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Review Article

Genetics and Therapies of Mastitis in Common Milch Animals: A Review

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Abstract

Domesticated cattle represent not only a large source of sustenance but also a source of income for billions of people. The dairy sector has a very significant role in the Indian economy, but many tasks need to be addressed in order to preserve governmental agencies, in order to maintain the competitiveness and long-term viability of the industry, we have been attempting to identify healthy dairy cows with enhanced or decreased potential. For many years, several diseases in cattle, including the development of mastitis, were reducing the milk industry. Furthermore, the disease has a significant detrimental influence on dairy industry production as a result of poor milk quality and decreased industrial yield. The present review aimed to provide complete information on mastitis in one place and to be helpful for researchers.

Keywords: Bacteria; Antibiotic; Mastitis; Dairy animals; Natural Products

Introduction

Mastitis is defined as inflammation of the mammary gland, which includes not only intramammary tissues but also related anatomical structures like nipples, mammary areolas, milk ducts, and so on. It manifests as an inflammatory reaction of the mammary gland parenchyma that can be contagious, traumatic, or poisonous. It is a common disease in dairy cattle and one of the most serious diseases affecting the global dairy sector, as it reduces milk output and has negative consequences for the chemical and cytological composition of milk. Inflammation of one or more quarters of the mammary gland occurs in most cases, and it frequently affects not only particular animal but the entire herd or at least multiple animals [1].

Mastitis is predicted to cost roughly 150 euros per year in economic losses. bacterial infection of the breast gland known as clinical mastitis causes symptoms that are obvious and can take many different forms, including abnormal milk appearance (clots or serum), swelling, redness, or necrosis of one or more halves, or severe systemic symptoms including anorexia, fever, or agalactia. Inflammation of the udder is identified by counting inflammatory cells in the milk in subclinical mastitis. Milk from cows with subclinical mastitis is not altered in appearance by definition, and testing of the milk is required to identify affected animals [2].

Milk production is decreased when mastitis of the mammary gland, is the most frequent illness in dairy animals, resulting in poor quality. The viable microorganism that causes many diseases include a variety of gram-positive and gram-negative bacteria, and can be either contagious (e.g., *Staphylococcus aureus*, *Streptococcus agalactiae*, *Mycoplasma* spp.) or environmental (e.g., *Escherichia coli*, *Enterococcus* spp., coagulase-negative *Staphylococcus*, *Streptococcus uberis*) [3].

Pathogens such as *E. coli*, *Staphylococcus aureus*, and *Staphylococcus aureus* invade the mammary gland. In certain herds, coagulase-negative staphylococci represent the biggest threat [4], although they may or may not be an issue in other herds. As a result, the causal factors listed in this assessment may not be the most common in every region or herd (Figure 1).

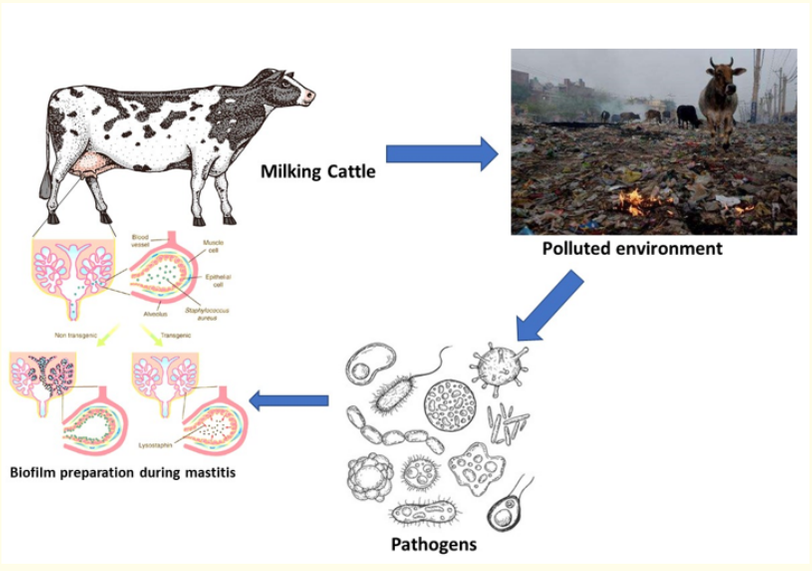

Figure 1: Diagrammatic representation of causative pathogens (possible cause) of mastitis [48].

S. aureus, *S. agalactiae*, and *S. uberis* are the most contagious organisms causing intramammary inflammation, according to [5]. The rectal, rumen, and vaginal areas, as well as the mammary glands, are the principal reservoirs of infectious infections. *E. coli*, *S. aureus*, and *Streptococci* are the most common pathogens that cause mastitis, according to [6] and [7]. Because *E. coli* and *S. aureus* are zoonotic diseases, they can potentially be transferred to people.

E. coli is one of the most common bacteria that cause environmental mastitis. It commonly targets the mammary gland during the early stages of nursing, and if left untreated, it can be fatal. The mild variant of *E. coli* causes only local signals in the udder and milk, and the symptoms last just a few days. It can have very serious or even fatal implications in other more serious circumstances [8].

E. coli's outer cell wall includes an endotoxin with infective potential that plays a key role in the bacteria's pathogenicity. Although endotoxin is the principal virulence factor of Gram-negative bacteria and is responsible for udder tissue destruction, its presence in the mammary gland also stimulates leucocyte activity.

According to research by [9], the conventional belief that *S. uberis* is an environmental causal agent is questionable, and transmission from cow to cow may be the most common mode of transmission. *S. uberis*, which is found in the animals' habitat, has been classified as an environmental causal agent by the majority of researchers *S. uberis*, like *K. pneumoniae*, is mostly found in bedding materials like peat or straw.

Effect of mastitis in milk quality

Mastitis reduces milk yield and quality, which can result in significant financial losses for dairy farmers and cheese producers. Alterations in composition in mastitis milk decrease coagulation, cheese yield, and composition; some composition changes result in poor cheese quality, and higher Stem Cell Count was linked to the generation of cheese with a high moisture content (Figure 2).

Mastitis has an impact on overall milk production, as well as milk composition and technological applicability. As a useful predictor of subclinical mastitis in cows, the somatic cell count (SCC) is a significant component of milk in terms of quality, hygiene, and mastitis control. Changes in fatty acid content, lactose, ion and mineral concentration, increased enzymatic activity, and a higher pH of raw milk are all linked to increased milk SCC. Losses of milk production were estimated to be 5% of total milk production during lactation and 0.5 kg milk every 2-forld increase in inflammatory cells in a cow.

Candidate genes involve in mastitis disease

An integrated research tool encompassing diverse forms of information enabling a genomic approach to study lactation, udder development, and health has been established using a cow database of potential genes and genetic markers for milk output and mastitis. The database comprises 943 genes and genetic markers involved in mammary gland development and function, which could be investigated further [10] (Table 1).

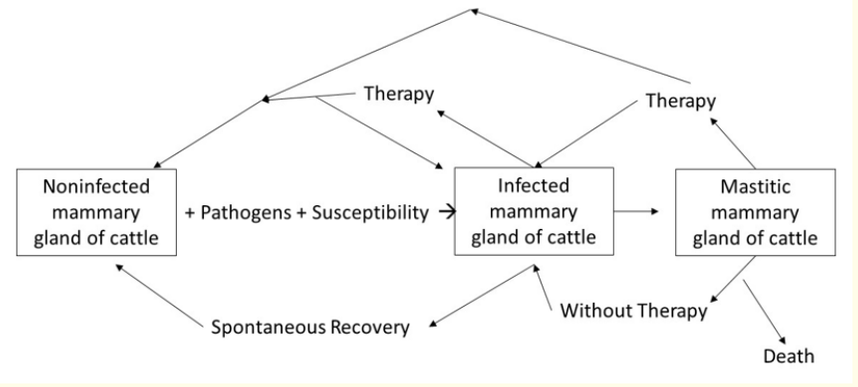

Figure 2: Imaginable arrangement of events in expansion of contagion and mastitis [40].

Gene	Gene name
ABCG2	*ATP-binding cassette, sub-family G (WHITE), member 2*
ATP2B2	*ATPase, Ca++ transporting, plasma membrane 2*
B4GALT1	*UDP-Gal: betaGlcNAc beta 1,4- galactosyltransferase, polypeptide 1*
BTN1A1	*Butyrophilin, subfamily 1, member A1*
CSN1S1	*Casein alpha s1*
CSN1S2	*Casein alpha s2*
CSN2	*Casein beta*
CSN3	*Casein kappa*
DGAT1	*Diacylglycerol O-acyltransferase 1*
EGF	*Epidermal growth factor (beta urogastrone)*
GHR	*Growth hormone receptor*
ID2	*Inhibitor of DNA binding 2, dominant negative helix-loop-helix protein*
LALBA	*Lactalbumin, alpha*
LEP	*Leptin*
LGB	*Lactoglobulin, beta*
MFGE8	*Milk fat globule-EGF factor 8 protein*
NME1	*Non-metastatic cells 1, protein (NM23A) expressed in*
PRL	*Prolactin*
PTHLH	*Parathyroid hormone-like peptide*
STAT5A	*Signal transducer and activator of transcription 5A*
XDH	*Xanthine dehydrogenase*
ACTB	*Actin, beta, cytoplasmic*
C5AR1	*Complement component 5a receptor 1*
CD14	*CD14 antigen*
ETS2	*E26 avian leukaemia oncogene 2, 3′ domain*
FEZF2	*fez family zinc finger 2*
IFNG	*Interferon gamma*
IL1B	*Interleukin 1 beta*
IL6	*Interleukin 6*
IL8	*Interleukin 8*
IL8RA	*Interleukin 8 receptor, alpha*

LBP	*Lipopolysaccharide binding protein*
PTGS1	*Prostaglandin-endoperoxide synthase 1*
SAA3	*Serum amyloid A3*
TLR-2	*Toll-like receptor 2*
TLR-4	*Toll-like receptor 4*
TNF	*Tumor necrosis factor*
ACLY	*ATP citrate lyase*
BoLA-DRB3	*Major histocompatibility complex, class II, DRB3*
CCL2	*Chemokine (C-C motif) ligand 20*
KCNK1	*Potassium channel, subfamily K, member 1*
LTF	*Lactoferrin*
RORA	*RAR-related orphan receptor alpha*
TP53	*Transformation related protein 53*

Table 1: The names of the genes that cause mastitis and the key candidate genes discovered using correlating data sets from independent investigations by [50].

Mastitis has long been regarded as the disease with the biggest global impact in the dairy herd, owing to its high incidence and the financial losses it causes [11], Furthermore, the disease has a significant detrimental influence on dairy industry production as a result of poor milk quality and decreased industrial yield. The immune system has two defense systems that protect the mammary gland tissue: innate or nonspecific immunity and acquired or specific immunity. In order to provide protection against mastitis-causing bacteria, both innate and acquired immunity interact.

Because of the variation in genetic background and population-specific interactions between loci, association and quantitative trait locus (QTL) studies in large farm animals are typically conducted in outbred populations, making the identification of robust QTL and candidate genes difficult and less reliable. In model and laboratory animal species, when highly inbred lines and targeted gene knock-outs are available, the situation is considerably different. As a result, the sole method for detecting QTLs and candidate genes in large farm animals is to combine various pieces of evidence that support the functionality of identified genomic areas in relation to multigenic traits.

Milk and mastitis QTL

In the Animal QTL database, there are 344 QTL connected with milk qualities in cattle (MY, MSPD, DCCI, PY, PP, EY, FP) and 71 mastitis-related traits (CM, SCS, and SCC). Except for BTA16, BTA24, and BTAX, QTL are found on all chromosomes. The multiple genetic and environmental elements that contribute to an animal's phenotype, including diverse characteristics and particular host-pathogen interactions, may explain why milk and mastitis QTL are scattered across so many chromosomes. BTA6 and BTA14 had the highest density of milk-related QTL, while BTA3 and BTA14 had the highest density of mastitis-related QTL [12].

SNPs associated with mastitis

Milk (MY, milk protein, PP, milk fat, and FP) and mastitis (CM and SCS) features were studied for allele-phenotype associations. For twenty-four potential genes, a link between DNA sequence variation and mammary gland phenotype has been shown. Ten potential genes have been revealed to have a link between DNA sequence variation and mastitis resistance or susceptibility. More than one study has found evidence for the connection of 11 genes (ABCG2, BoLA-DRB3, CSN1S1, CSN3, DGAT1, GHR, LGB, LEP, LTF, PRL, and STAT5A) with mammary gland phenotype, as well as three genes (IL8RA, TLR4, and BoLA-DRB3) with mastitis resistance or susceptibility [13].

AFLP markers associated with mastitis

In Canadian Holsteins, [14] looked for genome-wide QTL-linked AFLP markers for mastitis resistance. Selective DNA pooling and the AFLP approach were used to screen cows. Twenty-seven AFLP markers linked to CM were discovered, with the most promising marker, CGIL4, described and mapped to BTA22 q24. However, because of their dominant character, AFLPs are less informative than SNPs, which have become more popular as genome sequencing has progressed.

Expression profiles associated with milk production and mastitis

[15] used comparative mapping to identify candidate genes with expression patterns linked with milk production in cattle. They combined their mouse mammary gland gene expression experiments with two other expression investigations. The findings have been made available as a web tool for QTL candidate genes (cgQTL database). To date, twelve papers have been published employing microarrays and ELISA to describe 107 genes with expression patterns linked to mastitis cases in cattle.

Milk protein genes

In bovine milk, found 14 main proteins. Milk protein genes come in a variety of genetic variations that encode chemically distinct proteins. Several studies have looked into the link between genetic variants of milk proteins and yield traits, milk composition, and milk technical properties. The allele-specific effects, on the other hand, are highly dependent on the genetic background (breed) and experimental model (single locus vs. multi locus effects). Milk protein variations are known for nine milk protein families in bovine milk, however only a few of them have a major impact on milk characteristics.

Molecular mechanisms involved in mastitis disease

Mastitis is typically diagnosed with somatic cell counts and bacteriological investigations. In cases of acute mastitis, where clinical changes are visible and the chemical composition of milk has changed, diagnosing the problem and the need for treatment is usually not difficult, and the milk producer can usually notice the problem and the need for treatment [16] (Figure 3).

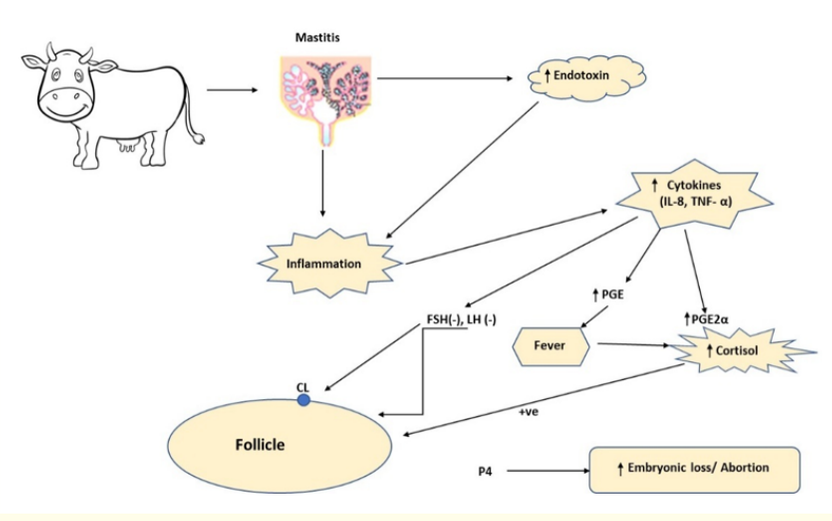

Figure 3: Conceivable mechanism by which mastitis sufferings the reproductive functions in the mastitis.

Molecular mechanism involves in mastitis

TLRs, NLRs, and RLRs all activate PPRs, which then activate the NF-B and MAPK signaling pathways in the cell, allowing pro-inflammatory cytokines, interferons (IFNs), and chemokines to be produced [17]. The creation of these mediators in the cell nucleus triggers the commencement of the immune response in host organisms, causing them to begin recruiting immune cells to the infection site [18].

TLRs signaling in mastitis

During Mastitis in animals, increased expression of Toll-like receptors (TLRs) has been identified as a significant signaling pathway [19]. The relationship between SCS and TLR2 and TLR4 in cattle has been thoroughly explored [20]. TLRs 1–10 are the TLRs found in cattle. Which are responsible for a wide range of pathogens and have been divided into two groups: those that express in the plasma membrane (TLR1, 2, 4, 5, 6, and 10) and those that are located in the endosome (TLR1, 2, 4, 5, 6, and 10) [21]. (TLR3, 7, 8, and 9). TLR1, 5, 6, and 10 are antibacterial, while TLR3, 7, 8, and 9 are antiviral; nonetheless, TLR2 and TLR4 are familiar with both pathogen groups' structures [22].

During infection, these receptors are critical for recruiting significant signaling pathways to downstream mediators, resulting in the generation of cytokines and type-I IFNs, but their activation can also cause cell death. TLRs recognize a variety of PAMPs from a variety of species.

Following the impacts of PAMPs, pattern recognition receptors (PRRs) are required for the start of innate immunity. TLR1, TLR2,

TLR4, and TLR 6 identify lipids from Gram-negative bacteria, such as lipopolysaccharide (LPS), which causes septic shock [23].

TLR 3, 7, 8, and 9 belong to the third class of TLRs, which recognize nucleic acids produced by bacteria and viruses through the cell. TLR3 recognizes dsRNA, whereas TLR7, 8, and 9 have been demonstrated to recognize single-stranded RNA (ssRNA), which is produced by many bacteria and viruses during replication. TLRs detect PAMPs and activate signalling pathways in the cell guiding the synthesis of inflammatory cytokine genes such as TNF, IL-6, IL-1, and IL-12. Similarly Intracellular TIR domains such as MyD88, TIRAP (MAL), Trif (TICAM1), and TRAM initiate TIR-TIR interaction (as TICAM2).

All TLRs share MyD88, which activates the MAP kinase (JNK, ERK, and P38) and NF-kB pathways, which influence the production of cytokines genes. TLR1-2, TLR4, and TLR6 recruit TIRAP, which acts as a linker-adaptor between TLR domains (TIR) and MyD88 [24]. Finally, this recruitment initiates a signaling cascade that activates transcription factors such as NFkB and IRFs.

Mechanism of RLRs during mastitis

Although virus infection in bovine mastitis is not as common as bacterial infection, various virus families have been linked to the disease. Recently, the FMD virus, Myoviridae, and Vaccinia virus [25] have been linked to bovine mastitis. RLRs are cytosolic PPRs that detect viral RNA in the cytoplasm of most cell types.

A DExD/H box RNA helicase domain and a C-terminal domain make up these receptors (CTD). RIG-I and MDA5 exhibit a strong sequence similarity and the same domain layout, however LGP2 lacks the N-terminal caspase recruitment domain (CARD) for signal transduction [26], RIG-I and MDA5, on the other hand, recognize structurally distinct viral RNA types. RIG-I detects RNAs with both panhandle structures and a 5'triphosphate moiety, whereas MDA5 detects long dsRNA or web-like RNA [27].

RIG-I is usually present in a dormant form, with RD covering RNA binding and helicase, and is expressed at a low level. IRF3 and NF-B are activated by RIG-I and MDA with the help of the adapter molecule mitochondrial antiviral signaling protein (MAVS) during pathogenic stimulus, where they form filaments with RNA binding to receptors Caspase recruitment domain (CARD) and initiate signaling [28]. RIG MAVs' CARDs form an SMOC structure at the mitochondrial surface, which stimulates the transcription factors type-I IFNs [29]. However, other organelles can also initiate signal transduction and direct to type-I IFN expression, similar to RIG-I, and a parallel pathway known as the sting pathway has been discovered.

NLRs and its expression during mastitis

NLRs are pathogen-sensing receptors that are only found in the cytosol and nucleus [30]. These, on the other hand, are categorized according to which signaling pathways they activate. Signal transduction is triggered by NOD1 and NOD2, which includes the pro-inflammatory NF-kB [31], NLRs elicit innate and adaptive immunity in the host cell by reacting to a wide spectrum of PAMPs/DAMPs. Bacterial toxins, flagellins, rod proteins, muramyl dipeptides (bacteria), RNA, M2 proteins (viruses), B-glucans, zymosan (fungi), and hemozoin are all PMMPs that can activate the inflammasome (protozoa) NOD1/2 is linked to CARD, which can activate NF-kB via the RIP2/RICK pathway, increasing the production of pro-inflammatory cytokines such IL-1b and IL-18.

g-D-glutamyl-mesodiaminopimelic acid (iE-DAP) in NOD1 and muramyl dipeptides (MDP) in NOD2 are recognized bacterial peptidoglycans after infection. Some NLRs, such as NLRC3 and NLRP2/4, function in the opposite direction of the NF-kB pathway, modifying TNF-alpha and TRAF6 [32]. NLRP1/3 is also linked to the apoptosis-associated speck-like protein (ASC) through a pyrin-pyrin domain, which can activate the caspase-1 inflammasome.

The peptidoglycan motif of bacteria activates the NLRP inflammasome, and the NLRP3-inflammasome is triggered by numerous PAMPs and DAMPs such as alum, silica, uric acid, and ATP. Because NLRC4 lacks a pyrin domain, it produces IL-1b and IL-18 when ASC is recruited; nonetheless, an NLRC4 inflammasome generated without ASC recruitment causes pyroptosis [33], and it is triggered by bacterial flagellin [34]. NODs, like TLRs, start an intracellular cascade of activity by phosphorylating NF-kB to activate it.

Mutation by which mastitis cause

CD14 mutations influence binding capacity, which has an impact on biological potentiality. In bubaline CD14, mutational hotspots were discovered with 58 non-synonymous SNPs, 18 of which were shown to be harmful and 34 as thermodynamically unstable. With 58 SNPs, eight distinct CD14 gene variations have been identified in all four buffalo breeds, suggesting a significant degree of polymorphism. The genotypes AA (genotypic frequency 0.468) and AG and AH (genotypic frequency 0.0174) were identified as the most common and least frequent genotypes, respectively.

When compared to the A allele of the amplified CD14 nucleotide of buffalo, alleles B (81.3%), C (97.0%), D (86.0%), E (97.4%), and F (85.8%) showed a high degree of variability, which could be due to coding for leucine-rich repeats, which confer recognition and binding ability for a wide range of pathogens. However, because

there was no change in amino acid at the glycosylation sites, the CD14 molecule's critical activities remained unchanged [35].

Furthermore, it is generally known that CD14 comes in two forms: membrane-bound (mCD14) and soluble (sCD14), each of which plays a little part in GN bacterium identification. Monocytes, macrophages, and polymorphonuclear neutrophils (PMNs) all express mCD14 on their cell surfaces.

[36] In the presence of LBP, mCD14 activates phagocytes at low LPS concentrations. CD14 is exclusively found in bodily fluids such as serum and breastmilk. Even in the absence of mCD14, either mCD14 or sCD14 can increase the LPS response and related signaling pathways in epithelial and endothelial cells.

Under low concentrations, sCD14 binding to LPS can promote the innate response to GN bacterial infection, reducing mastitis-induced stress and weakening LPS toxicity. Previous research has revealed differences in susceptibility to GN bacterial infection in dairy cows [37], as well as polymorphisms in the coding and promoter regions of the CD14 gene linked to the risk of a variety of diseases in humans and animals [38].

As a result, genetic differences in cow CD14 appear to influence the risk of GN bacterial infections [39]. However, nothing is known regarding the link between CD14 polymorphisms and mastitis. As a result, the single-strand conformation polymorphism (SSCP) approach was used to investigate CD14 polymorphisms and their relationship to clinical mastitis in dairy cattle, which would be useful for breeding anti-mastitis dairy cattle.

Characterization of CD 14 gene of cattle

The buffalo CD14 coding sequence was 1122 bp long and included 62.3 percent GC. The CD14 gene's open reading frame was 1116 nucleotides long, with a natural start codon and a TAA termination codon. When the generated amino acid sequences of cattle and buffalo were examined, the buffalo sequence had a slightly greater molecular weight (39705.07 Da) than the cow sequence (39679.96 Da).

The buffalo CD14 peptide sequence differed from cattle in that it had one additional highly basic amino acid and two polar amino acids. When the nucleotide sequences of cattle and buffalo were compared, there were 22 nucleotide alterations, eleven of which were synonymous codons with no amino acid change.

When the peptide sequences of buffalo CD14 and cow CD14 were compared, eleven amino acid substitutions were found at positions 14, 62, 131, 134, 139, 143, 154, 209, 235-236, 277, and 337. Six leucine-rich repeats (LRR) were found in the derived peptide sequence of buffalo CD14 on the other hand cow has 10 LRR. The leucine content of the Buffalo CD14 molecule was estimated to be 17.2%, which is close to mouse (17.66%) but greater than human (15.5 percent).

CD14 is a shape recognition receptor that predicaments lipopolysaccharide, lipoteichoic acid, and mannuronic acid as ligands. Bubaline CD14 was shown to be hypervariable, with a mutational hot spot, notably in the LRR region, which is responsible for pathogen identification. Both an *in-silico* investigation and experimental confirmation with somatic cell count, California mastitis test, and rennet coagulation time revealed Variant A to be the wild-type.

SNPs and Indel mutations in the CD14 gene result in a thermodynamically unstable and harmful CD14 peptide with decreased immune characteristics and illnesses. Eight bubaline CD14 variations were identified, with variants D and F being the most detrimental and thermodynamically unstable alterations, resulting in increased susceptibility to mastitis. Proper characterization could lead to future research into the therapeutic application of recombinant CD14 wild type variant A, somatic gene therapy, transgenic animal production with Variant A gene insert, and marker-assisted selection for variant A for the production of future livestock with reduced susceptibility to diseases, particularly mastitis.

Mastitis control and treatment

- **Vaccine**: *E. coli* J5 vaccines can lower the number and severity of coliform mastitis infections by 70% to 80% [40]. Recent research has concentrated on developing a DNA vaccine that produces virulence factors *in vivo* and is largely aimed against *S. aureus* mastitis, as antibiotic treatment is typically ineffective against this organism [41]. Mastitis is treated with vaccines such as StartVac or TopVac from Amer in Spain.
- **Antibiotics:** Antibiotics are typically used on dairy farms to treat clinical mastitis instances and to dry out animals. Drugs must reach all infection sites inside the infected quarter, persist at acceptable levels at all infection sites for an adequate amount of time, and kill all infecting microorganisms for antibiotic therapy to be successful.
- **Plant derived compounds**: Plant-derived antimicrobials such as trans-cinnamaldehyde (TC), eugenol, carvacrol, and thymol have antimicrobial effects against key bacterial mas-

titis pathogens in milk. Antimicrobial activity was shown in plant-derived antimicrobials such as trans-cinnamaldehyde (TC), eugenol, carvacrol, and thymol against the five mastitis pathogens examined (*S, agalactiae*, *S. dysgalactiae*, *S. uberis*, *S. aureus*) [42].

- **Animal derived compounds**: The use of animal-derived substances in the treatment of bovine mastitis has recently focused on bee products. The anti-inflammatory activity of bee venom, which contains the active component melittin, was investigated in LPS-induced MAC-T cells [43]. By inhibiting phosphorylation of ERK1/2 and nuclear translocation of NF-B, bee venom was able to reduce LPS-induced COX-2 protein expression as well as mRNA expression of pro-inflammatory cytokines TNF- and IL-6.
- The anti-inflammatory action of propolis, a resinous material produced by honeybees, has also been investigated in MAC-T cells [44]. When stimulated with various pathogenic factors such as LPS, lipoteichoic acid, TNF-, heat-inactivated *E. coli*, and *S. aureus*, pre-treatment of MAC-T cells with Chinese propolis (15 g/mL) prevented a decrease in cell viability as well as a decrease in pro-inflammatory cytokines mRNA levels such as TNF- and IL-6. Furthermore, in mastitis-infected cells, Chinese propolis increased the mRNA expression of antioxidant genes HO-1, TXNRD1, and glutamate-cysteine ligase modifier subunit, showing anti-oxidative actions.
- Immunomodulators such as lactoferrin, which are naturally generated by animals, were selected as prospective non-antibiotic antimicrobial agents for the treatment and prevention of bovine mastitis. Lactoferrin is an iron-chelating glycoprotein that may be found in milk, colostrum, and other exocrine secretions including saliva and tears [45]. It plays a vital function in the innate immune system's opsonization of microorganisms for phagocytosis as an immunomodulator [46]. It was shown to have antibacterial properties against *E. coli*, *P. aeruginosa*, *S. agalactiae*, and *S. aureus*, owing to its iron-chelating activity, which can prevent biofilm formation by sequestering iron.
- **Others:** Several bacteriocins are used in the treatment of Mastitis. Lacticin was initially isolated from Irish Keffirgrain and is generated by *L. lactis* subsp. lactis DPC3147, *Bacillus sp*., *Enterococcus sp*., *Lactobacillus sp*., *P. spentriceans*, *S. aureus*, streptococci, coliforms (*E. coli*), *C. perfringens*, *B. cereus*, *A. mpyogenesus*, *S. thermophi*lus, and most mastitis. And Nisin produced from *L. lactis* have an antimicrobial polypeptide that is used to treat bovine-clinical mastitis in nursing dairy cattle [47].

S. No.	Antibiotic	Activity
1	Cloxacillin, ampicillin	Septic mastitis. *S. aureus, streptococci, coliforms (E. coli and Klebsiella spp.)*
2	Cloxacillin, ampicillin	*S. aureus, streptococci, coliforms (E. coli and Klebsiella spp.)*
3	Penicillin, dihyrostreptomycin	*S. aureus, streptococci, coliforms (E. coli and Klebsiella spp.), Clostridium perfringens, Bacillus cereus*
4	Cloxacillin	*S. aureus, streptococci*
5	Ampicillin	*S. aureus, streptococci, coliforms (E. coli and Klebsiella spp.)*
6	Lincomycin, neomycin	*Staphylococcus aureus, streptococci*
7	Oxytetracycline, neomycin, bacitracin, cortisone	*S. aureus, streptococci, coliforms (E. coli and Klebsiella spp.)*
8	Penicillin, dyhrostreptomycin, nafcillin	*S. aureus, streptococci, coliforms (E. coli and Klebsiella spp.), Clostridium perfringens, Bacillus cereus, Arcanobacterium pyogenes*
9	Cloxicillin, blue tracer dye	*S. aureus, streptococci*
10	Cloxicillin, ampicillin, blue tracer dy	*S. aureus, streptococci, coliforms (E. coli and Klebsiella spp.)*
11	Penicillin, dihydrostreptomycin, blue tracer dye	Acute mastitis. *S. aureus, streptococci, soliforms (E. coli and Klebsiella spp.), Clostridium perfringens, Bacillus cereus, Arcanobacterium pyogenes*
12	Cephalexin, neomycin, cortisone	Acute and chronic mastitis
13	Penicillin, dihydrostreptomycin, novobiocin, polymyxin B, cortisone	Acute or chronic mastitis. *S. aureus, streptococci, coliforms (E. coli and Klebsiella spp.), Clostridium perfringens, Bacillus cereus, Pseudomonas aeruginosa, Arcanobacterium pyogenes*
14	Penicillin, dihyrostreptomycine, blue tracer dye	*S. aureus, streptococci, coliforms (E. coli and Klebsiella spp.), Clostridium perfringens*

Table 2: list of antibiotics that have been recommended for use in treating and fighting bacteria in lactating animals.

Conclusion

The financial losses in the dairy industry caused by cattle mastitis causative agents, the rapid emergence and display of multidrug resistance, and their high proclivity for causing persistent, chronic, and recurrent infections make this disease a constant challenge and a subject of investigation by several research groups, justifying continued attention in this area. Biofilms *i.e*., surface-associated microbial cells that is enclosed in an extracellular polymeric substance matrix. have been demonstrated to have a role in pathogenicity, regardless of the source of infection, and may thus play a function in the biology of recurring infections, antimicrobial agents, and immune defense system resistance, making mastitis control more difficult. The role of biofilms in mastitis contamination is crucial for defining and researching the most effective control methods for use in veterinary practice in order to maintain milk quality and safety.

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Conflict of Interest

Authors have no conflict of interest.

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