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Bovine mastitis, a worldwide impact disease: Prevalence, antimicrobial resistance, and viable alternative approaches

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ABSTRACT

Bovine mastitis is globally considered one of the most important diseases within dairy herds, mainly due to the associated economic losses. The most prevalent etiology are bacteria, classified into contagious and environmental, with *Staphylococcus aureus, Streptococcus agalactiae, Streptococcus uberis, Escherichia coli and Klebsiella pneumoniae* being the most common pathogens associated with mastitis cases. To date these pathogens are resistant to the most common active ingredients used for mastitis treatment. According to recent studies resistance to new antimicrobials has increased, which is why developing of alternative treatments is imperative. Therefore the present review aims to summarize the reports about bovine mastitis along 10 years, emphasizing bacterial etiology, its epidemiology, and the current situation of antimicrobial resistance, as well as the development of alternative treatments for this pathology. Analyzed data showed that the prevalence of major pathogens associated with bovine mastitis varied according to geographical region. Moreover, these pathogens are classified as multidrug-resistant, since the effectiveness of antimicrobials on them has decreased. To date, several studies have focused on the research of alternative treatments, among them vegetal extracts, essential oils, or peptides. Some other works have reported the application of nanotechnology and polymers against bacteria associated with bovine mastitis. Results demonstrated that these alternatives may be effective on bacteria associated with bovine mastitis.

1. Introduction

Milk and its derivatives are sources of important nutrients to people, which is why the dairy industry continues to consolidate into larger farms, However, this industry has been facing challenges, dealing with demands of accountability for animal welfare and product safety. In this sense identifying diseases is key to recognizing the multifactorial nature of almost all diseases of importance in dairy cattle and redefining them more broadly, to include subclinical conditions, such as bovine mastitis (LeBlanc *et al.*, 2006; Petersson-Wolfe *et al.*, 2018; Fetrow *et al.*, 2020; Nguyen; Briggs et al., 2022).

Bovine mastitis, defined as the inflammation of the mammary, is one of the most critical pathologies within dairy herds worldwide, due to its economic impact, causing huge losses not only reflected in decreased production but also in culling rates (Azooz *et al.*, 2020; Sharun *et al.*, 2021).

Bovine mastitis is mainly classified according to clinical (or subclinical) features and etiology (noninfectious and infectious). Infectious causes are most common, and in several cases, infections associated with bacteria are the most prevalent presentation within herds. Bacterial pathogens are also classified into different categories: Contagious, environmental, and opportunistic bacteria (Ndahetuye *et al.*, 2019). According to several studies, the pathogens most frequently present in mastitis cases are *Staphylococcus aureus, Streptococcus agalactiae, Streptococcus uberis, Escherichia coli and Klebsiella pneumoniae* (Klaas & Zadoks, 2018; Ashraf & Imran, 2020; Cadona-Hernandez et al., 2021).

In addition, bacterial resistance has become a rising threat since mechanisms of resistance are spreading globally. To date, traditional

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antibiotic treatments easy easily cause the apparition of resistant strains (Peng *et al.,* 2022). Resistance to antimicrobials such as, penicillin, amoxicillin, tetracycline, Amikacin, gentamicin, or erythromycin has been widely reported. Nevertheless, according to recent studies resistance to new antimicrobials has increased; bacterial profiles indicated resistance to piperacillin, ceftazidime, cefquinome, tigecycline, colistin and vancomycin. Moreover, the problem of drug residue is also increasing. (Carvalho-Castro *et al.,* 2017; Monistero *et al.,* 2021; Campos et al.;, 2022; Vidal-Amaral *et al.,* 2022; Bonardi *et al.,* 2023).

Due to the abovementioned concerns, the search for therapeutic alternatives that are not invasive and do not cause resistance is necessary (Junior *et al.,* 2023). Research shows that herbal or plant medicine in livestock production has been used as health promoters and for treating of diseases (Kuralkar & Kuralkar, 2021). Recently, new alternatives have been proposed including peptides, nanoparticles, nanocolloids or polymers, and more recently, phototherapy, all of which have demonstrated effectiveness (Gruet et al., 2001; Omara, 2017; Marques-Bastos *et al.,* 2022; Fidelis *et al.,* 2023; Saeed *et al.,* 2023).

In this respect the present review aims to summarize the reports over 10 years, emphasizing bacterial etiology, its epidemiology, and the current situation of antimicrobial resistance, as well as the development of alternative treatments for this pathology.

2. Methodology

A comprehensive search was conducted in the following databases: Google Scholar, PubMed, Scopus and ScienceDirect for studies published from 2013 to 2023. The following headings and keywords were used: “Bovine mastitis”, “antimicrobial resistance” and “alternative treatments”. In addition, the phrase “antibacterial activity” was employed to generate data for the biological activity discussed in the review. The methods used in this review were as follows: All the considered papers were analyzed according to each section of the review, and the most relevant information was taken and synthetized to obtain concrete information. Duplicate papers were removed, the data were screened, irrelevant work was excluded, and full-text documents were then screened. Inclusion criteria including original articles or reviews and work on natural or chemical alternative treatments. Exclusion criteria were inadequate methods and the lack of access to the full text.

3. Bovine mastitis classification

3.1. Clinical features

Mastitis can be classified according to clinical features, into clinical and subclinical mastitis. The first is characterized by the presence of flakes, clots, or watery secretions in milk. Generally the infected quarters are swollen, hot and painful. In some acute clinical cases, general signs can be found (hyperthermia, anorexia, and depression). The consequences are severe, causing cow’s death or agalactia, which leads to premature culling (Cobirka *et al.,* 2020) Subclinical mastitis is more difficult to diagnose, because of the lack of evident signs in milk or animals. Its major symptoms are related to increased somatic cell count and decreased milk production. Subclinical duration lasts longer than clinical and infection allows the spread of pathogens within the herd (Cobirka *et al.,* 2020).

3.2. Noninfectious causes

Mechanical injuries associated with machine milking can induce severe damages to quarters, which makes them more vulnerable, ascending into infections due to damage to keratin or mucous membranes lining the teat sinus (Schlafer & Foster, 2016; Ashraf & Imran, 2020). Poor hygienic practices are highly related, such as unclean udder at the start of milking. Moreover, Holstein cows are more susceptible to mastitis than other breeds (Ramírez *et al.,* 2014). Dietary imbalances are also related to mastitis cases (Bludau *et al.,* 2014). In addition, Perez-Morales *et al.* (2022), determined that cows with seven or more calving showed a higher prevalence of mastitis. Lactation days can also increase the prevalence of disease’s prevalence.

3.3. Infectious causes

Etiology is not completely described; to date almost 200 microorganisms are associated with mastitis, and new pathogens are continuously detected and reported, including yeast, fungi, viruses, and bacteria (Benić *et* al., 2018;Ashraf & Imran, 2020).

3.3.1. Yeast and fungal mastitis

In recent years, higher morbidity rates caused by mycotic mastitis in cattle have been reported. A recent study detected zoonotic yeasts, including *Candida albicans* and *Kodamaea ohmeri* (Awandkar *et al.,* 2021). Other *Candida* species were reported *C. guilliermondii, C. famata, C. tropicalis, C. colliculosa, C. krusei, C. rugosa, C. glabrata, C. parapsilosis, C. inconspicua; Trichosporon* sp., *Rhodotorula glutinis, Saccharomyces fragilis; Pichia kudriavzevii, Cyberlindnera rhodanensis*; mold species were also found *Aspergillus amstelodami, A. fumigatus* and *Geotrichum candidum* (Hayashi *et al.,* 2013; Zhou *et al.,* 2013; Ksouri *et al.,* 2015; Dalanezi *et al.,* 2018) *Prototheca zopfii* and *Prototheca blaschkeae* (yeast-like algae) could also be related (Ricchi *et al.,* 2013).

3.3.2. Viral mastitis

It is probable that virus-induced immunosuppression underlies mastitis. It has been reported that bovine herpesvirus 1, foot and mouth disease virus, and parainfluenza virus caused clinical mastitis, and bovine herpesvirus 4 cause subclinical mastitis. On the other hand teat lesions associated with bovine herpesvirus 2, cowpox, pseudo cowpox virus, foot and mouth disease, vesicular stomatitis virus, papillomavirus, and bovine leukemia virus indirectly contribute to mastitis (Herlekar *et al.,* 2013; Martinez Cuesta *et al.,* 2019; Cuesta et al., 2020).

3.3.3. Bacterial mastitis

Bacteria are the most common and prevalent etiologic agents associated with mastitis. More than 150 Gram-positive and Gram-negative bacteria are identified as mastitis pathogens, which can be divided into contagious (spread from other infected quarters) and environmental (surrounding environment; Ruegg, 2017; Ndahetuye *et al.,* 2019, Ashraf & Imran, 2020; Cobirka *et al.,* 2020).

The udder serves as the reservoir of contagious pathogens transmitted from infected to uninfected teats during the milking process. They mainly include *Mycoplasma bovis, Streptococcus agalactiae*, and *Staphylococcus aureus* (Cvetnić *et al.,* 2016; Ashraf & Imran, 2020; Cobirka *et al.,* 2020).

A higher incidence of *S. agalactiae* isolated from mastitic cows was reported. Due to this many countries consider this pathogen predominant among other contagious pathogens (Zhang *et al.,* 2018; Abd El-Aziz *et al.,* 2021; Cadona *et al.,* 2021). Despite this, a diverse number of reports still consider *S. aureus* the most prevalent contagious agent associated with mastitis, as this bacterium is persistent inside the udder (Lamari *et al.,* 2021;Rainard *et al.,* 2018). Another less common contagious pathogen is *M. bovis*, although few studies report its prevalence. Nevertheless, outbreaks due to *M. bovis* are becoming common and regarded as the most prevalent mycoplasma species causing bovine mastitis worldwide (Liu *et al.,* 2020; Gelgie *et al.,* 2022). On the other hand, environmental pathogens are transmitted through feces, the indoor environment, and pastures, the most common being *E. coli, Klebsiella pneumoniae* and *Streptococcus uberis* (Klaas & Zadoks, 2018).

E. coli is the most common Gram-negative coliform responsible for causing environmental clinical mastitis (Alawneh *et al.,* 2020; Campos *et al.,* 2022), mainly due to high genotypic variability (Bag *et al.,* 2021). *K. pneumoniae* is the second most common cause of bovine mastitis and, is considered the most detrimental in decreasing milk production and quality, as well as in economic terms. Although it is classified as an environmental pathogen, it has also been found to be transmitted from infected to healthy cows (Cheng *et al.*, 2021; Fu *et al.*, 2022). *Streptococcus uberis* causes about one-third of all intramammary infection cases in cows worldwide, invading the teat channel after milking or after damage (Abureema *et al.*, 2014; Monistero *et al.*, 2021). A study reported mycobacteria as causative agents of mastitis, two strains were identified as *Mycobacterium fortuitum* II and *Mycobacterium margeritense,* which are resistant to clarithromycin Cvetnić et al. (2022).

Kotzamanidis *et* al. (2021), stated that it is necessary to understand the population structure, transmission, virulence characteristics, and pathogenicity of pathogens associated with mastitis to develop strategies for reducing the pathogen's spread among herds in a specific geographical region. Epidemiological data (Table 1), virulence characteristics and resistance profiles (Table 2) of bacterial contagious and environmental pathogens associated with mastitis are given in the tables below. Regarding antimicrobial resistance, the existence of patterns between frequently used antimicrobials and increasingly resistant bacteria has been stated; these patterns could help to implement strategies to control mastitis and find opportunities for further reduction (Kovačević et al., 2022b).

4. Financial losses

Economic losses due to mastitis can be defined as a reduction of output due to this disease and an absence of benefits that would otherwise be accrued in the absence of mastitis. Costs are classified into direct costs (veterinary services, additional labor requirements, and discarded milk during treatment) and indirect costs (reduced milk yield and quality premiums, premature culling) (Azooz *et al.*, 2020; Kovačević et al., 2022a).

In their study, Azooz *et al.* (2020) determined the financial impact of mastitis in Egypt. Several criteria were included in this study. Milk yield losses per year associated with subclinical mastitis were 20,563, 656.4822 LE; lower costs were calculated when clinical mastitis cases presented (326,814 LE). Quality premium losses ascended to 1369, 602.12 LE, and the other two most important costs were associated with premature culling (736,000 LE) and discarded milk (100.172 LE). In Ethiopia the average failure cost associated with mastitis was 4765 Ethiopian Birr (ETB) or $213.94 per farm per year, while per lactating cow per farm per year costs were 1961 ETB ($88.04); (Mekonnen *et al.*, 2019).

In Thai dairy farms affected with mastitis, an average of $557 for three months was calculated; 10.4% of losses were caused by the reduction in raw milk price, and the remaining 89.6% was attributed to discharged milk due to clinical mastitis testing positive (Dejyong *et al.*, 2022). India estimated a cost of INR1390 per lactation, from which half of the costs were associated with the loss of milk. Furthermore, veterinary expenses represented 37% of the total costs, and higher losses are associated with crossbred cows (Sinha *et al.*, 2014). In China, the economic impact across large dairy farms from seven provinces ranged from $15,000 to $76,000 farm/month (He *et al.*, 2020).

Through a deterministic partial budget model, the direct and indirect costs of mastitis in the US were calculated. The obtained data showed that during the first 30 days of lactation, the total economic cost was $444. Direct costs included diagnostics ($10), therapeutics ($36), non-saleable milk ($25), veterinary service ($4), labor ($21), and death loss ($32), totaling $128.00. For indirect costs, premature culling and replacement were estimated at more than $180, milk production loss occupied second place with a loss of $125, and future reproductive loss was $9, totaling of $316 (Rollin *et al.*, 2015). Recently, using a Monte Carlo simulation model, costs associated with chronic mastitis were estimated, obtained data showed an average of € 118. In addition, the costs of mastitis per generic intramammary infections case were estimated at € 230 (Bonestroo *et al.*, 2023).

In Canada, mastitis costs represent reductions from $386 to $779 (Puerto *et al.*, 2021). A study performed in an important dairy region of Colombia determined that the impact due to milk losses was over $800.000 per year and $70.3 per cow per year. According to the authors, the impact was greater in small- and medium-sized farms than in large farms, because large farms are more homogeneous in their management of subclinical mastitis (Romero *et al.*, 2018).

A pharmacoeconomic analysis was conducted to determine the cost and effectiveness of conventional bovine mastitis in Serbia, determining a total of € 80.32 (Kovačević et al., 2022a). In Dutch farms the average total cost of mastitis was €240/ lactating cow per year; failure costs (€120) was attributed mainly to milk production losses (€32), discarded milk (€20), and culling (€20), while in preventive costs (€120/ lactating cow per year), labor costs were the main contributor (€82), followed by consumables and investments, €34 and €4, respectively(van Soest *et al.*, 2016).

The study conducted by Hadrich *et al.* (2018), estimated financial losses in 10 months. Daily losses in the first month were $1.20/cow per day, in the 10th month losses increased to $2.06/cow per day. Another study estimated losses associated with pregnancy; the results showed that during the first 75 days when clinical mastitis cases were present, the impact was $148.99 per case (Dahl *et al.*, 2018).

In terms of milk loss production, *S. aureus* infections represent losses

Table 1

Prevalence of bacterial contagious and environmental pathogens associated with bovine mastitis.

Continent	Country	*S. agalactiae*	*S. aureus*	*M. bovis*	*E. coli*	*K. pneumoniae*	*S. uberis*	References
Africa	Cameroon	–	–	–	7.0	2.4	–	(Abegewi *et al.*, 2022)
	Egypt	–	–	–	–	13.59	20.59	(Abd El-Aziz *et al.*, 2021; Tartor *et al.*, 2021)
	Ethiopia	10.3	46.5–72.3	–	6.18–13.31	1.6	–	(Abebe *et al.*, 2016; Seyoum *et al.*, 2018; Tesfaye & Abera, 2018; Lakew *et al.*, 2019; Belay *et al.*, 2022)
	Tunisia	–	–	–	–	20.0	–	(Saidani *et al.*, 2018)
	Zimbabwe	–	16.3	–	–	–	–	(Katsande *et al.*, 2013)
Asia	Bangladesh	–	74.0	–	35.8	–	–	(Hoque *et al.*, 2018; Bag *et al.*, 2021)
	China	–	–	–	11.1	3.0–51.0	74.40	(Bi *et al.*, 2016; Gao *et al.*, 2019; Yu *et al.*, 2020; Cheng *et al.*, 2021; Yang *et al.*, 2021; Zeng *et al.*, 2022)
	Iran	–	20.4	–	–	–	–	(Jamali *et al.*, 2014)
	Japan	–	–	3.8	–	12.30	–	(Murai & Higuchi, 2019; Taniguchi *et al.*, 2021)
	Pakistan	17.54	21.5		17.54–19.40	–	–	(Sadaf *et al.*, 2016; Ali *et al.*, 2021)
America	Canada	0.1	9.9	–	9.0	1.9	0.6	(Levison *et al.*, 2016)
	Argentina	4.4–5.5	21.3–28.1	–	2.1		0.4–31.8	(Dieser *et al.*, 2014; Neder et al., 2015; Srednik *et al.*, 2018)
	Brazil	–	–	3.0	6.9	–	71.0	(Junqueira *et al.*, 2020; Martins *et al.*, 2021; de Oliveira *et al.*, 2022)
	Mexico	–	–	–	7.5–9.0	5.0	–	(León-Galván *et al.*, 2015; Olivares-Pérez *et al.*, 2015)
Europe	Serbia	–	4.57–6.09	–	12.12–26.82	1.51	1.51–6.06	(Kovačević et al., 2022a)
Oceanica	Australia	–	–	6.2–76.0	–	–	16.0–39.2	(Al-Farha *et al.*, 2017; Hazelton *et al.*, 2020; Chung *et al.*, 2021; Dyson *et al.*, 2022)

Table 2
Virulence characteristics and resistance profiles of bacterial contagious and environmental pathogens associated with bovine mastitis.

Agent	Virulence characteristics	Antimicrobial resistance profile	Antimicrobial resistance genes	References
S. agalactiae	Biofilm formation, *Cps, cylE*, CAMP, cfa/cfb, hylB, cylE, iagA, bac, fb, fbsA, fbsB, PI-2a, PI-2b, PI-1, pau-A, *α enolase*, hyaluronate lyase	Amoxicillin Ceftazidime Ceftriaxone Penicillin Piperacillin	mprF, mreA, *TEM*	(Carvalho-Castro *et al.*, 2017; Miranda *et al.*, 2018; Abd El-Aziz *et al.*, 2021; Han *et al.*, 2022; Parasana *et al.*, 2022; Vidal-Amaral *et al.*, 2022)
S. aureus	Biofilm formation, capsules, Panton-Valentine leucocidin, Toxic shock syndrome toxin-1, Immune evasion cluster genes, type E, slime production	Amoxicillin Cefoxitin Ciprofloxacin Clindamycin Erythromycin Gentamicin Oxacillin Oxytetracycline Penicillin Sulfamethoxazole Tetracycline Trimethoprim Vancomycin	blaZ, tetM, tetK, tetL, mecA, mecC, spa fragment, icaA, icaD	(Jamali *et al.*, 2014; Bhattacharyya *et al.*, 2016; Hoque *et al.*, 2018; Seyoum *et al.*, 2018; Srednik *et al.*, 2018; Wang *et al.*, 2018; Zaatout *et al.*, 2020; Chen *et al.*, 2021; Cvetnić et al., 2021; Saidi *et al.*, 2021; Crespi *et al.*, 2022)
M. bovis	Adhesines, avoidance of phagocytosis, biofilm formation, hydrogen peroxide production	Kanamycin Oxytetracycline Tilmicosin Tylosin Florfenicol Tiamulin Enrofloxacin	–	(Kawai *et al.*, 2014; Bokma *et al.*, 2020; García-Galán *et al.*, 2020; Gelgie *et al.*, 2022)
E. coli	LpfA, Iss, astA, f17A, irp2, iucD, colV, papC	Amikacyn Ampicillin Carbenicillin Cefoxitin Ceftriaxone Cephalothin Chloramphenicol Ciprofloxacin Doxycycline Erythromycin Gentamicin Lincomycin Nitrofurantoin Oxacillin Oxytetracycline Penicillin Streptomycin Sulfamethoxazole Tetracycline Vancomycin	tetM, tetL, tetA, blaZ, blaEc, ampC, aadA, sul2, strA, strB, sul1, sul3, $bla_{CTX-M-1,}$ $bla_{CTX-M-9}$, $bla_{CTX-M-28}$, $bla_{CTX-M-14}$	(Blum & Leitner, 2013; Liu *et al.*, 2014; Olivares-Pérez *et al.*, 2015; Fazel *et al.*, 2019; Nüesch-Inderbinen *et al.*, 2019; Alawneh *et al.*, 2020; Ali *et al.*, 2021; Bag *et al.*, 2021; Bhandari *et al.*, 2021; Shafiq *et al.*, 2021; Campos *et al.*, 2022; de Oliveira *et al.*, 2022)
K. pneumoniae	EntB, FimH, Kfu, MrkD, β-D-lacZ, ituA, allS	Amoxicillin Ampicillin Cefazolin Cefotaxime Cefoxitin Cefquinome Ceftazidime Ceftriaxone Cephalothin Chloramphenicol Colistin Enrofloxacin Fosfomycin Gentamicin Kanamycin Neomycin Piperacillin-tazobactam Streptomycin Spectinomycin Sulfisoxazole Sulfonamides Tetracycline Tigecycline Trimethoprim Tylosin	TetA, TetB, OqxAB, qnrB1, sul1, sul2, strA, strB, aadA, blaCTX-M-15, AmpH, blaSHV-12, blaTEM, fosA, fosA5, fosA6, mcr-10, dfrA14	(Timofte et al., 2014; Koovapra *et al.*, 2016; Saidani *et al.*, 2018; Massé *et al.*, 2020; Cheng *et al.*, 2021; Tartor *et al.*, 2021; Yang *et al.*, 2021; Abegewi *et al.*, 2022; Bonardi *et al.*, 2023)
S. uberis	Biofilm production, gapC, oppF, pauA (skc), sua, hasC, mtuA	Amikacin Amoxicillin Ceftazidime Ceftriaxone Cephalothin	LinB, ErmB, tetS	(Chung *et al.*, 2021; Kabelitz *et al.*, 2021; Monistero *et al.*, 2021; Han *et al.*, 2022; Zeng *et al.*, 2022)

(*continued on next page*)

Table 2 (*continued*)

Agent	Virulence characteristics	Antimicrobial resistance profile	Antimicrobial resistance genes	References
		Enrofloxacin Erythromycin Gentamicin Lincomycin Penicillin Piperacillin Rifampin Spectinomycin Streptomycin Tetracycline		

of up to 2.30 kg/day. In the case of non-*aureus* staphylococci, losses range from 1.0 to 1.8 kg/day. Regarding, Gram negatives the most harmful pathogen was *E. coli* (3.5 kg/day), followed by *Corynebacterium bovis* (2.4 kg/day), *S. uberis* (2.1 kg/day), and *S. dysgalactiae* (2.0 kg/day; Heikkilä *et al.*, 2018). Information reported by Hogeveen and Van Der Voort (2017) indicated the costs of clinical mastitis due to *Klebsiella* spp.: $477; *E. coli*: $361; *Staphylococcus aureus*: $266; *Streptococcus* spp.: $174; and *Staphylococcus* spp.: $135. Likewise, *Mycoplasma* had on-farm economic consequences like common conventional mastitis pathogens (Al-Farha *et al.*, 2017). In accordance with the afore mentioned, Fu *et* al. (2022) stated that mastitis caused by Gram-negative pathogens is more expensive ($211.03) than Gram-positive bacterial cases ($133.73). Some authors have stated that economic losses due to clinical, subclinical and even chronic mastitis may vary among countries, factors such as prices, and veterinary services cost also influx (Heikkilä, Liski et al., 2018).

5. New approaches for the development of bovine mastitis treatments

As shown in table 2, conventional treatments based on chemical antimicrobials have lost their effectiveness. Thus, many recent research studies have proposed alternatives to antibiotic therapy that are not invasive and do not cause resistance. In the same sense, other authors have stated that protocols should be accurate, easy to perform, cost-effective, sabe, certifiable, and applicable in different areas of a country (Maćešić *et al.*, 2022). Authors such as Tomanić et al. (2023b), consider that novel and effective agents have potential to reduce the use of antibiotics, increasing productivity and environmental protection. In the following sections, some of the treatment alternatives for bovine mastitis will be addressed.

5.1. Medicinal plants

5.1.1. Vegetal extracts

The antibacterial activity of vegetal or plant extracts has been widely reported due to interest increasing in recent years, plants and their bioactive compounds have antibacterial effects, contributing to the treatment of mastitis (Šukele *et al.*, 2022).

The antibacterial activity of different extracts of *Quercus robur* bark and *Calluna vulgaris* herb was determined against common mastitis pathogens, S. *aureus, E. coli, S. agalactiae, S. uberis*, and *S. liquefaciens*. The *Q. robur* broadest spectrum was detected from 3.08 to 24.68 mg/mL, while *C. vulgaris* were effective from1.14 to 73.06 mg/mL; activity was attributed to the content of total phenolic compounds (*Q. robur*= 4374 mg/100 g GAE; *C. vulgaris*= 2755 mg/100 g GAE; Šukele *et al.*, 2022).

MIC (minimal inhibition concentration) values of ranging from 3.9 to 31.2 μg/mL and MBC (minimal bactericidal concentration) values ranging from 15.6 to 500 μg/mL were determined for *Ocimum tenuiflorum,* Ricinus *communis* inhibited bacterial growth at concentrations from 3.12 to 200 mg/mL and killed bacteria in a range of concentrations from 25 to 200 mg/mL against some major mastitis pathogens (Kebede & Shibeshi, 2022; Srichok *et al.*, 2022).

Prapaiwong *et al.* (2021) determined that the hydrolysable tannin extract showed inhibitory activity at concentrations from 27.3 −190 mg/mL and bactericidal activity at range of concentrations from 58.8 −235 mg/mL. Moreover, antibacterial activity was comparable to penicillin and gentamicin at concentrations over 630 mg/mL. The sorghum phenolic extract at a concentration of 4000 μg/mL inhibited *S. aureus* (7.7 mm), *K. pneumoniae* (0.8 mm) and *E. faecalis* (6.5 mm). No activity was detected against *E. coli* (Schnur *et al.*, 2021).

Ethyl acetate extract of fruits from *Terminalia chebula* (100, 500, and 100 μg/mL) was evaluated against *S. aureus, B. megaterium, E. coli* and *P. aeruginosa*, 1000 μg/mL generated growth inhibition zones from 32.06 to 39.02 mm (Kher *et al.*, 2019). *Knema retusa* wood extract had inhibitory activity and bactericidal effects against the Staphylococcal isolates ranging from 32 - 256 μg/mL and 64 - 512 μg/mL, respectively. Biofilm inhibition of *S. aureus* and *S. haemolyticus* was also determined; its major compound was identified as endo-2-hydroxy-9,9-(ethylenedioxy)−1-carbethoxy bicyclononane (Chuprom *et al.*, 2022).

Antibiofilm activity of the hydroalcoholic extracts of *Eucalyptus globulus*, alone and in combination with *Juglans regia*, against *S. aureus* isolates from bovine mastitis was tested, MIC values of *E. globulus* ranged from 0.19 to 0.39 mg/mL and from 0.78 to 1.56 mg/mL for *J. regia*. Extracts mixtures were more effective than singly used (Gomes et al., 2019a). MIC values from 500 to 3000 μg/mL were reported for the methanolic extract of underground parts of *Aquilegia fragrans* and its five pure compounds (2, 4-dihydroxyphenylacetic acid methyl ester, β-sitosterol, Aquilegiolide, Glochidionolactone-A, and Magnoflorine) against major pathogens associated with mastitis (Mushtaq et al., 2016a).

Rhodomyrtus tomentosa leaves extract was evaluated against multidrug-resistant *S. aureus* strains. MIC and MBC values ranged from 16−64 μg/mL and 64−128 μg/mL, respectively (Mordmuang and Voravuthikunchai, 2015b; Mordmuang *et al.*, 2019). *Clinacanthus nutans* can be considered an alternative treatment for bovine mastitis since it exhibits both antibacterial and anti-apoptosis activities (Panya *et al.*, 2020). *Mentha pulegium, Nepeta cataria, Melissa officinalis, Agastache foeniculum, Lavandula angustifolia, Origanum vulgare, Althaea officinalis, Plantago lanceolata, Artemisia absinthium, Populus nigra* and *Evernia prunastri* were evaluated on 14 Gram negative and 18 Gram positive bacterial strains, isolated from bovine mastitis cases. MIC values varied between 0.09 and 12.5 mg/mL, with bactericidal concentrations from 0.39 to 50 mg/mL. Better results were recorded for *Evernia prunastri, Artemisia absinthium* and *Lavandula angustifolia* (Pașca *et al.*, 2017).

Aquatic plants, such as salvinia auriculata has been shown to possess promising properties for the treatment of Staphylococcus aureus bovine mastitis. The hexane extracts of roots inhibited *S. aureus* at concentrations from 0.04 to 2.50 mg/mL. Moreover, these extracts inhibited the biofilm formation of three strains, the antibacterial activity was attributed to the presence of stigmast-22-ene-3,6-dione, β-sitosterol and octadecanoic acid. Inhibitory activity was detected at concentrations from 0.01 to 0.50 mg/mL. In addition, cytotoxicity was determined. According to the obtained data, the extract was considered as safe. Herbal antiseptic, an ex-vivo assay, demonstrated that the extract caused a log reduction of approximately 4.0, similar to some commercial antimicrobials (Purgato *et al.*, 2021).

A bio-guided study reported the antibacterial activity of the hydroalcoholic extract, aqueous and ethyl acetate fractions from L. *tridentata*. Among these treatments, ethyl acetate showed better activity since MIC and MBC, from 0.04 to 3.12 mg/mL and 0.09 and 6.25 mg/mL, respectively, had lower values than those obtained with the other treatments. Antibacterial activity was associated with the presence of lignan *nor* 3′demethoxiisoguaiacin Morales-Ubaldo et al. (2022).

The compounds Manool, *ent*-kaurenoic acid, and *ent*-copalic acid, from *Salvia officinalis* leaves exhibited inhibitory effects (MIC= 1.56 to >400 μg/mL) on *S. aureus, E. coli, S. epidermidis, S. agalactiae* and *S. dysgalactiae*. Being the most active *ent*-copalic acid, this compound was not cytotoxic at concentrations up to 62.5 μM (Fonseca *et al.*, 2013). In a similar study *nor* 3′ demethoxyisoguaiacin from L. *tridentata* inhibited bacterial growth in a range of concentrations from 10 to 780 μg/mL. Moreover, bactericidal effects were determined at concentrations from 20 μg/mL to 3.12 mg/mL against a wide range of mastitis bacteria; most promissory results were determined against *S. aureus* (Morales-Ubaldo *et al.*, 2022). Three alkaloids were isolated from the roots of *Thalictrum minus*, compounds identified as 5′-Hydroxythalidasine, thalrugosaminine, and O-Methylthalicberine inhibited the growth of common mastitis pathogens such as *S. aureus, K. pneumoniae, E. coli*, and other less common agents (*S. xylosus, S. lentus, S. equorum, E. faecalis* and *P. agglomerans*; MIC= 64- 500 μg/mL; Mushtaq et al., 2016b).

The combination of *Angelica dahurica* and *Rheum officinale* was an effective antibacterial treatment in a bovine model; effectiveness was attributed to the presence of emodin, rhein, and polysaccharides (Yang *et al.*, 2019). Similarly, tea saponin, a mixture of saponin from the seeds, leaves, or roots of the tea tree, was reported as an antibacterial against *S. agalactiae*. Furthermore, the proposed treatment inhibited biofilm formation, bacteria exhibited looser structure and lower density, possible mechanism of action propose that tea saponin down-regulate the transcription of genes *srtA, fbsC, neuA*, and *cpsE* associated with biofilm (Shang *et al.*, 2020). 7-epiclusianone, extracted from the *Rheedia brasiliensis* fruit, in combination with copper, named as 7-epiclusianone-copper complex was active against *S. agalactiae* and *S. uberis*; MIC= 7.8 μg/mL and MBC= 31.3 μg/mL. Furthermore, no cytotoxicity was observed in bovine mammary alveolar cells (de Barros *et al.*, 2017). The antibacterial activities of vegetal extracts and their related bioactive compounds are summarized in Table 3.

5.1.2. *Essential oils*

Essential oils from the medicinal aromatic plants, *Mentha pulegium, Nepeta cataria* and *Melissa officinalis* were tested over two major pathogens associated with mastitis. Volumes of 30 μL and 20 μL generated inhibition zones of 23 mm and 19 mm, respectively, against S. *aureus*. Lower activity was determined for *E. coli* since halos of 5.0 - 7.0 mm were generated (10 μlL; Arbab *et al.*, 2022).

The antibacterial effect of *Thymus vulgaris, Thymus serpyllum* and *Origanum vulgare* was reported in, the inhibitory and bactericidal effects on *Proteus mirabilis* and *Serratia marcescens* (MIC= 1.56 −3.12 mg/mL; MBC= 3.12 - 6.25 mg/mL). Thymol and carvacrol were the predominant compounds contained in the three essential oils (Tomanić *et al.*, 2022). Similarly, *Thymus vulgaris* and *Thymus serpyllum* showed both inhibitory and bactericidal effects on 11 different bacteria associated with mastitis; MIC values ranged from 0.39 mg/mL to 6.25 mg/mL and MBC values from 0.78 mg/mL to 12.50 mg/mL. The main bioactive compounds were thymol, *p*-cymene and γ -terpinene (Kovačević et al., 2021b).

In another study, *Origanum vulgare* and *Satureja montana* essential oils were evaluated on bacteria from clinical or subclinical mastitis cases. The obtained data showed that inhibitory activity presented at concentrations from 0.39 to 6.25 and bactericidal effects at concentrations from 0.78 to > 12.50 mg/mL, *p*-cymene thymol, carvacrol γ-terpinene, α-thujene, *trans*-β-caryophyllene and β-bisabolene were the main compounds (Kovačević et al., 2021a).

Table 3
Antibacterial activities of vegetal extracts and their related bioactive compounds against pathogens associated with bovine mastitis.

Plant-extract	Mechanisms of action	Associated compounds	Reference
Quercus robur, Calluna vulgaris, ethanolic and acetonic	Antimicrobial activity on S. *aureus, E. coli, S. agalactiae, S. uberis, S. liquefaciens*	Phenolic compounds	(Šukele *et al.*, 2022)
Ocimum tenuiflorum, Ricinus communis	Bacteriostatic and bactericidal effects	–	(Kebede & Shibeshi, 2022; Srichok *et al.*, 2022)
Hydrolysable tannin extract	Bacteriostatic and bactericidal effects	Tannins	(Prapaiwong *et al.*, 2021)
Sorghum phenolic extract	Growth inhibitory effects	Phenolics	(Schnur *et al.*, 2021)
Terminalia chebula, ethyl acetate	Growth inhibitory effects	–	(Kher *et al.*, 2019)
Knema retusa wood extract	Inhibitory and bactericidal effects, biofilm inhibition on Staphylococcal isolates	endo-2-hydroxy-9,9 (ethylenedioxy)−1-carbethoxy bicyclononane	(Chuprom *et al.*, 2022)
Eucalyptus globulus, Juglans regia, hydroalcoholic extracts	Antibiofilm activity on *S. aureus*	–	(Gomes et al., 2019a)
Aquilegia fragrans underground parts, methanolic	Inhibitory effects on major pathogens of mastitis and on *Staphylococcus xylosus, Staphylococcus equorum, Enterococcus faecalis and Pantoae*	2, 4-dihydroxyphenylacetic acid methyl ester, β-sitosterol, Aquilegiolide, Glochidionolactone-A and Magnoflorine	(Mushtaq et al., 2016b)
Rhodomyrtus tomentosa leaves extract	Inhibitory and bactericidal effects on multidrug-resistant *S. aureus*	–	(Mordmuang et al., 2015a; Mordmuang *et al.*, 2019)
Clinacanthus nutans	Antibacterial and anti-apoptosis activities	–	(Panya *et al.*, 2020)
salvinia auriculata, hexane	Antibacterial activity on *S. aureus*, biofilm inhibition formation	stigmast-22-ene-3,6-dione, β-sitosterol and octadecanoic acid	(Purgato *et al.*, 2021)
Larrea tridentata, ethyl acetate fraction	Bactericidal activity on pathogens associated with mastitis	*nor* 3′demethoxiisoguaiacin	(Morales-Ubaldo *et al.*, 2022)
Salvia officinalis	Inhibitory effects on *S. aureus, E. coli, S. epidermidis, S. agalactiae* and *S. dysgalactiae*	Manool, *ent*-kaurenoic acid, and *ent*-copalic acid	(Fonseca *et al.*, 2013)
Thalictrum minus	Growth inhibition of inhibited growth of *S. aureus, K. pneumoniae, E. coli*, and other less common agents	Alkaloids5′-Hydroxythalidasine, thalrugosaminine and O-Methylthalicberine	(Mushtaq et al., 2016b)
Angelica dahurica, Rheum officinale	*In vivo* antibacterial activity	emodin, rhein and polysaccharides	(Yang *et al.*, 2019)
Tea tree	Inhibtion of biofilm formation, down-regulation of genes *srtA, fbsC, neuA*, and *cpsE*	Saponins	(Shang *et al.*, 2020)
Rheedia brasiliensis	Antibacterial activity on *S. agalactiae* and *S. uberis*	7-epiclusianone	(de Barros *et al.*, 2017)

Minthostachys verticillata essential oil and limonene exerted inhibitory effects on *S. uberis* from 14.3 mg/mL to 114.5 mg/mL and bactericidal effects at 114.5 mg/mL and 229 mg/mL. Concerning limonene, lower concentrations were determined; MIC 3.3 mg/mL to 52.5 mg/mL and MBC = 210 mg/Ml. Both compounds affected biofilm formation (Montironi *et al.*, 2016). Tea tree essential oil (*Melaleuca alternifolia*) and thymol and carvacrol extracts alone and in combination were evaluated against bacteria isolated from clinical mastitis cases. Tea tree oil + thymol and thymol + carvacrol combinations were the most effective treatments since additive effects were determined (Corona-Gómez *et al.*, 2022).

Recent studies determined that thymol, carvacrol, and trans-cinnamaldehyde highly inhibited bacterial growth at concentrations of 0.38 - 1.32 mg/mL. Carvacrol and octanoic acid, in combination, exhibited better inhibitory effects. Changes in cell morphology, leakage of electrolytes, and macromolecules were observed within 1–2 h after treatment (Rani et al., 2022a). The important activities of some of the aforementioned treatments were determined in multi-drug resistant bacteria associated with mastitis (Rani et al., 2022b).

The effect of *Syzygium aromaticum* and *Cinnamomum zeylanicum* and their major components, eugenol and cinnamaldehyde, were evaluated on *S. aureus* biofilm formation. The MIC value of *S. aromaticum* was 0.237 mg/mL, while its main compound eugenol, was active at a higher concentration (0.392 mg/mL), in contrast to that determined for *C. zeylanicum* since the MIC value was higher (0.243 mg/ mL) compared with cinnamaldehyde (0.199 mg/mL). *S. aromaticum* was considered the most effective treatment for the inhibition of biofilm formation (Budri *et al.*, 2015). Table 4 contains details of the antibacterial activities of essential oils.

5.1.3. Combination of plant treatments and antimicrobials

E. globulus and penicillin G in combination, demonstrated synergy against *S. aureus* strains isolated from bovine mastitis (Gomes et al., 2019b), *Ocimum tenuiflorum* exhibited synergistic activity with penicillin G and amoxicillin against *S. aureus*, coagulase-negative Staphylococci, *S. agalactiae*, and *E. coli*, and additive effects when the extract was combined with cefazolin and gentamicin Srichok et al. (2022). *Plectranthus ornatus* extract exhibited a synergistic effect with ampicillin, kanamycin, and gentamicin, reducing eight-fold in the MIC value. Similar results were determined for *Salvia officinalis* and *Senna macranthera*, activity was determined on *S. aureus* (Silva *et al.*, 2019). The efficacy of *Melaleuca armillaris* as an adjuvant of erythromycin was reported, and the obtained data showed a synergistic effect on *S. aureus*; this combination was considered bactericidal (Buldain *et al.*, 2022).

The two active compounds of guttiferone-A and 7-epiclusianone, from the fruits of *Garcinia brasiliensis*, important potentiation was observed when 7-epiclusianone was combined with ampicillin. The MIC values of ampicillin alone were 31.25 μg/mL and 125.0 μg/mL against *S. agalactiae* and *S. uberis*. When an active compound was added, MIC values decreased between 15.63 μg/mL and 62.50 μg/mL. Similar effects were observed for the combination 7-epiclusianone- gentamicin. Regarding guttiferone-A, this compound exhibited better effects on both bacteria in combination with gentamicin Maia et al. (2018). Table 5 summarizes the main results of the combination of plant treatments and antimicrobials.

5.1.4. Plant based-products

A soap with added *Salvina auriculata* extract inhibited the total growth of *S. aureus*. The bioactive compounds were identified as stigmasterone, stigmasterol, and friedelinol (Lima *et al.*, 2013). *S. aureus* was highly inhibited by a suspension of herbal soap (1%), with added *Senna mactanthera* extract. The active compounds were the anthraquinone compounds emodine, physione, and chrysophanol (Inoue-Andrade *et al.*, 2015).

Two herbal gels based on: aqueous extract of propolis, alcoholic extracts of brewers gold and Perle hops, plum lichen, common mallow, marigold, absinthe wormwood, black poplar buds, lemon balm, and essential oils of oregano, lavender, and rosemary, were administrated intramammary in a 10 mL volume to 20 cows diagnosed with clinical

Table 5
Combination of plant treatments and antimicrobials against pathogens associated with bovine mastitis.

Combination	Mechanisms of action	Reference
E. globulus + penicillin G	Synergistic effect against *S. aureus* strains	(Gomes et al., 2019b)
Ocimum tenuiflorum + Penicillin G *Ocimum tenuiflorum* + amoxicillin *Ocimum tenuiflorum*+ cefazolin *Ocimum tenuiflorum*+ gentamicin	Synergistic and additive effects against *S. aureus*, coagulase-negative Staphylococci, *S. agalactiae*, and *E. coli*	(Srichok *et al.*, 2022)
Plectranthus ornatus+ Ampicillin *Plectranthus ornatus*+Kanamycin *Plectranthus ornatus*+ gentamicin	Synergistic effects on important pathogens of bovine mastitis	(Silva *et al.*, 2019)
Melaleuca armillaris + erythromycin	Bactericidal effects on *S. aureus*	(Buldain *et al.*, 2022)
Guttiferone-*A* + gentamicin 7-epiclusianone + ampicillin 7-epiclusianone + gentamicin	Synergistic effects on *S. agalactiae* and *S. uberis*	(Maia *et al.*, 2018)

Table 4
Antibacterial activities of essential oils and its related bioactive compounds against pathogens associated with bovine mastitis.

Essential oil origin	Mechanisms of action	Bioactive compounds	Reference
Mentha pulegium, Nepeta cataria and *Melissa officinalis*	Antimicrobial activity on *S. aureus* and *E. coli*	–	(Arbab *et al.*, 2022)
Thymus vulgaris, Thymus serpyllum and *Origanum vulgare*	inhibitory and bactericidal effects on *Proteus mirabilis* and *Serratia marcescens*	Thymol and Carvacrol	(Tomanić *et al.*, 2022)
Thymus vulgaris, Thymus serpyllum, Origanum vulgare and *Satureja montana*	Inhibitory and bactericidal effects	Thymol, *p*-cymene and γ -terpinene, carvacrol γ-terpinene, α-thujene, *trans*-β-caryophyllene and β-bisabolene	(Kovačević et al., 2021a; Kovačević et al., 2021b)
Minthostachys verticillate and limonene	Inhibitory and bactericidal effects on *S. uberis*, inhibition of biofilm formation	–	(Montironi *et al.*, 2016)
Melaleuca alternifolia and thymol	Antimicrobial activity on bacterial strains from clinical mastitis cases	–	(Corona-Gómez *et al.*, 2022)
Carvacrol, trans-cinnamaldehyde	Inhibitory effects, changes in cell morphology, leakage of electrolytes and macromolecules	–	(Rani et al., 2022a)
Syzygium aromaticum and *Cinnamomum zeylanicum*	Inhibition of *S. aureus* biofilm formation	Eugenol and cinnamaldehyde	(Budri *et al.*, 2015)

and subclinical mastitis. The results showed a decreasing number of bacteria (*S. epidermidis, S. aureus, S. schleiferi, S. hominis, Micrococcus* spp.*, streptococcus* spp.*, Aerococcus* spp.*, Bacillus* spp.*,and Corynebacterium* spp.) and somatic cells after treatment (Pașca *et al.*, 2020).

In a similar study, a homeopathic preparation containing natural compunds was administered intramammary, and the obtained data showed a 75% cure rate of clinical mastisis. Moreover, on Day 7 of treatment, healing rates were 51.85% for subclinical mastitis, increasing to 59.29% on Day 14 (Mimoune *et al.*, 2021).

A pharmaceutical formulation (Phyto-Bomat) composed of essential oils (*Thymus vulgaris, Thymus serpyllum Origanum vulgare, Satureja montana*) in combination with oil macerates *(Calendula officinalis, Hypericum perforatum)* was effective on diverse pathogens associated with bovine mastitis. The results indicated that MIC values ranged from 22.72 mg/mL to 45.40 mg/mL, and MBC values from 45.40 mg/mL to 90.09 mg/mL, with thymol and carvacrol being the main constituents (Kovačević et al., 2022c). The antibacterial activity of this product was confirmed in a very recent study, since the resolution of symptoms post-treatment and prevention of clinical mastitis development in cases with subclinical mastitis were determined (Tomanić et al., 2023a). Table 6 contains information about natural compounds-based products.

5.2. Nanotechnology

S. aureus and *S. epidermidis* were sensitive to silver nanoparticles added with *R. tomentosa* ethanolic extract and the liposomal encapsulated rhodomyrtone (MIC= 2–8 μg/mL and MBC= 8–32 μg/mL). Moreover, treatments decreased the adhesion of the bacterial cells to the mammary gland tissues (Mordmuang et al., 2015a). Silver-nanoparticle-decorated quercetin nanoparticles exhibited important antibacterial and antibiofilm activities over a multi-drug resistant strain of *E. coli* isolated from a mastitis case (Yu *et al.*, 2018). Gold nanoparticles added with *Dodonaea angustifolia* extract and honey exhibited both, inhibitory and bactericidal effects over methicillin-resistant and vancomycin-resistant *S. aureus* strains (Omara, 2017).

Zinc-oxide nanoparticles were effective on some major pathogens associated with bovine mastitis; MIC values ranged from 1.0 mg/mL to 20.0 mg/mL, while bactericidal effects were determined at concentrations from 1.0 mg/mL to 30.0 mg/mL (Hozyen *et al.*, 2019). Chitosan -nanoparticles exerted bacteriostatic and bactericidal effects on *S. xylosus* and *S. aureus* at concentrations from 800 μg/mL to 1600 μg/mL; the inhibition of biofilm formation was also determined (Orellano *et al.*, 2021). The efficacy of graphene oxide was determined, was tested against *S. aureus,* at 100 μg/mL; *S. aureus* biofilm mass was reduced by up to 70%, and at 200 μg/mL, graphene oxide treatment killed 80% of bacteria (Saeed *et al.*, 2023).

Using polyherbal nanocolloids formulated with five different extracts (*Syzygium aromaticum, Cinnamomum verum, Emblica officinalis, Terminalia belerica, Terminalia chebula*, and *Cymbopogon citratus*) showed bacteriostatic, bactericidal, and antibiofilm activity effects on *Acinetobacter junii, Klebsiella pneumoniae, Pseudomonas stutzeri*, and *Acinetobacter baumannii*. Interestingly polyherbal nanocolloid reduced bacterial virulence factors of different bacterial strains (Ranjani *et al.*, 2022).

Table 6
Antibacterial activity of plant based-products against pathogens associated with bovine mastitis.

Product	Mechanisms of action	Bioactive compounds	Reference
Salvinia auriculata soap	Inhibition of *S. aureus* growth	Stigmasterone, stigmasterol, friedelinol	(Lima *et al.*, 2013)
Senna mactanthera soap	Inhibition of *S. aureus* growth	Emodine, physione, and chrysophano	(Inoue Andrade *et al.*, 2015)
Herbal gels	Antimicrobial activity on diverse pathogens	–	(Pașca *et al.*, 2020)
Phyto-Bomat	Bacteriostatic and bactericidal effects on pathogens associated with mastitis	Thymol and carvacrol	(Kovačević et al., 2022c; Tomanić et al., 2023a)

An intramammary nanosuspension based on α-linolenic acid exhibited benefic effects on cows with subclinical mastitis, after treatment the milk color changed from pale yellow to white. Similarly, consistence turned from watery to thick and pH was normalized; on day 10, the parameters of the clinical mastitis test, Whiteside test, bromothymol blue test and bacterial cell count decreased. Moreover, anti-inflammatory and peripheral analgesic properties were determined (Yadav *et al.*, 2020). Table 7 shows some of the most relevant findings about the application of nanotechnology against bovine mastitis pathogens

5.3. Polymers

To provide alternatives for the treatment and prevention of cattle mastitis, Bhattari *et al.* (2021), evaluated *in vitro* 14 hydrophilic polymers and six solvents determining their cytotoxicity and biocompatibility on bovine mammary epithelial cells for their use as carriers for sustained drug delivery. The obtained data showed that polyethylene oxides, hydroxypropyl methylcellulose, carboxymethyl cellulose, sodium alginate and xanthan gum were safe, since no significant cytotoxicity was determined. On the other hand, polycarbophil, carbopol, glycerin, propylene glycol, polyethylene glycol 400, ethanol, N-methyl-2-pyrrolidone and 2-pyrrolidone showed higher cytotoxicity, some of them in a concentration-dependent way. Nevertheless, according to the authors, all formulations could form nontoxic gels with good biocompatibility.

Polymeric particles composed of alginate/chitosan and chitosan/sodium tripolyphosphate were used to encapsulate mercaptosuccinic acid. Treatments showed potential antibacterial activity on *S. aureus* and *E. coli* (MIC= 125 μg/mL to 250 μg/mL; Cardozo *et al.*, 2014). In another study, it was determined that chitosan at a specific molecular weight exhibited activity on *S. aureus*, molecules of 2.6 kDa inhibited biofilm formation, killed bacteria, and prevented the persistence of *S. aureus*. Moreover, these kinds of molecules showed synergy with macrolides (Asli *et al.*, 2017). Felipe *et al.* (2019) reported that chitosan (60–120 kDa) inhibited *S. aureus* and *S. xylosus* growth at concentrations from

Table 7
Application of nanotechnology against pathogens associated with bovine mastitis.

Alternative treatment	Mechanisms of action	Reference
Silver nanoparticles added with *R. tormentosa/* quercetin	Decreased adhesion of the bacterial cells to the mammary gland tissues, antibacterial and antibiofilm activities	(Mordmuang et al., 2015a; Yu *et al.*, 2018)
Gold nanoparticles added with *Dodonaea angustifolia* extract and Honey	Inhibitory and bactericidal effects over *S. Aureus*	(Omara, 2017)
Zinc oxide nanoparticles	Bacteriostatic and bactericidal effects	(Hozyen et al., 2019)
Chitosan nanoparticles	Bacteriostatic, bactericidal and antibiofilm effects on *S. xylosus* and *S. aureus*	(Orellano *et al.*, 2021)
Graphene oxide	Reduction of biofilm mass, bactericidal activity against *S. aureus*	(Saeed *et al.*, 2023)
polyherbal nanocolloids formulated with extracts	Bacteriostatic, bactericidal and antibiofilm activity, reduction of bacterial virulence factors	(Ranjani *et al.*, 2022)
Nanosuspension, α-linolenic acid	Exhibited benefic effects on cows with subclinical mastitis	(Yadav *et al.*, 2020)

100 μg/mL to 800 μg/mL, being *S. xylosus* the most sensitive bacterium, bactericidal effects were determined at concentrations of 200 μg/mL against *S. xylosus*, and concentrations of 1600 μg/mL were determined for *S. aureus*. In addition, in a range of concentrations from 100 μg/mL to 1600 μg/mL chitosan inhibited biofilm formation, reduced biofilm viability and disrupted the established biofilms.

The combination of polymers with conventional antimicrobials has been reported. A study evaluated the addition of chitosan to cloxacillin, demonstrating that this combination increased the efficacy of the antibiotic, reducing the required concentration (16 to 64 fold reduction). Moreover, the combination inhibited bacterial biofilm establishment and increased preformed biofilm eradication (Breser *et al.*, 2018). In another study the design of polymeric nanoparticles (poly-ε-caprolactone), which encapsulated cloxacillin benzathine, obtained data showed that in an *in vivo* assay, this treatment at a concentration of 600 mg eliminated 100% of *Corynebacterium* spp. and *S. uberis* (Araújo *et al.*, 2019).

A study stated that polyethylene oxide-based inserts could act as a physical barrier against pathogens invading the teat canal of cows and possibly control the release of drugs for mastitis treatments (Bhattarai *et al.*, 2015). Polyhexamethylene biguanide, an antimicrobial polymer, showed positive effects, killing 99.9% of intracellular *S. aureus* at 15 mg/L; at the same concentration the biofilḿs mass was reduced up to 37%. This study stated this compound was tolerated by host cells at high concentrations (Kamaruzzaman *et al.*, 2017). In a later study, this same compound was evaluated, confirming its efficacy on *S. aureus* (≥0.5 μg/mL). Polyhexamethylene biguanide nanoparticles showed higher effects with a MIC value of 0.03 μg/mL on said bacterium. Another study determined that this polymer is effective in treating of *Prototheca* spp., associated with mastitis, determining effects at lower concentrations (≥1.0 to ≥4.0 μg/mL; Fidelis *et al.*, 2023).

The emerging photodynamic therapy has achieved mastitis prevention and treatment benefits. A recent study reported the efficiency of chlorophyll-rich spinach extract and curcumin, both incorporated into a micellar copolymer (Pluronic® F127). *In vitro* assays showed that treatments had inhibitory and bactericidal effects on *S. aureus* and *E. coli*; the *in vivo assay* demonstrated that the application of formulations considerably decreased bacterial loads and maintained the milk quality (Junior *et al.*, 2023). These findings suggest that polymers have the potential to be used in the treatment and prevention of mastitis-causing pathogens (Table 8).

Table 8
Application of polymers against pathogens associated with bovine mastitis.

Alternative treatment	Mechanism of action	Reference
Hydrophilic polymers	formulations could form biocompatible nontoxic gels	(Bhattarai *et al.*, 2021)
Polymeric particles + mercaptosuccinic acid	Antibacterial activity on *S. aureus* and *E. coli*	(Cardozo *et al.*, 2014)
polyethylene oxide-based inserts	Physical barrier against pathogens of bovine mastitis	(Bhattarai *et al.*, 2015)
poly-ε-caprolacton + cloxacillin benzathine	Bactericidal effects on *Corynebacterium* spp. and *S. uberis*	(Araújo *et al.*, 2019)
Chitosan	Antibiofilm and bactericidal activity on *S. aureus* and *S. xylosus* synergistic effect with antimicrobials	(Asli *et al.*, 2017; Felipe *et al.*, 2019)
polyhexamethylene biguanide	Bactericidal and antibiofilm activity on S. *aureus* Antibacterial activity against *Prototheca* spp.	(Kamaruzzaman *et al.*, 2017; Fidelis *et al.*, 2023)
Pluronic® F127+ spinach extract and curcumin	inhibitory and bactericidal effects on *S. aureus* and *E. coli*	(Junior *et al.*, 2023)

5.4. Peptides

The effect of an *S. aureus* bacterin and nisin on bovine subclinical mastitis was evaluated in the study carried out by Guan *et al.* (2017). Treatment reduced intramammary infections reduced count of somatic cells and increased protein and fat contents. A nisin derivative demonstrated its potential to eradicate and inhibit biofilms of *S. uberis* strains (Pérez-Ibarreche *et al.*, 2021). A peptide named pm11, inhibited the growth of *S. aureus, S. uberis, S. agalactiae* and *E. coli*. MIC values ranged from 0.32 μM to 2.07 μM. Bactericidal effects were determined at concentrations from 2.5 μM to 10 μM. Furthermore, pm11 reduced viable cell counts within 1 to 4 h (Popitool *et al.*, 2022). Aureocin A53, a peptide produced by *S. aureus,* showed to be bactericidal against staphylococci and streptococci strains. The study determined that A53 was not toxic to bovine mammary gland epithelial cells after 24-h exposure. Moreover, the peptide maintained its antimicrobial activity (Marques-Bastos *et al.*, 2022).

The antimicrobial activity of peptide NZ2114 was reported, and the obtained data showed its efficacy against *S. dysgalactiae* strains (0.11–0.45 μM). This peptide was able to eradicate bacterial biofilm; the *in vivo* assays determined that NZ2114 alleviated mammary gland inflammation, inhibited bacterial proliferation, and reduced the number of mammary gland bacteria (Yang *et al.*, 2022). A similar study determined that the NZ2114 derivative peptide H18R (H2) inhibited *S. aureus* growth at concentrations from 0.5 μg/mL to 1.0 μg/mL (Wang *et al.*, 2019).

The recombinant fungal defensin-like peptide- P2 was effective in inhibiting the growth of *S. dysgalactiae, S. agalacti*ae, and *S. aureus* (1- 4 μg/mL).The minimal biofilm inhibition and minimal biofilm eradication concentrations were from 8 μg/mL to >512 μg/mL only against *S. dysgalactiae*. The obtained data showed that the plasma membrane of *S. dysgalactiae* was disrupted by P2 in a time and dose-dependent manner; the *in vivo* assays demonstrated that the peptide decreased the number of mammary bacteria and inflammation (Table 9; Zhang *et al.*, 2021).

5.5. Other alternatives

Bacteria are considered sources of diverse antimicrobial agents, in this sense, the antimicrobial activity of crude extracts from actinomycetes was determined on *Staphylococcus aureus, Staphylococcus chromogenes, Streptococcus dysgalactiae*, and *Streptococcus uberis*. Treatments were active at concentrations from ≥ 0.78 μg/mL to 100 μg/mL (Leite *et al.*, 2018). In the same sense, the search for antiseptics is increasing. The *in vitro* and *in vivo* evaluations of wood vinegar from *Eucalyptus urograndis* demonstrate to have benefic effects on major pathogens (multidrug-resistant) associated with mastitis. The MIC and MBC values ranged from 0.781 to 1.562% and from 0.781 to 3.125%, respectively. In

Table 9
Recent studies regarding the application of peptides against bovine mastitis pathogens.

Alternative treatment	Mechanism of action	Reference
S. aureus bacterin Nisin	Reduction of intramammary infections, bactericidal and antibiofilm activity	(Guan *et al.*, 2017; Pérez-Ibarreche *et al.*, 2021)
pm11	bacteriostatic and bactericidal activity	(Popitool *et al.*, 2022)
Aureocin A53	Bactericidal activity	(Marques-Bastos *et al.*, 2022)
NZ2114	Inhibition of bacterial proliferation, reduction of bacterial loads	(Yang *et al.*, 2022)
H18R	Bacteriostatic effects on *S. aureus*	(Wang *et al.*, 2019)
Defensin-like peptide-P2	Inhibitory and antibiofilm activity	(Zhang *et al.*, 2021)

cows treated with this wood vinegar (1%) a decreased number of colony-forming units were present in the mammary gland, and no signs of hyperemia, pain, edema or crusts were detected (da Silva *et al.*, 2023). An antiseptic preparation containing 5% lactic acid with modified rice gel was evaluated on *S. aureus* and *S. epidermidis*, showing potential bactericidal activity (Chotigarpa *et al.*, 2018). Similar results were determined on *E. coli* (Chotigarpa *et al.*, 2019).

An *in vivo* assay demonstrated that an emulgel based on copaiba oil-resin extracted from *Copaifera reticulata* can reduce bacterial loads in bovine mastitis cases. Moreover, anti-inflammatory effects were determined (Campanholi *et al.*, 2023), Quarters with bacterial infection progressively reduced after the subcutaneous injection of an emulsified oil from the rhizome of *Atractylodis macrocephalae* (32 mg), infection was attributed to *S. aureus, S. agalactiae, S. dysgalactiae, S. uberis* and coagulase-negative staphylococci (Xu *et al.*, 2015). Another study demonstrated that dietary supplementation with zeolite clinoptilolite diminished risk of intramammary infections in pregnant cowa aged 3 to 6 years (Samardžija *et al.*, 2017).

6. Conclusion

According to the analyzed epidemiological data, the prevalence of both, contagious and environmental pathogens may vary according to geographical region. Regarding resistance profiles, most of the above-mentioned studies determined that isolated strains were multidrug-resistant,On this note, therapeutic strategies, such as herbal therapy, nanotechnology, polymers or peptides have been proposed as alternatives for mastitis treatments. Both, *in vitro* and *in vivo assays* showed potential results, demonstrating that these alternative may be effective on bacteria associated with bovine mastitis.

Ethical statement

The authors declare that no animals were used.

Declaration of Competing Interest

Authors declare there is no conflicts of interest.

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