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REGULAR ARTICLES

Bovine mastitis prevention and control in the post-antibiotic era

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Abstract

Mastitis is the most important disease in the dairy industry. Antibiotics are considered to be the first choice in the treatment of the disease. However, the problem of antibiotic residue and antimicrobial resistance, in addition to the impact of antibiotic abuse on public health, leads to many restrictions on uncontrolled antibiotic therapy in the dairy sector worldwide. Researchers have investigated novel therapeutic approaches to replace the use of antibiotics in mastitis control. These efforts, supported by the revolutionary development of nanotechnology, stem cell assays, molecular biological tools, and genomics, enabled the development of new approaches for mastitis-treatment and control. The present review discusses recent concepts to control mastitis such as breeding of mastitis-resistant dairy cows, the development of novel diagnostic and therapeutic tools, the application of communication technology as an educational and epidemiological tool, application of modern mastitis vaccines, cow drying protocols, teat disinfection, housing, and nutrition. These include the application of nanotechnology, stem cell technology, photodynamic and laser therapy or the use of traditional herbal medical plants, nutraceuticals, antibacterial peptides, bacteriocins, antibodies therapy, bacteriophages, phage lysins, and probiotics as alternatives to antibiotics.

Keywords Bacteriocins · Bacteriophage therapy · Dairy · Disinfectants · Education · Mastitis · Microbiota · MRSA · Nanotechnology · Nutraceuticals · Probiotics · Resistant breeds · *Staphylococcus aureus* · Stem cells

Introduction

Mastitis is a major disease of the dairy industry with global annual losses of approximately 35 billion USD (Sathiyabarathi et al. 2016). The disease usually induces permanent and irreversible damage to milk-producing glandular tissues (Sharma and Jeong 2013). Mastitis is a complex multi-etiological disease which has various environmental and microbial predisposing factors (Castañeda Vázquez et al. 2013). It is estimated that about 150 various bacterial species/subspecies can induce mastitis in dairy cattle. However, more than 95% of the cases are induced by members of 10 groups only. These groups are divided into environmental or contagious pathogens according to their reservoir and mode of transmission (El-Sayed et al. 2017, Reinoso et al. 2008). The major mastitis-inducing bacteria include *Staph. aureus*, Mycoplasma spp., *Strept. uberis*, *Strept. dysgalactiae*, coliform bacteria, and other gram-negative bacteria such as *E. coli* and *Klebsiella pneumoniae*. Other pathogens such as *Arcanobacterium pyogenes*, different Streptococci (*Strept. parauberis, Strept. agalactiae, Strept. equinus, Strept. canis*, and *Strept. zooepidemicus*), *Corynebacterium bovis*, and *Mycobacterium bovis* may be involved to a lesser extent (El-Sayed, et al. 2017, El-Sayed et al. 2019). According to the literature, *Staph. aureus* is responsible for about 50% of the mastitis cases, and only 10–30% of the cases are curable upon using antibiotics (Gomes and Henriques 2016, Mella et al. 2017).

Field diagnosis of mastitis, followed by the bacteriological and biochemical identification of the causative agents and their antibiotic sensitivity profiles, is time-consuming. The development of molecular biological tools could provide direct, accurate, and rapid diagnosis (El-Sayed, et al. 2017). For the treatment of mastitis, antibiotics usually come as the first

Highlights
1. Nanotechnology use in mastitis diagnosis and control
2. Alternative therapeutic concepts as replacers to antibiotics
3. Improvement of management concepts and mastitis control
4. Vaccines and immunomodulators lead to mastitis control
5. Mastitis-resistant cows for mastitis control

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choice. However, the already available antibiotics for mastitis treatment are limited due to the growing bacterial resistance and public health restrictions (Khazaie and Ahmadi 2021). Meanwhile, the development of new antibiotic generations is extremely costly, and new antimicrobial concepts for overcoming bacterial resistance are under development. One of them is the use of nanotechnology to develop antimicrobial agents that exert their effect via physical mechanisms instead of the chemical mode of action. For example, the use of nanosized emulsions of soya bean oil shows a potent antimicrobial effect even against multidrug-resistant pathogens (El-Sayed and Kamel 2019b). The emulsion bactericidal properties depend on the surface tension effect where the oil merges with the bacterial membrane selectively and destroys it. These new antimicrobial agents are not only efficient against multiple resistant and intracellular microbes, economic, friendly to environment, and have minimal side effects/host toxicity but also difficult to outdate, as the bacteria are not expected to develop resistance against them (El-Sayed and Kamel 2018, El-Sayed and Kamel 2019a). Other approaches like the use of stem cell therapy were also investigated. The udder tissue normally contains stem/progenitor stem cells which are maintained throughout the animal life. The progenitor cells, in contrast to stem cells, have a limited capacity to proliferate and differentiate (Sharma and Jeong 2013). The application of stem/progenitor cell therapy for the treatment of mastitis will be discussed later in the present work, in addition to other novel therapeutic and preventive tools.

In parallel to efforts aimed at providing novel therapeutic preparations, new concepts about mastitis control were developed. The applied prevention and control strategies can be noticed on different axes with a special focus on the management of the dairy herds, their housing, feeding, milking and drying protocols, and providing mastitis vaccines. The main axes to be discussed in the present work are improvement of diagnostic and alternative therapeutic concepts and improvement of management concepts of mastitis.

Improvement of diagnostic and therapeutic tools

Advanced molecular biological diagnostic assays

Culture was considered to be the gold standard for mastitis diagnosis for a long time. However, the improvement in the sensitivity and specificity of PCR and PCR-based techniques made it a new gold standard (El-Sayed, et al. 2017). Classical bacteriological diagnosis of mastitis inducing pathogens is usually an intensive lab work over several days. The development of PCR and PCR variants enabled rapid, economic, accurate, and sensitive diagnosis of the pathogens as well as the determination of the responsible genotype and the presence of antibiotic resistance genes (Fig. 1). However, molecular analysis must be carried out in equipped labs. The development of a new promising variant of the PCR (namely the Recombinase Polymerase Amplification (RPA) and its variants Multiplex RPA and on-chip RPA) enabled for the first-time field molecular diagnosis of mastitis in situ, as it requires a small portable cycler. The RPA cycler programs, in contrast to PCR, do not require cooling and heating of the samples and can be carried out as a field test (El-Sayed, et al. 2017). Other molecular tools are now also available for routine commercial diagnostic purposes such as the new-generation sequencers or loop-mediated isothermal amplification (LAMP) which is a rapid, efficient, and economic tool for detection of *S. agalactiae* in milk (Almeida 2012, El-Sayed, et al. 2017). The detection of certain circulating endogenous non-coding micro RNA (miRNA) is also an advanced tool for the early diagnosis of mastitis and for the identification of udder invading pathogens (Ashraf et al. 2017, Sun et al. 2015).

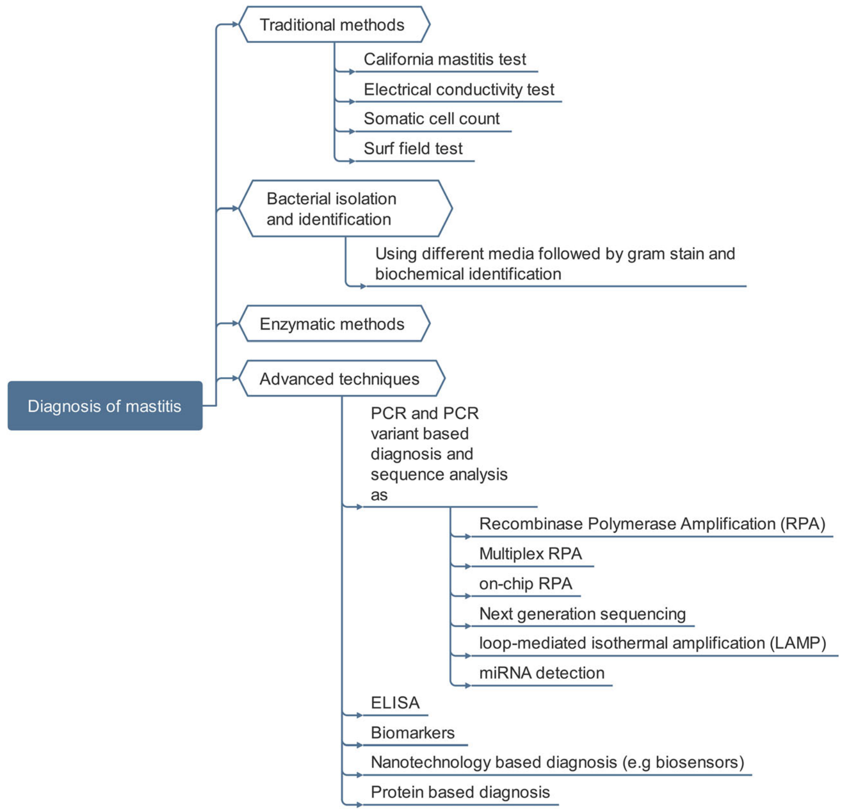
Use of nanotechnology in the diagnosis and therapy of mastitis

The development of new techniques to manipulate materials at their nanoscale started a new era in almost all medical applications, including disease diagnosis, therapy, and vaccine preparation. The rapid development of nanotechnology provides advanced diagnostic assays for early and accurate diagnosis of mastitis. One of these major diagnostic assays is the use of nano-biosensors which represent a novel class of analytical systems for the diagnosis of mastitis. Biosensors are devices that contain bioreceptors specific for the investigated antigen or molecule combined with a physical nano-transducer (sensor). These sensors report the presence of certain biological substances via electric signals. There are several variants of biosensors according to the used NP, type of transductor, nature of the target molecule, and signalling/recognition system (Martins et al. 2019).

For example, the use of nanotechnology allowed the development of a real-life sensing diagnosis of mastitis through the detection of hepatically derived acute-phase proteins (e.g., haptoglobin). Haptoglobins are biomarkers which are released by the liver in response to infections or inflammation. However, haptoglobins can also be produced by mammary vascular cells; therefore, they can be detected in serum and milk samples upon infection or inflammation. The diagnostic immunoassay is an opto-chemical approach based on chemiluminescence coupled with magnetic NPs. The bioassay could detect haptoglobins (i.e., mastitis biomarker) very early and with very high sensitivity level in mastitic milk samples (Nirala et al. 2020).

Beside their use in diagnostics, NPs are widely used for therapeutic purposes in human and veterinary medicine. Nanosizing of therapeutic active materials makes them more

Fig. 1 Diagnostic techniques of mastitis in animals



active and more soluble so that they can pass through various physiological barriers in the body. These preparations become more efficient, sustained release, and smart and have fewer side effects. The NPs usually obtain additional properties which are not available in their counterparts. As an example, nanosized streptomycin and doxycycline are much more effective in the treatment of brucellosis than their original counterparts (El-Sayed and Kamel 2018, El-Sayed and Kamel 2019a).

Due to the limitations of mastitis conventional therapeutic approaches, the development of alternatives to antibiotics such as NP in the treatment of mastitis was necessary (Fig. 2). Meta-analysis and collective data recommend the use of NP as an ideal alternative to antibiotics. They have a broad-spectrum antimicrobial potential and do not advocate the development of bacterial resistance. They can exert their toxic effects via many mechanisms. The antimicrobial effect of the metal nanoparticles is attributed to (1) liberation of nascent reactive oxygen, (2) peroxidation of bacterial proteins and lipids, (3) leakage of sugars inside the bacterial cells, (4) degradation of microbial DNA, and (5) damaging cell membrane leading to an increase in membrane permeability (Kalińska et al. 2019, Yuan et al. 2017). The bacteria subjected to NP during mastitis therapy exhibited lower lactate dehydrogenase activity and lower levels of adenosine triphosphate (ATP) which indicates inefficient energy regulation in the bacteria. Gene expression levels are also dysregulated in pathogens including the genes glutathione (GSH), glutathione S-transferase (GST), and superoxide dismutase (SOD) and catalase (CAT) leading to bacterial death (Yuan, et al. 2017). Results obtained from pilot studies investigated the potential of metal nanoparticles as silver, copper, or silver–copper nanoparticles were successful and the first commercial products are already available in the market (Kalińska, et al. 2019).

The successful application of chitosan nanoparticles (Ch-NPs) in the treatment of mastitis has also been reported. The NP induced bacterial membrane damage and prevented biofilm formation without interfering with the viability of udder tissues (Orellano et al. 2019).

Commercial NPs are also used to improve the general health conditions, animal productivity, immune response, and reproductive condition of the animals. For instance, nano-ZnO can improve udder health in dairy cattle suffering from subclinical mastitis and decrease the milk somatic cell count (SCC). Their high potential to eliminate mastitis inducing pathogens and at the same time their safety for mammalian cells and being inexpensive favor their application in mastitis therapy (El-Sayed and Kamel 2018, Hozyen et al. 2019, Reddy et al. 2007).

However, as the use of nano-products in the treatment of mastitis is not yet well established as an alternative to the classical antibiotic approach in the field, many researchers prefer to go through a transit stage, in which they combine nanoparticles with antibiotics for the treatment of mastitis. This trend prefers to couple NP with the already in use

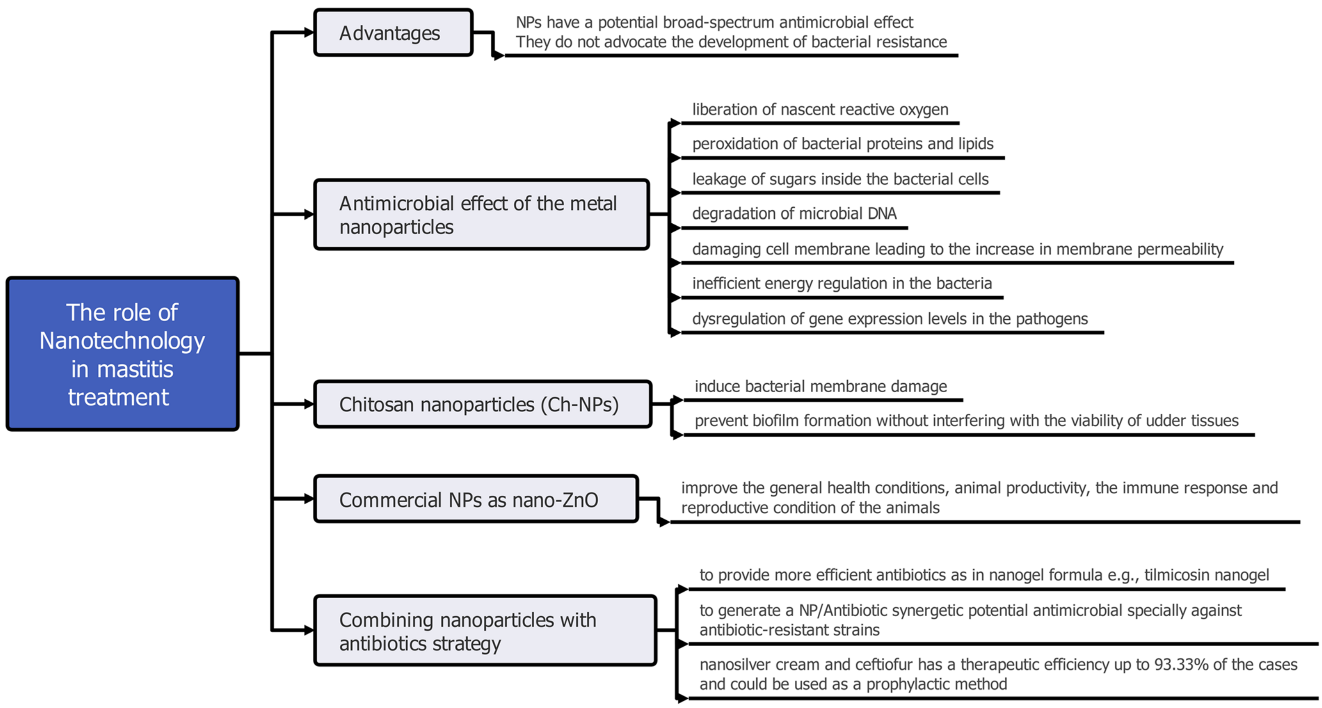


Fig. 2 Role of nanotechnology in mastitis treatment

antibiotics to provide more efficient antibiotics in nanogel formula, e.g., tilmicosin nanogel (Zhou et al. 2019), or to generate a NP/Antibiotic synergetic antimicrobial potential especially against antibiotic-resistant strains (Deng et al. 2016). Pilot studies showed that the combined NP-Antibiotic formula exerted great success when given for the treatment of mastitis. Intramammary infusion of nanosilver cream and ceftiofur has a therapeutic efficiency of up to 93.33% of the cases. The formula could also be used for prophylactic purposes when given 2 W before calving (Chau et al. 2019).

Alternative therapeutic concepts

Most therapeutic concepts of mastitis are usually antibiotic-based. These approaches get more and more global restrictions due to the growing antimicrobial resistance, antibiotic residues and public health concerns (Figure 3). Therefore, novel anti-mastitis preventive and therapeutic strategies have been explored including the use of nanoparticles, nutraceuticals, herbal extracts, probiotics, laser radiation, lysozymes, saponin, propolis, lysosubtilin, antibacterial peptides and the intramammary infusion of lactoferrin or ozone in addition to traditional medicine (Malinowski et al. 2019).

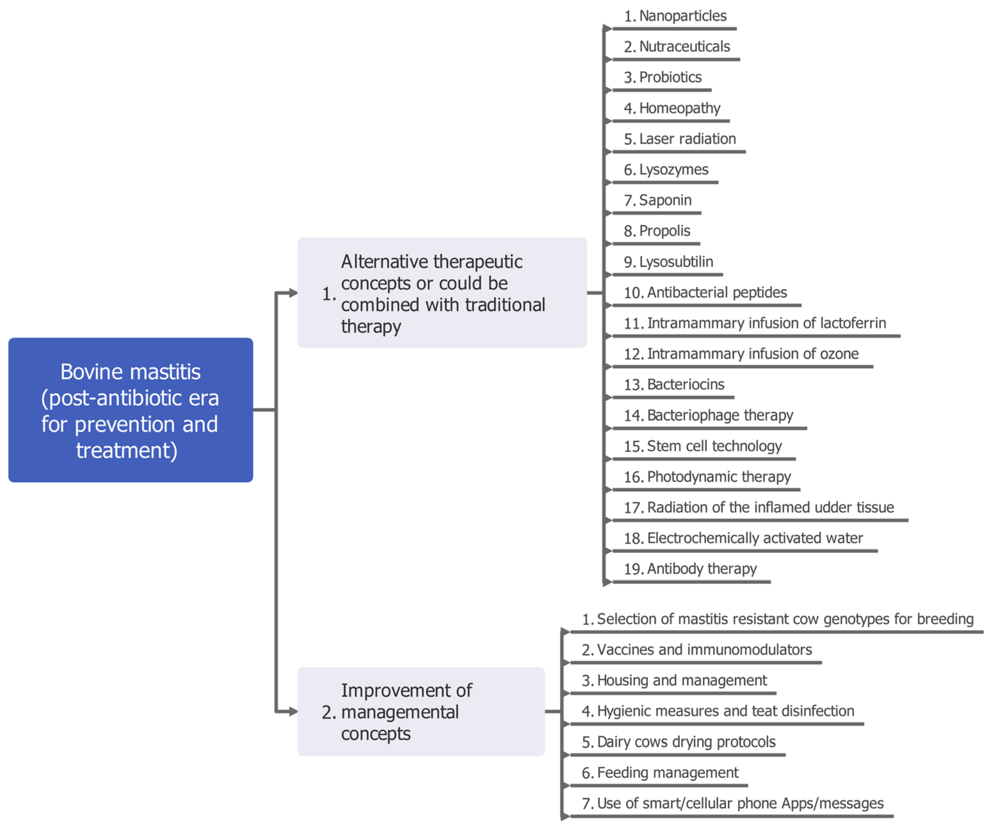
Beside the previously described applications of nanotechnology in this review, other promising concepts in mastitis treatment are also under investigation. The use of herbal extracts in traditional medicine (nutriceutical) is known in old cultures worldwide. Certain plants with antimicrobial, anti-inflammatory or immunomodulatory effects are under investigation with primary promising effects (Cho et al. 2015, Kaithwas et al. 2011, Kher et al. 2019, Mushtaq et al. 2018, Sahle 2002, Verma and Nauriyal 2009).

These extracts can be (1) applied topically (Bhatt et al. 2014) and (2) injected subcutaneously (Hu et al. 2001) and (3) can also be carried on lipid-based nanocarriers (nanophytosomes) to protect them from digestion and degradation in the GIT (Choimet et al. 2016) (4) or given in combination with antibiotics to generate a synergetic potential (e.g., the extracts of *Baccharis dracunculifolia*, *Plectranthus ornatus*, *Inga edulis, Salvia officinalis*, and *Senna macranthera*). The combination of these plant extracts with ampicillin, kanamycin, or gentamicin reduces the minimum inhibitory concentration (MIC) by eightfold (Silva et al. 2019) or the combination of *Eucalyptus globulus* and *Juglans regia* extracts with penicillin G (Gomes et al. 2019) and also *Calliandra surinamensis* leaf extract in combination with tetracycline or ampicillin (Procópio et al. 2019).

Garlic is one of the most commonly used plants in human and animal herbal medicine. The healing effects of garlic are mainly attributed to the presence of the organosulfur compound (Allicin). Allicin exerted a potent anti-inflammatory effect and could stop the pathological changes in udder tissues following Staph. aureus infection (Chen et al. 2019).

One of the major sources of knowledge concerning medical herbs is traditional medicine in old cultures like China. In literature, several plant extracts have been used in traditional Chinese medicine to treat mastitis in dairy animals. These

Fig. 3 Post-antibiotic era for preventing and treating bovine mastitis



plant extracts have detoxifying, anti-inflammatory, and antibacterial effects, such as *Taraxacum mongolicum*, *Lonicera japonica*, *Viola patrinu*, *Folium isatidis*, *Angelica dahurica*, *Coptis chinensis*, *Phellodendron amurense*, *Rheum officinale*, *Scutellaria baicalensis*, *Angelica dahurica*, and *Rheum officinale*. However, the oral administration of these extracts makes the required doses for mastitis therapy very high. This, in turn, increases the cost of therapy and is a lab. intensive(Yang et al. 2019).

The application of citrus oil infusions for mastitis control was also investigated. Various cold-pressed citrus oils are used as food preservatives. Pilot studies are running to evaluate their use as a mammary gland infusion to control mastitis. Citrus oils are either dissolved in dimethylsulfoxide (DMSO) or ethanol. However, the use of DMSO in dairy animals is not allowed by the FDA. The primary results of using citrus oils for the treatment of mastitis are not yet satisfactory (Scholte 2019).

The use of living bacteria (probiotics) in the poultry industry has been well established for many decades. However, new knowledge about the physio-pathological role of microbiota makes it interesting for the dairy industry also. Recent works indicated and incriminated the microbiota and their metabolites in mastitis induction mainly the lipopolysaccharide found in the cell wall of gram-negative bacteria. The overproduction of LPS (lipopolysacchride) in the gut and their absorption to blood disrupt the physiological udder barrier and facilitate the invasion of the udder (Hu et al. 2020, Hu et al. 2019a). In opposite to LPS, other microbial metabolites express udder protective properties. The production of short-chain fatty acids as a metabolic by-product by fibers fermenting the anaerobic microbiome improves the immune response and protective capacity of the udder tissues (Hu et al. 2019b). However, pilot investigations using probiotics in the treatment of mastitis have revealed mixed results and are confusing (Amir et al. 2016).

While the prevalence of mastitis among breastfeeding women was higher among those who consumed probiotic milk during pregnancy (Bouchard et al. 2015), other reports documented the beneficial use of probiotics during pregnancy. Actually, these conflicting results can be explained easily. The effects of probiotics vary according to the used isolate even among those belonging to the same bacterial species. Their effects were described to be strain-specific and not species-specific (Amir, et al. 2016). Bacteriological examination of women milk revealed the presence of specific isolates of *Lactobacillus* and *Lactococcus spp*. The isolated bacteria were found to have immunomodulatory properties (Bouchard, et al. 2015). For examples, *Lactobacillus fermentum* CECT5716 and *Lactobacillus salivarius* CECT5713 can be isolated from breast milk as a normal milk microbiota. The two strains exert specific immunostimulatory and anti-inflammatory effects, respectively (Díaz-Ropero et al. 2007). Beside their immunomodulatory effects, these strains, like several other *Lactococcus* and *Lactobacillus* strains, are capable of inhibiting both adhesion and internalization of invading pathogens to mammary epithelial cells (Armas et al. 2017).

Oral/intramammary administration of certain bacterial strains can re-establish microbial equilibrium and prevent/treat mastitis. In women suffering from mastitis, the treatment with probiotics was superior to that with antibiotics according to some reports (Arroyo et al. 2010). In breastfeeding women, oral administration of *Lactobacillus fermentum* and *Lactobacillus salivarius* prove their efficacy as alternatives for antibiotics in the treatment of mastitis. Some of these strains were found to provide additional mastitis preventive/prophylactic properties (Bond et al. 2017, Hurtado et al. 2017). Similarly, in dairy cows, oral administration of certain genotypes of microbiota had the ability to prevent and even cure mastitis. The reported bacterial species with therapeutic potential were *Bacillus subtilis* or *Lactobacillus salivarius* strains (Fernández et al. 2015) or via intramammary infusion with *Lactococcus lactis* or *Lactobacillus perolens* (Armas, et al. 2017, Crispie et al. 2008, Frola et al. 2013, Klostermann et al. 2008).

The use of bacteriocins as alternatives to antibiotics was also investigated. Bacteriocins are bacterial peptides with antimicrobial potential. Some bacteriocins (e.g., nisin) are already in use for food conservation because of their antimicrobial efficiency and at the same time their high safety to consumers. However, purified bacteriocins can be either directly administered in pure form or indirectly through the administration of probiotics (viable bacteriocin producing bacteria, mainly lactic acid bacteria, e.g., *Lactococcus lactis* strain CHCC5826) (Kitching et al. 2019, Yang et al. 2014). Recently, therapeutic preparations containing bacteriocins produced by *Strept. equinus* HC5 were developed to treat mastitis. Pilot studies confirmed their potential to inhibit the growth of more than 80% of investigated streptococcal and staphylococcal strains (Fernández et al. 2008, Godoy-Santos et al. 2019, Pieterse and Todorov 2010).

The disturbance in mammary gland microbiota enhances the development of mastitis. The intramammary inoculation of probiotics such as lactic acid producing bacteria leads to their colonization in the udder. They are capable of the establishment of equilibrium in the udder micro-environment and protect against mastitis due to their key role as immune-modulatory factors (Sharun et al. 2021).

Bacteriophage therapy has been well established in human medicine since 1923, mainly in Russia and East Europe. They have the advantage of being host-specific in opposite to antibiotics, which also kill beneficial gut bacteria. However, its efficient use in mastitis treatment provided varied levels of success due to their narrow host-range and inability to replicate in raw milk inside the udder (Angelopoulou et al. 2019, Scholte 2019). In parallel, researchers intensify their search for broad host range bacteriophages, which can be used to treat mastitis apart from the causative agent (Iwano et al. 2018). They can achieve this goal also via injection with a phage cocktail which improves the treatment efficiency as reported in the literature (Geng et al. 2019).

On the other hand, the use of phage endolysins (enzymes responsible for bacterial cell lysis) provided more satisfactory results. However, repeated injection of lysin proteins leads to the formation of immunoglobulins against injected phage enzymes which restrict the antimicrobial activity of the enzymes in the infected udder (Angelopoulou, et al. 2019, Gill et al. 2006). An additional limitation to the use of phage endolysins is their narrow antimicrobial spectrum. Most endolysins are not effective against gram-negative bacteria because the outer membrane protects the underlying carbohydrates and peptidoglycan from coming in direct contact with the lysins. Among the well-characterized and most potent lysins is the streptococcal-specific lysin, PlyC prepared from the C 1 bacteriophage. Only one nanogram of it can eliminate 10^{7} CFU of various streptococcal species in a few seconds (Scholte 2019). One of the major advantages of using bacteriophages and phage endolysins is their ability to eliminate antibiotic-resistant pathogens which cannot be treated by conventional therapeutic assays (Fan et al. 2016). At the time, a large number of commercial phage products are available in the market (Basdew and Laing 2011).

In dairy industry, mastitis treatment aims mostly to stop the deterioration of condition. Therefore, application of regenerative medicine approaches (e.g, Stem Cell Therapy) can aid to reverse tissue damage or resume the original production (Sharma et al. 2017). Stem cell technology is one of a very promising alternative in the medical field. Following the elimination of pathogens, mastitis mostly results in different permanent degrees of damage in the udder tissue. Although the available stem cell techniques for commercial use are improving very rapidly, however, the use of stem cells remains limited to regenerative medical applications rather than as a therapeutic tool. For regeneration and revascularization of damaged mammary tissues, both epithelial and myoepithelial progenitor cells can be used (Sharma and Jeong 2013). Stem cells prepared from adipose tissue could repair damaged udder tissues due to chronic mastitis. The replacement of fibrosed tissues with healthy glandular tissue leads to the resumption of the original milk production capacity of mastitic animals. Stem cells from adipose tissue are selected for this mission due to their high angiogenesis capacity which is needed for the regeneration of highly vascular udder tissues (Costa et al. 2019).

However, the use of mesenchymal stem cells instead of epithelial and myoepithelial progenitor cells is a revolutionary step. Mesenchymal stem cells are self-renewal; they divide in an asymmetric way to generate undifferentiated cells and keep their stem capacity. Recent reports have reported the additional therapeutic effect of mesenchymal stem cells extracted from bovine adipose tissue of cattle. The stem cells can cure cows suffering from mastitis and decrease the number of somatic cells in milk (Markoski 2016, Singh et al. 2020). This curing effect of mesenchymal stromal cells is attributed to their anti-inflammatory, antimicrobial, and immunomodulatory properties via the activation of innate immunity (Lange-Consiglio et al. 2019). Moreover, mesenchymal stromal cells enhance the expression of bBD4A and NK1 genes which encode antibacterial peptides (APs) such as cathelicidin, indolamine 2,3-dioxygenase, and hepcidin which have potent broad-spectrum bacteriostatic and bactericidal properties (Cahuascanco et al. 2019).

Photodynamic therapy is another recently developed approach for mastitis therapy. The concept is based on the release of nascent oxygen and the formation of hydroxide radicals (i.e., convert oxygen to reactive oxygen species (ROS) compounds) inside the target tissues through photosensitization of certain nano-compounds (e.g., safranine-O photosensitizer). The oxygen and hydroxide radicals kill the present bacteria selectively and overcome the problem of antibiotic resistance (da Silva Junior et al. 2019, Scholte 2019).

Radiation of the inflamed udder tissue with low-intensity laser in combination with antibiotic therapy revealed superior therapeutic results in comparison with antibiotic therapy alone. Irradiation of inflamed udder tissues with laser was seen to improve their regenerative capacity, reduce pain and inflammation and enhance the phagocytic activity of milk granulocytes (Malinowski, et al. 2019)

Electrochemically activated water "Anolytes" is an expression used to describe electrochemically activated water (sometimes called electrolyzed oxidizing water). The activation of normal water takes place by electrolysis of NaCl solution to produce hypochlorous acid (HOCl) and sodium hydroxide. Both compounds own antimicrobial properties and can be applied in the dairy industry as disinfectants (Kaoud 2015).

Antibody therapy is also one of the newly investigated approaches for mastitis treatment. Trails to treat mastitis with pathogen-specific antibodies delivered fewer promising data. This may be attributed to the narrow therapeutic spectrum of the antibodies which makes this approach not practical for field application (Wang et al. 2019b).

Improvement of management concepts

Selection of mastitis-resistant cow genotypes for breeding

There are genetic differences among different dairy breeds; for instance, Holstein normally has higher SCC than dairy breeds in central Europe. Moreover, within the same breed, genetic differences are also noticed. They determine productivity and disease resistance including mastitis (Rupp and Boichard 2003). The determination of these genetic differences enables the selection of cattle with mastitis resistance genetic profiles for reproduction. According to published data, certain genomic mutations/genotypes have drawn attention for their possible role in mastitis resistance. In many cases, the role of these genes in mastitis resistance could be explained as the lactoferrin (BTA22) which encodes a protein with bacteriostatic properties in the mammary glands. On the other hand, BTA5 encodes lysozymes which cleave the bacterial cell wall and eliminate them from the udder. Both MHC and BoLA (bovine major histocompatibility complex) and BTA23 exert their role in mastitis resistance through the regulation of acquired immune response against udder invaders. However, in most cases, the exact role remains unclear to date (Rupp and Boichard 2003). The gene mutations/polymorphisms in the focus of research are listed in Table 1.

Genetic predisposing factors determining teat shape and dimension reflect the genetic diversity in the herd. Teat morphology was found to influence cow susceptibility to mastitis. Therefore, crossbred cows which possess pointed or round teat ends are more susceptible to tissue pathological changes after milking with milking machine compared with teats with flat ends (Gouvêa et al. 2020).

Vaccines and immunomodulators

Many farms depend on preparing autogenous vaccines (mainly against *S. aureus* or *Mycoplama bovis* and to a less extent streptococcal vaccines against environmental streptococci, as *Strep. uberis*). These vaccines are locally prepared from native strains isolated from mastitis cows in the herd and are then applied to the entire herd are not commercialized. However, commercial mastitis autogenous vaccines are also available (BestVac, herd-specific autologous *S. aureus* vaccine, IDT, Germany) (Ismail 2017). Commercially, mono (against one pathogen) and polyvalent (against more than one pathogen) vaccines are produced with a special attention for vaccines against *E.coli* and coliform bacteria was given. The importance of protecting the udder against this group of pathogens is due to the continuous exposure of the udder to manure in the yard. The commercially available *E.coli* vaccines include (1) *ENVIRACORTM J-5* Vaccine (*E. coli* J5 mutant bacterin) made by Zoetis, given S/C in three doses (at drying off, 4 weeks later, and within 2 weeks of calving); (2) *J-VAC® Escherichia coli Bacterin-Toxoid (E.coli* mutant strain is the J-VAC) made by Merial, given S/C or I/M in two doses (at drying off and boosted after 2-4 weeks); and (3) *ENDOVAC-Dairy* coliform vaccine (bacterin-toxoid formulated from a Re-17 mutant of *Salmonella typhimurium) made by* Immvac Inc., given at drying off and boosted after 2-3 weeks). Beside *E.coli*, vaccines targeting *S. aureus* are also available such as Lysigin, made by Boehringer Ingelheim, given S/C in the supramammary LN in three doses (4 and 2 weeks before calving, boostered after 6 months), or against *Mycoplasma bovis*, e.g., Mycomune bacterin, made by AgriLabs and given S/C in

Table 1 List of main genotypes which are linked to mastitis resistance in literature

Gene/locus significantly linked to mastitis resistance	References
CXC chemokine receptor (CXCR 1 and 2)	(Youngerman et al. 2004)
bovine major histocompatibility complex (bolA)	(Yoshida et al. 2012)
Toll-like receptor 9 (TLR9)	(Badami et al. 2019)
Locus number G519663A (chromosome 4), bovine Calcium channel, voltage-dependent alpha-2 delta subunit 1 gene CACNA2D1	(Deb et al. 2014, Yuan et al. 2011)
Bovine breast cancer 1 gene (BRCA1) namely the variants G22231T, T25025A and C28300A, in addition to variants of the intron 1/TLR4 gene, C4A gene (chromosome 8), ATP1A1 (chromosome 3), PGLYRP-1 gene (chromosome 18), CD14 gene (Chromosome 7), MBL-1 gene (Chromosome 28), and finally the cattle belonging to ATP1A1 genotype	(Beecher et al. 2010, Chen et al. 2018, Deb et al. 2013, Yuan et al. 2012)
AACD genotype of the Cluster of differentiation 14 (CD14)	(Pal et al. 2011, Selvan et al. 2016)
TRAPPC9 and ARHGAP39	(Wang et al. 2015)
48 different SNPs (single nucleotide polymorphism) located on Bos taurus autosome (BTA) 2, 6, 10, 14, 15, and 20	(Wang, et al. 2015)
Loci BM1818, BM1258, BM1443, BM1905, DIK20, BM302, BM4505, CYP21, and BMS2684	(Prajapati et al. 2017)
SNPs in Janus kinase 2 (JAK2) and diacylglycerol acyltransferase (DGAT1) genes	(Khan et al. 2019)
APP (BTA1), FOXL2 (BTA1), SSFA2 (BTA2), OTUD3 (BTA2), ADORA2A (BTA17), TXNRD2 (BTA17), NDUFS6 (BTA20), BTA15, and the gene (ENSBTAG00000008519) on BTA27, BTA12, MET (BTA04), RNF122 (BTA27)	(Szyda et al. 2019)
RAS guanyl-releasing protein 1 gene (RASGRP1)	(Kurz et al. 2019)
bovine leukocyte adhesion deficiency (Blad), lactoferrin (BTA22), lysozyme (BTA5), BTA3, 4, 11, 18, 23, and 27. MHC and BoLA, Class II DRB3 locus and QTL (quantitative trait loci) present on chromosome number 1, 3, 7, 8, 14, 18, 21 and 23	(Rupp and Boichard 2003)
In dairy sheep: C6, C7, C9, CTLA4, CARD6, DAB2, FYB, IDH1, ICOS, LYFR, OSMR, PLXNC1, PTGER4, and SOCS2	(Banos et al. 2017)
In dairy sheep, Several QTL regions that control milk SCC (SNP) in the OAR3 and OAR2 regions, the suppressor of cytokine signalling 2 (SOCS2) gene	(Oget et al. 2019)
In mouse model, the epigenetic profile (DNA Methylation pattern) of NCK-associated protein 5 (Nckap5) and transposon MTD	(Wang et al. 2019a)

two doses with 2–4 weeks interval during pregnancy and boosted at 2–3 weeks before calving. On the other hand, commercially available polyvalent vaccines include *STARTVAC*®, which is an inactivated vaccine contains a mixture of *E. coli* J5 and *S. aureus* (CP8) strains SP 140 (Guccione et al. 2017), also Hipramastivac, which contains *S. aureus* (TC5 ve TC8 strain), and *E. coli* (J5 strain), in addition to *S. agalactiae*, *S. uberis*, *S. dysgalactiae*, *S. pyogenes*, *P. aeruginosa*, and *A. pyogenes* bacterins (Keskin et al. 2007) and MastaVac (*Staphylococcal* enterotoxin Type C mutant vaccine) (Chang et al. 2008).

Although various mastitis vaccines are commercially available, none of them provide sufficient protection and are not cost-effective at the same time(Sharun, et al. 2021). Comparing two dairy groups receiving two different commercial vaccines with the control group did not reveal significant differences in the incidence of mastitis and the SCC of the milk (Tashakkori et al. 2019). The insufficient protective potential could be attributed to many factors including factors related to the cow (e.g., age and health status), related to the environment, or related to the invading pathogen, such as the high number of mastitis-inducing pathogens even with genetic variations among mastitis-provoking genotypes belonging to the same species, in addition to the variation in immune response among individual animals according to genetic and environmental conditions (Côté-Gravel and Malouin 2019, Merrill et al. 2019, Scholte 2019).

Therefore, the application of advanced molecular biological assays is not only important for diagnosis of the disease but also for the identification of the pathogen at the subspecies level and determination of their genotype. This is important in order to select suitable candidates for local vaccine production. Molecular techniques also enabled a revolutionary improvement in vaccine design and manufacturing. Using the right pathogen isolates and suitable vaccine designs ensure high efficiency, broad coverage protection, and maximal safety measures (Kamel et al. 2019, Merrill, et al. 2019).

However, recent trials to immunize young heifers with staphylococcal immune evasion proteins before starting milk production showed promising results and could protect them following exposure to Staphylococcus aureus challenge (Benedictus et al. 2019). Pilot studies to immunize dairy cows with staphylococcal surface proteins prepared from *Staph. aureus* or *Staph. chromogenes* were promising as the surface antigens prepared from *Staph. chromogenes* provided cross protection against different *Staph. aureus* field strains involved in the study (Merrill, et al. 2019).

The use of nanotechnology in the preparation of mastitis vaccines was also investigated. Nasal mastitis vaccine based on conjugated cCHP nanogel and inactivated *Staph. aureus* antigens could release protective levels of anti-*Staph. aureus* IgA (Nagasawa et al. 2019)

In a mouse model, the use of a DNA vaccine encapsulated in chitosan NPs (pPCFN-CpG-CS-NPs) against *Trueperella pyogenes* (*Arcanobacterium pyogenes) was investigated*. The vaccine could provide protection against challenge with mastitis inducing pathogens. However, no data are available on whether this vaccine could protect against intramammary invasion also (Huang et al. 2018).

In parallel to the efforts focused on the development of efficient mastitis vaccines, trails to use immunomodulators such as short and medium fatty acids and cholecalciferol to prevent staphylococcal internalization into the mammary gland epithelial cells are under development. The use of sodium butyrate and sodium octanoate modulated the regulation/expression of genes responsible for staphylococcal adhesion and internalization in the udder such as spa, *clf*B, and *sdr*C genes (Frutis-Murillo et al. 2019). Similarly, the injection of thymopentin near the supra-mammary lymph nodes of dairy cattle was shown to exert immunomodulatory activity in lymphocytes of the supra-mammary LN which enhances the better immune response against udder invaders (Guan et al. 2019).

Housing, milking, and management

- Outdoor overwinter housing systems of dairy cattle kept on straw-bedded packs was seen to be superior to indoor housing systems. The cattle kept outdoors had lower mastitis records in addition to healthy and clean udders/legs. Cattle that kept indoors must be provided with clean and dry beds to minimize the risk of mastitis (Sjostrom et al. 2019). Breeding for higher milk yields of dairy cows results in higher flow rates and with that wider teat canals. Open teat canals make it easier for bacteria to penetrate the teat canal and infect the quarter. Consequently, milking machines and milking methods must constantly be improved and milk the animals gently and completely. The teat canal area must be massaged during milking, which removes old keratin where bacteria may have entered. Although milking machines provide many advantages for the dairy industry, yet they may be acting as the bacterial reservoirs and spread the infection (Sharun, et al. 2021). The milking machine and procedures must keep a good teat condition that maintains blood circulation and preserve the passive and active immune defence of the teat (Martin et al. 2018, Odorčić et al. 2019). It was estimated that about 20% of the new mastitis cases are directly/indirectly related to milking machines. Beside the application of strict hygienic measures, the adjustment of the milking machine taking into consideration the production level, age and milk flow of the cows are very important to avoid mastitis. There are several managemental factors to take into consideration, such as milking animals with intramammary infections last. Several factors lead to the increase in the prevalence of mastitis in the herd and should be well managed (Mein 2012, Romero et al. 2020). These factors include malfunction of milking machines through inefficient teat massage (wrong pulsation characteristics), suction power that allow sudden, transient inflow of air through teat-cups, liner slips, vacuum fluctuations, clusters kicked off or rough cluster removal at the end of milking process, and over-milking of cows for longer than 2 min,

Hygienic measures and teat disinfection

It is very important to prevent the establishment of udder infection as some pathogens are difficult to eliminate once established. *Staph. aureus* is a facultative intracellular pathogen which enables it from escaping the antibiotics or being attacked by the immune system (Zhou, et al. 2019).

Therefore, pre- and post-milking teat disinfection remains one of the most important procedures of mastitis control. Different application forms as teat spray or teat dip can be applied. Commercially available disinfectants include potassium permanganate, zinc-, copper-, iodine or chlorhexidine preparations, in addition to herbal extracts and oils (Miseikiene et al. 2020, Mubarack et al. 2011, Sserunkuma et al. 2017, Sukumar et al. 2019, Vissio et al. 2019).

Although dipping may eliminate up to 91% of teat bacteria, it is important to carefully select the suitable dipping substance according to local farm circumstances (Fitzpatrick et al. 2019, Gospodarek-Komkowska 2019).

On the other hand, the delivered data concerning the safety, potency, and broad-spectrum bactericidal effects of nanometals when applied for the prevention and treatment of mastitis encouraged their possible use as teat disinfectants (Kalińska, et al. 2019). Other natural disinfectants which could replace chemical products included herbal extracts with antimicrobial potential. They were successfully tested as natural teat dips (Kummee et al. 2015)

Bacteriocins have also been used as natural teat seals (Twomey et al. 2000) and teat dips. They could stop the emergence of *Staph. aureus* to the teat and decreased the prevalence of mastitis in the herd (Klostermann et al. 2010).

The commensal mammary microbiota of the udder (e.g. *Ruminococcus, Oscillospira, Roseburia, Dorea, Prevotella, Bacteroides, Paludibacter, and Bifidobacterium*) are responsible for immune homeostasis (Derakhshani et al. 2018). Their disturbance (dysbiosis) will enhance the development of mastitis. Wide teat orifice (congenital defect, in old dairy cows or because of the milking machine) exposes the udder to the external microbes (Falentin et al. 2016). Probiotics can also be applied as disinfectants/teat dip. In a recent study, lactobacilli-based disinfectants could alter the composition of the bacterial population in the teat canal and reduce the prevalence of pathogenic mastitis inducing bacteria. The use of lactobacilli-based disinfectants as pre- and post-milking disinfectants was recommended by the research team (Yu et al. 2017).

Dairy cow drying protocols

There are many protocols used for drying cows at the end of the season. Most of them depend on the excessive use of parental and intramammary infusion of antibiotics (Cızmecı et al. 2019). However, the selection of a suitable protocol can save up to 63% of the used antibiotics and minimize the risk of mastitis (Bucher and Bleul 2019). The awareness of the growing problem of antibiotic resistance and their public health concern encouraged the development of non-antimicrobial approaches to be applied for cow drying off especially in organic milk herds (Dufour et al. 2019).

Use of smart/cellular phone apps/messages

The evolutionary improvements in communication technology have provided emerging technological advancements for the dairy industry in many aspects. Communication technology was applied either as (1) a source of information for the breeders (informative tips). Mastitis control programs were established, in which dairy breeders become daily updates in Kenya and Indonesia (Ardjo et al. 2017, Makau et al. 2018). Kenyan farmers who shared in the investigation received one-way SMS supplying them with information on a daily basis. Although the messages were useful in general, farms deleted older messages due to the limited size of their mobile memory. However, most farmers kept relevant old message (Makau et al. 2019) (2) used for monitoring livestock health especially for the diagnosis of mastitis or estrus detection (Beyene et al. 2018, Neethirajan 2017, Steeneveld et al. 2015) (3) for general disease diagnosis (Beyene et al. 2017, Michael and Geleta 2013) (4) applied as nano-biosensors connected to smartphone Apps for rapid detection of pathogens present in the milk samples (Chinnappan et al. 2017, Poltronieri et al. 2014) (5) sensors connected to Apps in farms with an automatic milking system in order to provide real-time reports on the udder health and milk composition. Digitalization of milking machine control systems also resulted in a reduction in the prevalence of clinical mastitis due to faulty machine control (Steeneveld, et al. 2015) or (6) collect epidemiological data about dairy herds in the region for epidemiological studies (Aanensen et al. 2009)

Feeding management

Supplementation of feed with certain feed additives such as vitamins, probiotics and probiotics can improve udder health, cow immunity and general body condition. Nutrition can influence udder immunity in many ways: (1) supply the raw materials for building the immune components, the lack of these elements leads to improper functioning of the immune system, and (2) supply the required elements for milk production. Among the major nutritional elements required for udder health and milk production are (1) antioxidants such as ascorbic acid: trap free radicals and prevent Cu and Fe from sharing in the oxidative reactions, (2) Cu, Zn, and Mn for the superoxide dismutase enzyme which converts superoxide to hydrogen peroxide to protect the tissues, and (3) selenium and iron for glutathione peroxidase and catalase enzymes, respectively. These enzymes are essential for the degradation of hydrogen peroxide to water, (4), 25-hydroxyvitamin D 3 to alter udder immunity in dairy cows (Dey et al. 2019, Poindexter et al. 2020) and (5) Vit A and Vit E: for α-tocopherol and β-carotene which are required to stop fatty acid peroxidation reactions. Cattle fed on stored forages are more susceptible to Vit E deficiency which is an essential component of the udder antioxidant defense system of udder tissue. The same problem is seen in many European countries as the soil is poor in selenium. Supplementation of these cows with Vit E and selenium can reduce the risk of development of mastitis (Kommisrud et al. 2005, O'Rourke 2009).

Deficiency of nutritional elements may induce metabolic diseases which will negatively reflect on udder health. Hypocalcemia results in milk fever. Lying cows are more susceptible to mastitis, dystocia, and retained placenta (Mulligan et al. 2006). Similarly, cows suffering from ketosis due to imbalanced nutrition (negative energy balance) are twofold susceptible to clinical mastitis (O'Rourke 2009).

It is also important to consider the form of the supplied trace element. Supplementation of the minerals in the form of chelate (organic form coupled with methionine or lysin A.A.) instead of their inorganic form increases the bioavailability of the minerals in the serum and therefore decreases the risk of their deficiency (Keshvari et al. 2016). Equally, nanoformulations of the supplied materials increase also their bioavailability through the improvement of their absorption (e.g., increase solubility by nanoencapsulation) and the reduction in their degradation (e.g., by the increase in molecular stability). The use of nano-capsules of lipophilic and hydrophilic materials enhances the absorption of substances in the gut and enables their passage through the membranes (Jampilek et al. 2019). Nano-emulsions can also be used to stabilize oil drops in water or vice versa (El-Sayed and Kamel 2018).

Finally, rumen dysbiosis due to acidosis or the intensive use of antibiotics changes the composition of rumen microbiome and the bacterial metabolites such as short-chain fatty acids (SCFAs) and microbial lipopolysaccharide (LPS). Disturbance in microbiome and the associated high level of secreted LPS promotes the absorption of LPS to the circulation where they are transported to other organs of the body, including the udder. The high levels of LPS in the circulation are responsible for the inflammation of mammary glands (mastitis) but other organs. These data were confirmed by the transplantation of microflora of cows healthy and suffering from mastitis to the digestive tract of germ-free mice. Mice inoculated by microflora of mastitic cows developed mastitis in opposite to those received microflora of healthy cows (Ma et al. 2018, Sharun, et al. 2021). These new data underline the importance of keeping the cattle on a proper nutritional plan to avoid acidosis. Pilot studies investigating rumen microflora transfer as a therapeutic approach for mastitis delivered promising results (Hu, et al. 2019a, Ma, et al. 2018).

In conclusion, since the second world war, the antibiotics solved nearly all infectious diseases which faced man and animals. The era of antibiotics is almost over due to growing antibiotic resistance and public health concerns. Many alternative approaches are now under development to replace antibiotics in the prevention and control of mastitis. While many of these approaches proved their efficiency, such as the use of nanotechnology and stem cells, other techniques were less successful and controversial such as homeopathy and the use of bacteriophages.

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