastitis-causing infections down to the species and subspecies level. It is essential to identify the species of bacteria in order to select the appropriate antibiotic for medicinal purposes and the optimal processing procedure for producing dairy products. Various automated commercial identification methods, such as VITEK identification cards, are available for this purpose, yielding stable results in the identification of bacteria (Kandeel *et al*., 2018) [34].

Chakraborty *et al*. (2019) [14] evaluated different advancements in diagnostics applicable to the fast and reliable detection of mastitis, including phenotyping and genotyping. The former consists of physico-biochemical, non-specific cultural, and proteomics tests, whereas the latter consists of a specific culture, polymerase chain reaction (PCR) and its various versions (e.g., qRT-PCR) (Behera *et al*., 2018) [8], loop-mediated isothermal amplification (LAMP), lateral flow assays (Cornelissen *et al*., 2016; Sheet *et al*., 2016) [16, 73], (Barreiro *et al*., 2017) [7]. Haptoglobin (acute phase protein) is a frequently utilised diagnostic biomarker for assessing cow mastitis (Kalmus *et al*., 2013) [33]. In a study, magnetite nanoparticles (MNPs)-based label-free chemiluminescence bioassay was demonstrated for early, sensitive, and rapid detection of haptoglobin at clinically relevant concentrations in milk, resulting in quantitative detection of haptoglobin within a range of 1 pg/mL to 1 lg/mL with a detection limit of 0.89 pg/mL. (Nirala *et al*., 2020) [52]. The inflammatory prote*in vitro*nectin was shown to be overexpressed in both the asymptomatic and clinical forms of mastitis. Therefore, vitronectin is a crucial mediator in the onset of mastitis and a useful biomarker for the detection of subclinical mastitis (Turk *et al*., 2012) [89]. In subclinical mastitis, oxidative stress and inflammatory response greatly decreased the activity of paraoxonase-1 in the blood and milk of affected cows. Therefore, paraoxonase-1 activity may serve as a biomarker for identifying subclinical mastitis (Nedic *et al*., 2019) [51]. Multilocus sequence typing (MLST) system has been devised for the investigation of Mastitis molecular epidemiology (Sordillo 2011; Shibata *et al*., 2014) [79, 74]. Recently, Internet of Things (IOT) has been applied to the detection of mastitis and foot-and-mouth disease (FMD), which, with the help of Neural Networks and smart sensors, could aid in the major reduction of these diseases. This can minimize the extremely poor quality of milk provided by cows; as a result, it can lower the processing costs of dairies, so benefiting the Agriculture and Dairy Industries in a number of economic ways (Vyas *et al*., 2019) [94].

Treatment of Mastitis

Effective mastitis prevention needs the early discovery of infection by understanding the etiology, developing novel sensitive tests for early screening, implementing sound management practices to limit the likelihood of transmission, and preventing the infection of uninfected animals. To mitigate the concerns of antibiotic residue in milk and antimicrobial resistance, the control programme must involve the strategic use of antimicrobials (Ruegg *et al*. 2017a) [65]. Before beginning antibiotic treatment, the primary cause of udder infection must be determined. The ailments of the teat or udder, such as teat fistula, leaking teat, teat spider, and udder sores, require rapid care. Since these conditions likely to breach the protective barrier and expose the teat canal or udder to external microorganisms, prompt treatment is required (Keefe, 2012) [35]. Improve the health and cleanliness of dairy cows by disinfecting the teats before and after milking, and by removing all of the milk. Due to their management and physiological state, clinical and subclinical mastitis occur more commonly in heifers in early lactation than in cows (Yu *et al*., 2017) [99].

Due to their management and physiological state, clinical and subclinical mastitis occur more commonly in heifers in early lactation than in cows. To control heifer mastitis, improved prepartum management methods in the realms of environmental and animal hygiene, including the use of teat sealants and antiseptics, vector control, isolation of heifers from older cows, and restricted giving of mastitic milk to calves, are advised (McDougall *et al*., 2009) [45]. Prepartum treatment of heifers yields a significantly greater cure rate, negligible milk loss, and minimum danger of antibiotic residues; nevertheless, SCC reduction and high milk output are not necessarily accomplished in all herds (Borm *et al*., 2006) [11]. Antimicrobial treatment, causal agent identification, parity, stage of lactation, history of previous SCC, clinical mastitis, and other systemic disorders influence the success of clinical mastitis treatment (Steeneveld *et al*., 2011) [82].

Organic farmers in the United States treat clinical mastitis cases with various alternative therapies, such as homoeopathy, botanicals, vitamin supplements, and whey-based products, due to restrictions imposed by the organic certification process, such as no use of antimicrobials or hormones, use of organic feeds, and stress-free husbandry practices, which left organic farmers with very few options for mastitis control (Ruegg 2009) [64]. The management of mastitis comprises both preventive and therapeutic techniques, with antibiotic medication serving as the primary treatment modality. Recent methods for treating mastitis, however, entail the use of natural therapies such as zeolites and propolis, which could serve as an alternative to antibiotic therapy (Benic *et al*., 2018) [9].

Antibiotic Therapy

During the dry period, antibiotics are usually taken as a preventative step against mastitis. Dry cow therapy with antimicrobials is permitted as a preventative intervention for animals. The selection of antibiotics for the treatment of clinical mastitis should be based on the disease's history, aetiology, antibiotic sensitivity profile, and, most critically, on suggested therapeutic principles. In context of the evolution of antibiotic resistance, the selection of antibiotics for the treatment of mastitis should be based on culture and sensitivity results, as opposed to empirical therapy (Tiwari *et al*., 2013) [86]. Antibiotic therapy has the potential to leave harmful antibiotic residues in milk, which could be harmful to the consumer's health. These antibiotic residues are proven to remain stable for a considerable amount of time and can have unfavourable consumer consequences in addition to resistance (Kurjogi *et al*., 2019) [40].

Anika *et al*., (2019) [3] reported that the use of antibiotics such as oxytetracycline, amoxicillin, and ciprofloxacin in cows resulted in the presence of antibiotics residue both in raw and boiled milk at different time intervals. This suggests the strict maintenance of antibiotic withdrawal periods in order to reduce the risk of post-treatment antibiotic exposure. Even while antibiotics are widely used for the treatment of mastitis without regard to the severity of the disease, the majority of cases of non-severe types of clinical mastitis will not be helped by such uncontrolled use. Current recommendations for controlling clinical mastitis caused by Gram-positive pathogens involve antibiotic therapy focused against specific species. Such therapy approaches allow ample time for the spontaneous healing of the remaining instances (Ruegg 2017b) [66]. Combination therapy including several routes of administration, such as systemic and intramammary administration, increases the clinical cure rate. This may be owing to the greater concentration of antimicrobials in milk and mammary tissues (Lima *et al*., 2018b) [44].

S. aureus-caused mastitis is susceptible to a variety of antibiotics *in vitro*; however, due to the peculiar biology of staphylococci as well as their adaptation to the bovine host environment, development of microabscesses, and biofilm formation, certain antibiotic agents become ineffective in clinical settings. To ensure the optimal and appropriate use of antibiotics, there is a need for critical and thorough interpretation of laboratory results to avoid antibiotic therapy of staphylococci without considering clinical relevance in suspected mastitis cases in bovine species (Wald *et al*., 2019) [95].

Multiple studies on the *in vitro* antibiotic sensitivity of bacteria isolated from bovine mastitis found varied levels of antibiotic resistance across isolates worldwide (Shah *et al*., 2019) [68]. The bovine mastitis isolates from Mexico displayed a trend of resistance to penicillin, clindamycin, and cefotaxime mostly (Leon Galvan *et al*., 2015) [42]. In a study conducted in southern Taiwan, all E. coli isolates from clinical mastitis-affected cows' milk were resistant to cloxacillin, while some isolates were resistant to tetracycline, neomycin, gentamycin, ampicillin, ceftriaxone, cefotaxime, and ceftazidime (Su *et al*., 2016) [83]. Genes for methicillin resistance were prevalent in S. aureus isolates isolated from bovine mastitis patients in India and Thailand (Shah *et al*., 2019) [68]. There are also reports of numerous resistant bacteria isolates occurring simultaneously in clinical cases of cow mastitis in India. To treat subclinical S. agalactiae mastitis, fourth-generation cephalosporin was found to be marginally superior to the usual cloxacillin and ampicillin combination (Rossi *et al*., 2019) [63]. Oxytetracycline could be utilised as a first-line treatment for acute E. coli mastitis in cattle; however, its efficacy cannot be predicted (Shinozuka *et al*., 2019) [75]. In mild to moderate E. coli mastitis, antibiotics should be avoided, but in severe cases, parenteral administration of antibiotics such as fluoroquinolones and cephalosporins is advised to reduce bacteremia-associated risk (Suojala *et al*., 2013) [84]. It has been determined that ceftizoxime is an effective therapy for acute staphylococcal mastitis in crossbred Indian cows. Such changes in the susceptibility spectrum will alter the microorganism's reaction to antimicrobial medicines (Buragohain *et al*., 2019) [12].

In mastitis, the success rate of antibiotics is determined by a number of factors, including the types of microbes, the environment of the udder, and the method of milking (machine/hand). In comparison to antibiotic therapy alone, the inclusion of non-steroidal anti-inflammatory medicines resulted in decreased SCC, decreased milk yield losses, improved clinical results, and decreased culling rates (McDougall *et al*., 2009b) [46]. In E. coli mastitis, nonsteroidal anti-inflammatory medications (NSAIDs) were reported to be helpful and were recommended as supportive therapy for the treatment of clinical mastitis (Suojala *et al*., 2013) [84]. S. aureus is one of the few etiological agents responsible for clinical mastitis that can cause a great deal of trouble for the clinician or veterinarian due to its peculiar pathogenesis, contagiousness, environmental persistence, skin or mucosal colonisation, and poor response to current therapeutics. S. agalactiae can be eradicated fast with treatment, whereas S. aureus is frequently resistant to treatment (Rainard *et al*., 2018) [58].

Antibiotic therapy is no longer effective in S. aureus-induced mastitis, either due to its overuse or the formation and persistence of biofilm-associated antibiotic resistance in S. aureus-induced mastitis (Babra *et al*., 2013) [4]. This may be the reason why attempts to produce vaccinations against mastitis induced by S. aureus have not yet been successful (Cote Gravel and Malouin 2019) [18]. Recent research indicates that the NZ2114-derived peptide H18R (H2) is a safe and promising candidate for treating S. aureus-induced mastitis (Wang *et al*., 2019) [97]. A study suggested that nasal immunisation against S. aureus-associated mastitis in bovine leads to an increase in anti-S. Aureus-specific IgA antibodies in milk and a negative correlation between anti-S. Aureus-specific IgA antibodies and the number of S. aureus counts in the treated udder, which may lead to the use of nasal vaccines in S. aureus-associated mastitis (Nagasawa *et al*., 2019) [50]. Taking into account the cost of treating mastitis and the possible advantages, prudent use of antibiotics must be exercised with proper awareness, a scientific basis for decrease in antibiotic use, and a legislative mandate for prudent use. Continuous monitoring of antibiotic resistance of main bacterial pathogens causing mastitis in cows and immediate standardization of technique and interpretations are required (van den Borne *et al*., 2019) [90].

Bacteriophage Therapy

Bacteriophages are a class of viruses that can infect and kill bacteria. They have the innate ability to target and eliminate specific bacterium and the capacity to proliferate

exponentially, making them a possibility against pathogenic bacteria (Haq *et al*., 2012; Tiwari *et al*., 2014) [30, 87]. Biofilm-forming bacteria that constitute a significant problem due to their resistance to standard antibiotics may be treated with bacteriophage therapy. Geng *et al*. (2019) [27] revealed that a phage cocktail was more efficient than a single Bacteriophage for treating S. aureus-induced mastitis in a mouse model. Phages elicit phage-specific humoral response and memory, which can hinder the efficacy of therapeutic interventions. Against S. aureus isolates, the lytic efficacy of a bacteriophage mixture containing three phages, STA1.ST29, EB1.ST11, and EB1.ST27, was investigated. The considerable reduction in S. aureus germ density demonstrates the therapeutic potential of bacteriophage therapy, which must be validated through *in vivo* research (Titze *et al*., 2020) [85]. To demonstrate the *in vivo* efficacy of bacteriophage therapy in treating bovine mastitis, additional research is required. Use of Bacteriophage-derived proteins-endolysins, peptidaes, and peptidoglycan hydrolases as anti-staphylococcal agents is in its infancy and requires additional research. Antimicrobial peptides (AMPs) such Bacteriocins, defensins, and cathelicidins are new generation antibiotics that eliminate invading bacteria and play a significant role in the innate immune system. Due to the short half-life, high production cost, enzymatic breakdown, and cytotoxic effects on eukaryotic cells, the therapeutic application of AMPs is extremely limited in the current environment (Moravej *et al*., 2018) [48].

Probiotics Therapy

According to Dhama *et al*. (2017) [21], probiotics are gaining popularity in the treatment of a variety of inflammatory disorders and diseases. Due to their high immunomodulatory action, lactic acid bacteria constitute the largest group of probiotic organisms that can protect against mastitis when utilised as feed supplements, teat dip, and intramammary inoculation. The lactic acid bacteria colonise the udder and prevent mastitis by producing a biofilm that inhibits the growth of pathogens that cause mastitis (Rainard and Foucras 2018; Wallis *et al*., 2018) [58, 96]. The addition of lactic acid bacteria to animal feed can be regarded as an efficient method for preventing cow mastitis (Pellegrino *et al*. 2017) [55]. Various strains of lactic acid bacteria, such as *Lactobacillus brevis* 1595, *L. brevis* 1597, and *L. plantarum* 1610, *Lactobacillus lactis* subsp. lactis CRL 1655, *L. perolens* CRL 1724, and *L. casei* BL23, have high colonization capacities, the ability to compete with mastitis pathogens, and inhibitory activity against bovine mastitis pathogens (Pellegrino *et al.*, 2019) [56]. They have the ability to regulate the innate immune response of S. aureus-infected bovine mammary epithelial cells. It inhibited the expression of many pro-inflammatory cytokines, including IL-6, IL-8, IL-1a, IL-1b, and tumour necrosis factor-alpha (TNF-a), in S. aureus-stimulated bovine mammary epithelial cells, demonstrating substantial anti-inflammatory activity (Souza *et al*. 2018) [81]. Additionally, they enhanced the concentration of immunoglobulin (IgG isotypes) in blood and milk. These findings suggested that lactic acid bacteria possess powerful immunomodulatory properties that are produced through triggering local and systemic immune responses (Pellegrino *et al*. 2017) [55]. As an intra-mammary infusion or a teat dip, Lactobacillus can be utilised to lower the quantity of somatic cells (Yu *et al*., 2017; Rainard and Foucras 2018) [99, 58]. There is no solid scientific evidence supporting the use of probiotics to treat mastitis in dairy cattle; nonetheless, probiotics can modify the microbiota of the teat apex, hence preventing the colonisation of the teat canal by mastitis-causing pathogens (Rainard and Foucras 2018) [58].

Herbal Therapy

In the era of organic and natural cattle husbandry, herbal therapy for mastitis has a great deal of promise and potential because it has no negative side effects. Ethno-veterinary medicine is a discipline of veterinary medicine that focuses on the use of herbal remedies to cure disease (Tiwari *et al*., 2018) [88]. As an alternative therapeutic option or as an antibacterial, anti-inflammatory, and immunomodulatory agent, medicinal herbs can be used to treat mastitis. They can also be used in place of antibiotics and antipyretics, which are typically employed to treat mastitis (Mushtaq *et al*. 2018) [49]. The methanolic extracts of the herbal preparation including *Diploclisia glaucescens* leaf and *Curcuma longa* rhizomes in equal amounts exhibited both analgesic and anti-inflammatory properties. The herbal extract exhibited analgesic properties comparable to those of ibuprofen and indomethacin (Ranjith *et al*. 2018) [62]. In a study comparing the efficacy of homoeopathic complex therapy, herbal therapy (Neem seed extract), and antibiotic therapy for the treatment of subclinical mastitis in dairy buffaloes, antibiotic therapy was found to be more effective than herbal therapy (Neem seed extract) and homoeopathic complex therapy. When cost was considered, it was determined that herbal therapy was the least expensive (Younus *et al*. 2018) [98]. Consequently, it can be used effectively as an adjuvant to antibiotics in the treatment of clinical mastitis without generating a significant change in cost. uddermint, golden udder, mastilep, and therapeutic usage of oil extracts of Ocimum sanctum (tulsi) with Azadirachta (neem) and aqueous extract of Tinospora cordifola found good results for lowering bacterial load and enhancing phagocytic capacity (Joshi and Gokhale 2006) [32]. In a recent study evaluating the *in vitro* antibacterial activity of Terminalia chebula's ethyl acetate extract against the molecularly identified isolates of S. aureus, E. coli, Pseudomonas aeruginosa, and Bacillus megaterium, a 500 mg/mL concentration of the extract was found to be as effective as standard amoxicillin (Kher *et al*. 2019) [37]. This research demonstrates the possibility for herbal extracts to replace antibiotics as the sole treatment for clinical mastitis.

Homeopathic Therapy

In their study, Varshney and Naresh (2005) [92] found that the overall efficacy of homoeopathic combination medicine in the treatment of acute non-fibrosed mastitis was 86.6%, with a mean recovery length of 7.7 days and a total therapy cost of 21,4 Indian Rupees. We find that the combination of Phytolacca, Calcarea fluorica., Silica, Belladonna, Bryonia, Arnica, Conium and Ipecacuanha (Healwell VT-6) was successful and cost-effective for the treatment of mastitis in nursing dairy cows. In their study, Ebert *et al*. (2017) [24] reported that homoeopathic treatment had no additional effect over placebo in terms of duration to recovery, somatic cell count, risk of clinical cure within 14 days of disease onset, risk of mastitis recurrence, and risk of culling. For

each farm, the pros and disadvantages of homoeopathy must be carefully evaluated. No medicine could be prescribed for the treatment of bovine mastitis. In eight of nine selected studies, Belladonna, Bryonia, Lachesis, and Phytolacca were the most common medicines. All four of these homoeopathic treatments related to mastitis in their medication pictures. Due to this, homoeopathic remedies should be administered according to the cow's indication and specific symptoms. Due to their distinct modes of action, it is difficult to compare the efficacy of homoeopathy with antibiotic therapy. It was feasible to cut antibiotic usage by up to 75% when homoeopathy was used in conjunction with antibiotics. This was accomplished using homoeopathy or, if necessary, a combination of homoeopathy and antibiotics. This phenomenon suggested that homoeopathy may have a lasting effect, which could aid to maintain animal health (Zeise and Fritz, 2019) [100]. In the case of clinical mastitis in dairy nursing cows, homoeopathic, non-antimicrobial, and alternative conventional treatments are not recommended (Francoz *et al*., 2017) [26]. *In vitro* mastitis treatment options include immunotherapy, nanoparticle-based therapy, and stem cell therapy, among others. Additional research is required to develop an alternative to antibiotic treatment for mastitis.

Conclusions

Mastitis problem in dairy animals is very common and its economic losses is highest among all animal diseases. In field condition it can be diagnosed on the basis of clinical sign and symptoms and ready to use kit such as CMT kit and after diagnosis prompt treatment can be initiated for better prognosis. In the era of antimicrobial resistant (AMR), for the treatment of mastitis, first homeopathic or herbal treatment initiated for early recovery. The best lesson for dairy farmers is to maintain regular cleaning of dairy farm, animals, utensils and maintain biosecurity in farm and adopt one health approach for proper prevention of all types of mastitis. Prevention is better than cure should be main mantra for Mastitis control in dairy animals.

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Conflict of Interest

There is no conflict of interest in conduction of the present research work.

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