Role of Nanotechnology in Treatment of Bovine Mastitis

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Abstract

Mastitis is an inflammatory transformation of the mammary along with chemical and microbiological changes. Mastitis is a serious problem in dairy animals as it affects both their welfare and productivity and is associated with economic loss and public health concerns. Antibiotics have a key role in mastitis control programs, although there's a continuous search for new effective therapeutic alternatives. Another public health concern about mastitis is the antibiotic residues in milk owing to the improper use of antibiotics in treatment and control and the withdrawal time, which is not considered. These residues may cause a severe allergic reaction and sensitization in normal individuals when present at a low level. Drug delivery depending on nanotechnology allows medications to be deposited, maintained, and released gradually at specific sites, addressing some of the drawbacks of traditional medications, such as antibiotic resistance. To overcome antibiotic resistance Nanoparticles have emerged as new tools against bacterial infections. Metals, including copper, silver, and zinc, have been used due to their antibacterial properties. This chapter presents an overview of alternative solutions that may become popular in mastitis treatment.

Keywords: Nanotechnology, Bovine mastitis, Metal nanoparticles, Drug delivery, Antibiotic resistance

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Introduction

Mastitis, an inflammatory retort of the udder tissue due to mammary gland infection, is an intricate, multifactorial, chronic, and deadly disease in cattle (Argaw 2016; Shoukat, et al. 2018). It was classified as contagious and environmental according to the causative agent. The contagious is classified into clinical, subclinical, and chronic mastitis. Mastitis is a crucial problem that affects dairy animals and influences their milk production, leading to heavy culling (Cobirka et al. 2020). Mastitis is the biggest economic burden of the dairy industry, and its control is a global challenge (Gad et al., 2025). Various conventional and advanced therapeutics and methodologies are used for mastitis control (Cheng and Han 2020). Traditional treatment of subclinical mastitis includes intramammary broad-spectrum drug administration however, the limitations of this therapy are well known (Ruegg 2017; Klaas and Zadoks 2018). Bacteriophages, bacteriocins, probiotics, stem cell therapy, herbal therapy, dry cow therapy, nutritional, genetic selection, vaccination, and nanoparticle-based therapeutics were tested for their effect on mastitis treatment and control (Gomes and Henriques 2016; Sharun et al. 2021). Antibiotics, such as penicillin, are considered the most used strategy for mastitis treatment (Gomes and Henriques 2016). It is believed that 80% of the antibiotics administered in dairy animals are used for the control of mastitis globally (Ganda et al. 2016a) but detection of the pathogens using a drug sensitivity test is important before starting antibiotic treatment (Koskinen et al. 2010). Although misusing and overusing antibiotics, in addition to their cost, in the case of bovine mastitis could introduce a serious problem of resistance and introducing resistant bacteria to the food chain (White and McDermott 2001). Being intracellularly residing, the bacteria within the mammary glands form abscesses and are hard to kill because of the restriction of their contact with antibiotics (Gomes and Henriques 2016). Moreover, another disadvantage of antibiotics is the presence of their residues in bovine milk which could represent a public health concern due to its human consumption (Motaung et al. 2017). Also, biofilm formation could contribute to antibiotic-resistant infections and recurrent mastitis (Babra et al. 2013). As no milk is produced during this period, a dry cow is considered the best period to control mastitis (Biggs 2017). Also, using strict biosecurity protocols and strategic culling could be effective in preventing and controlling the virulent strains of *S. aureus* and *S. agalactiae* (Kefee 2012). An alternative approach, such as using bacteriocins, antimicrobial peptides produced by bacteria, offered many advantages better than the traditional antibiotic choices (Twomey et al. 2000). Additionally, combining antibiotic treatment and culling of unresponsive cows declined the transmission rate of mastitis (Halasa 2012). Another approach involved subcutaneous injections of different concentrations of Selenium, Copper, Zinc, and Manganese (Machado et al. 2013) which reduced cases of subclinical mastitis and retained udder health without any effect on milk quantity or quality (Ganda et al. 2016b). This chapter concentrated on the application of nanotechnology as an antibiotic substitute in the treatment of mastitis.

Nanotechnology in Mastitis Treatment as Alternatives to Antibiotics

Nanotechnology research has been known since the previous century. Nanotechnology was introduced by Nobel laureate Richard P. Feynman in his celebrated 1959 speech "There's Plenty of Room at the Bottom", this topic has seen several ground-breaking advancements (Feynman, 1960). Different kinds of materials were created at the microscopic level using nanotechnology. Materials that have one dimension smaller at least than 100 nm are referred to as nanoparticles (NPs) (Laurent et al., 2010). 0D, 1D, 2D, or 3D materials can be used, relying on the general form (Tiwari et al., 2012).

NPs could be generically divided into many classes built on their shape, chemical, size, and shape makeup, this classification is according to the chemical and physical properties (Khan et al., 2019). The unique chemical and physical features of inorganic nano-sized particles, whether simple or complex, make them an increasingly significant component in the invention of novel nanodevices with a large range of biological, physical, pharmacological, and biomedical approaches (Loureiro et al., 2016; Khan et al., 2019). For the assembly of NPs, a variety of techniques can be used, two classes are broadly categorized into two classes: (i) top-down approaches and (ii) bottom-up approaches (Wang and Xia, 2004; Iravani, 2011; Bayda et al., 2019) (Fig. 1).

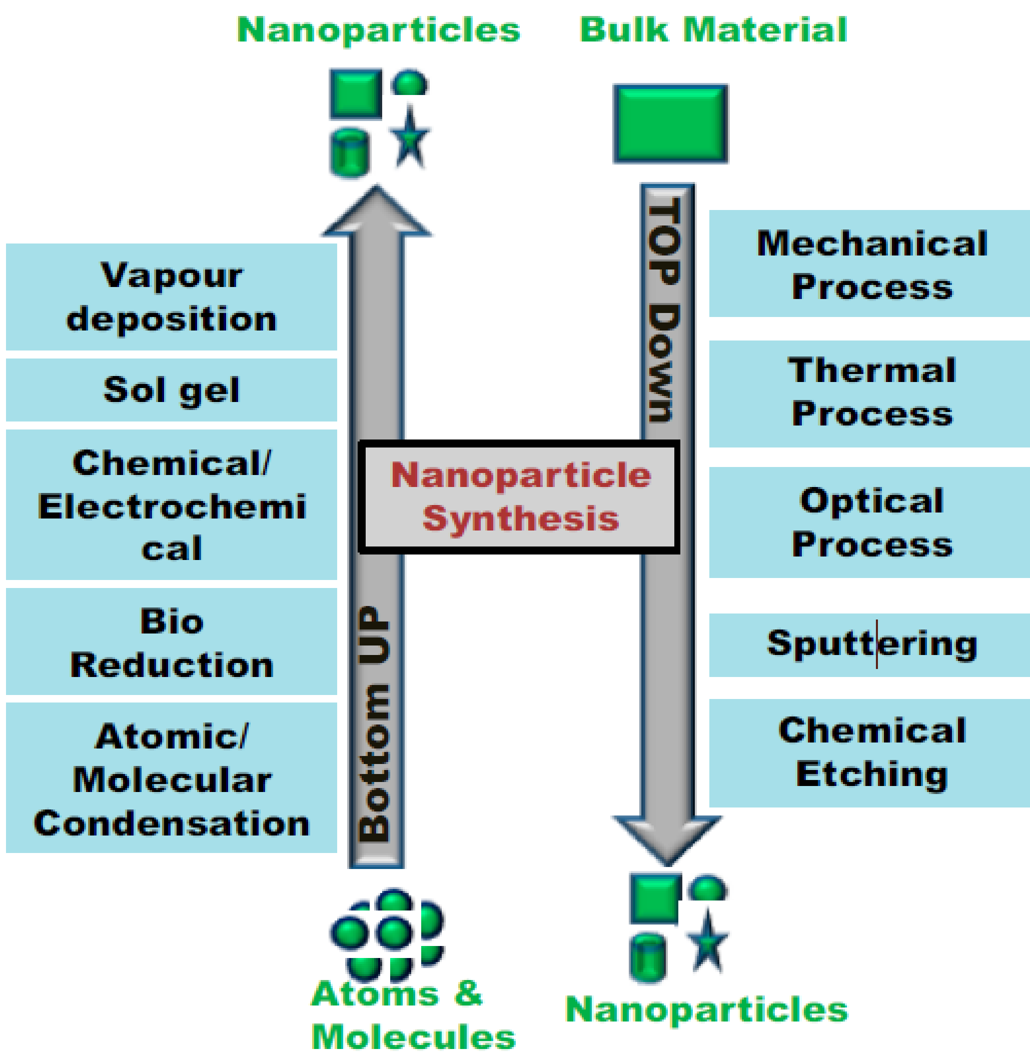

Fig. 1: The concept of top-down and bottom-up technology: different methods for nanoparticle synthesis (Bayda et al., 2019)

Three layers make up NPs (i) a superficial layer that could be functionalized with a range of polymers, tiny molecules, metals, and surfactants; (ii) an outer shell layer; and (iii) a core moiety that is the exact term for the NPs. As nanotechnology develops and new NPs are produced, the famous structure of NPs is changing, especially via bio-NPs as well as co-assembly (Noman et al., 2022; Wang et al., 2022).

Drug delivery depending on nanotechnology allows medications to be deposited, maintained, and released gradually at specific sites, addressing some of the drawbacks of traditional medications, such as antibiotic resistance (Ferreira et al., 2021; Li et al., 2023). Release of adherent drug from the surface of nanoparticles, through the erosion, diffusion, and the diffusion/erosion of the NPs are the main three key factors that affect the release of drug rate from the NPs. Thus, diffusion of drug and polymer biodegradation will control the pace of the released drug from the nanoparticles. In addition to deeper understanding the physiological parameters implicated in this procedure, the composition of the NPs (e.g., pH-sensitive and thermosensitive substances) and their engineering (e.g., nanoparticles, nanocapsules, monolayer and multilayer) can be used to control the time and location of the released drug (Klymchenko et al., 2020; Tan et al., 2021; Harish et al., 2022) (Fig. 2).

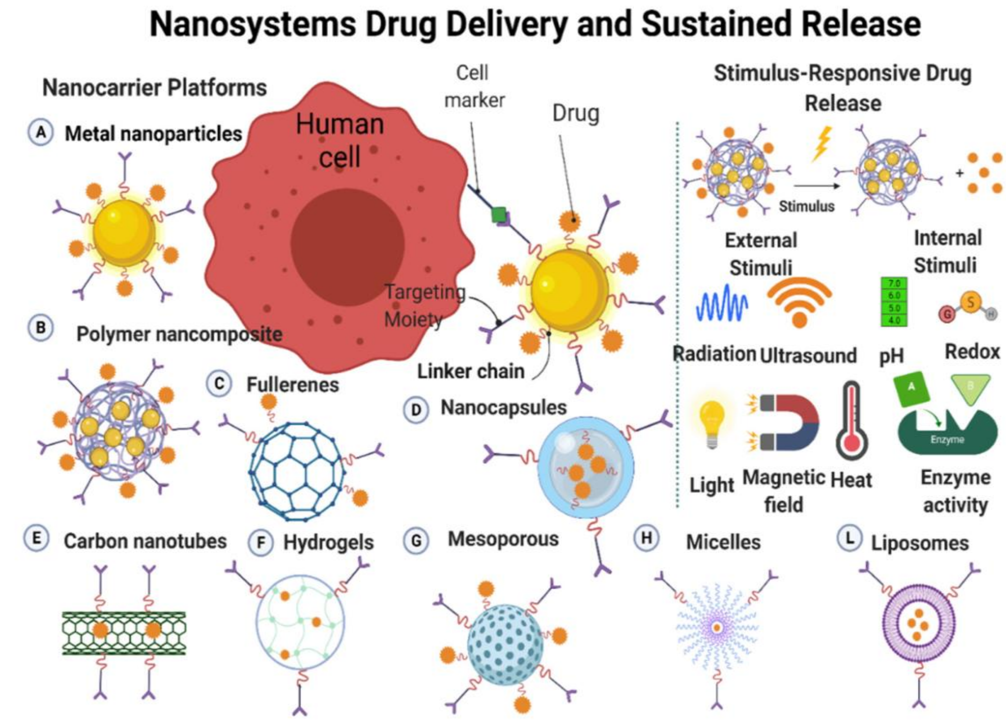

Fig. 2: Characteristics of nanomaterials that can cross the biological membranes to deliver a drug to a specific site and mechanisms influencing controlled drug release (Harish et al., 2022)

Since tiny molecules can alter the biological characteristics of nanomaterials, their use in surface functionalization has opened up new possibilities for biomedical applications. Antimicrobial resistance can be further prevented in this way by mediating the engagement to cell receptors (Masri et al., 2019; Spirescu et al., 2021) (Fig. 3).

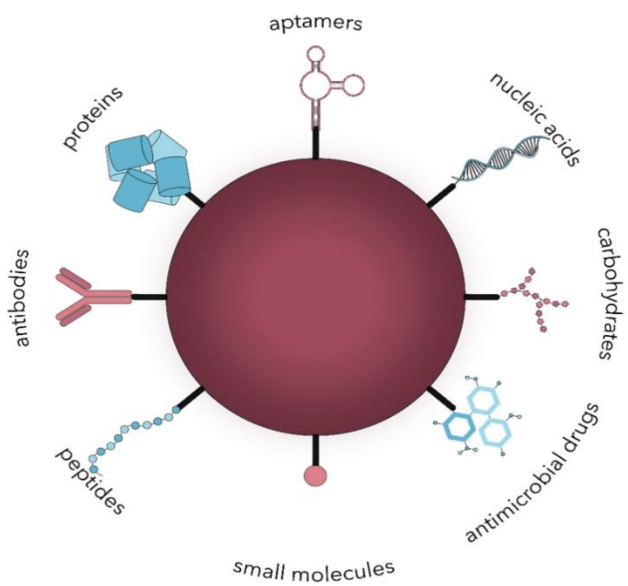

Fig. 3: The main types of biomolecules used for the surface modification of nanoparticles for active microbial targeting (Spirescu et al., 2021)

Nano Particles and Mastitis

To overcome antibiotic resistance Nanoparticles have emerged as new tools against bacterial infections. Metals, including copper, silver, and zinc, have been used due to their antibacterial properties (Haider et al., 2023) (Fig 4). With advances in nanotechnology, functional nanomaterials have been developed and widely used in various fields such as cosmetics, device coatings, and food preservation (Yılmaz *et al.,* 2023). Zhou et al. (2019) recorded that treatment of cows with *S. aureus* mastitis, with tilmicosin nanogel showed a greater rate of recovery than a group receiving traditional treatment. Silver nanoparticles and cinnamon oil both had bactericidal effects on *S. agalactiae*. Phyllanthus emblica, Terminalia, Citronella, Dandelion, and cinnamon were among the polyherbal nanocolloids that demonstrated effective, dose-dependent antibacterial activity against microorganisms obtained from mastitis (Abd El-Aziz et al., 2021; Ranjani et al., 2022).

Nano minerals are reported to produce unexpected biological responses when fed to cows due to their significant physical, chemical, and biological activities. The translocation of 100-nm nanoparticles is 15–250 times more than that of micromolecules. They improve the health and production of bovine at even lower doses. Being nanometer-sized, nano minerals can easily cross the animals' small intestines and spread into blood, brain, lung, heart, kidney, spleen, liver, intestines, and stomach. However, many factors, like, size, shape, zeta potential, other ligands, surface chemistry, age and species of animal, intestinal health, and dose of use, may affect the absorption and metabolism of these particles (Yılmaz *et al.,* 2023).

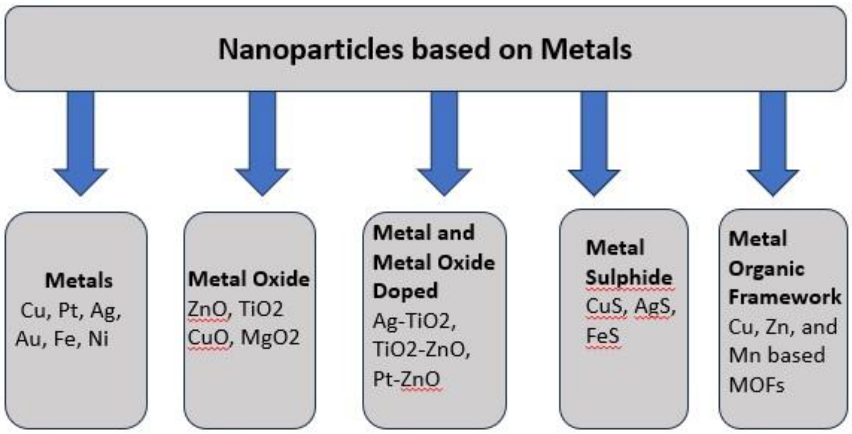

Fig. 4: Various types of metal-based nanomaterials

Metal Nanoparticles

Silver nanoparticles (AgNPs) are medical nanomaterials used commonly between the varied kinds of metal nanoparticles (metallic and metal oxide), they are detected to be most efficient against viruses, bacteria, and many other eukaryotic microbes because of their noticeable antibacterial characteristics and low toxic effect (Franci et al., 2015; Sharma et al., 2009; Chamundeeswari et al., 2010; (Mohamed *et al.,* 2024). It is thought to substitute antibiotics in the future due to its significant effect against many of the resistant pathogens. Silver ions work by allowing exposure of bacteria to harmful external factors as a result of depriving it of its protection when it interacts with its cell wall and cell membrane causing rupture and death of the cell (Siddiqi et al., 2018). They are also found in nucleic acids, disturb ribosomes, and basic functions of the cell (Salas Orozco et al., 2019; Haider et al., 2023) (Fig 5).

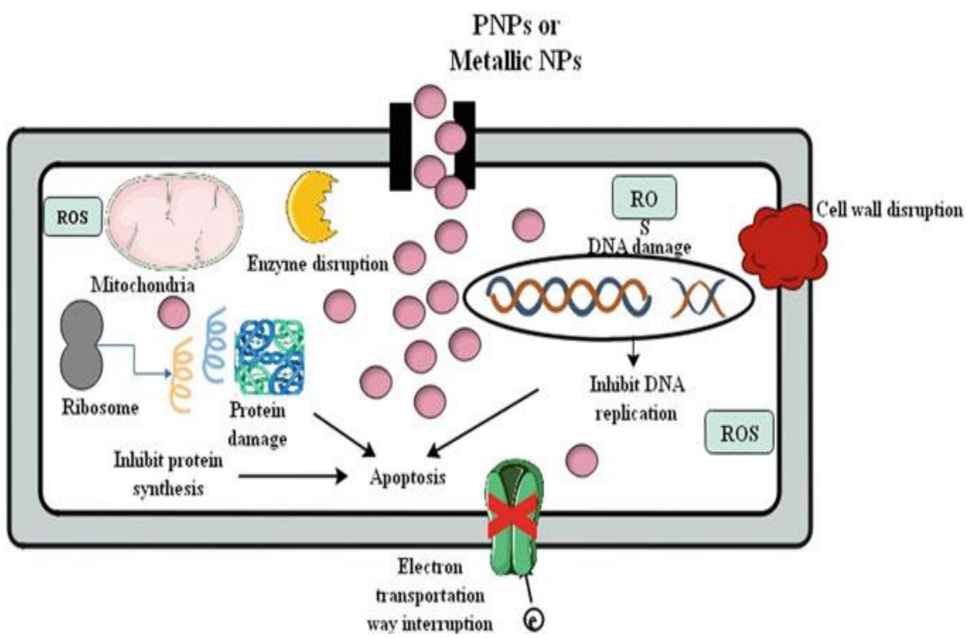

Fig. 5: Metal-based nanoparticle's general mechanism for antimicrobial potential (Haider et al., 2023)

There is an amplified antibacterial effect against both *S. aureus* and *E. coli,* which are common species of Gram-negative and Gram-positive bacteria, such as, when silver (Ag) nanoparticles and antibiotics including amoxicillin, penicillin G, vancomycin, and erythromycin are combined (Shahverdi et al., 2007; Fayaz et al., 2010). Moreover, green synthesized Ag NPs showed significant results against isolates of *Aspergillus species* and *Candida species* isolated from the milk of mastitis cows (Hasanin et al., 2022).

Copper nanoparticles (Cu NPs), have a high surface attention, and easy surface activation with other components so they have great potential as antimicrobials (Ingle et al., 2014). According to Seo et al. (2018), copper nanoparticles act on Methylobacterium species through inhibition of the growth of its biofilm, as well as highly resistant *Pseudomonas aeruginosa spp.* (LewisOscar et al., 2015; Mohamed et al., 2024).

Zinc Oxide, (ZnO) NPs can manufactured under harsh conditions and exhibit a specific toxic effects on bacterial cells, Additionally, it's thought that ZnO nanoparticles interfere with the cell membrane of bacteria, leading to the final bacterial death. (Sawai 2003). On the other hand, it has minimal effect on animal and human cells. Zinc oxide nanoparticles are considered as a potential medication carrier due to their antibacterial function against essential food-borne pathogens and because they are biocompatible and relatively harmless to humans (Roselli et al., 2003; Brayner et al., 2006).

Titanium Dioxide, (TiO_2) NPs were found to be the most for photocatalytic antibacterial activity (Gelover et al., 2006). Strong antibacterial action obtained by TiO_2 nanoparticles when exposed to UV beams. The Antimicrobial effect relies on the size, wavelength of the light source of the TiO_2 and intensity. The effective concentration to kill microbes is between 100 and 1000 parts per million. Furthermore, it was detected that the photocatalytic efficacy of TiO_2 as antimicrobial nanoparticles was reliant mostly on the thickness of the cellular membrane of the microbe (Kühn et al., 2003).

Gold, (Au NPs) have been employed to treat bacterial infection by irradiating with an appropriate wavelength (Sekhon and Kamboj, 2010). The antimicrobial activity of gold nanoparticles (Au NPs) was exhibited through Strong electric attraction to the cell membrane with a negative charge (Johnston et al., 2010). For example, gold nanoparticles (Au NPs) combined with anti-protein A that aim at the bacterial surface, have been found to selectively destroy *S. aureus* (Pissuwan et al., 2010). Bacteria were mostly destructed by the hyperthermic actions that were influenced by clustered gold nanoparticles (Au NPs). Strong antimicrobial effects obtained by gold nanoparticles coated with antibiotics, like streptomycin, neomycin, and gentamicin, have been searched in numerous studies against strains that are highly resistant to antibiotics, as well as both Gram-negative and positive (Grace and Pandian, 2007).

Chitosan is a polymeric nanoparticle and has an antimicrobial effect; the action of chitosan against variant kinds of bacteria, fungi, and yeasts is still not known (Guarnieri et al., 2022; Haider et al., 2023). The interactions between the microbial cell membranes which are negatively charged and the positively charged NH_3^+ sites of chitosan interfere with microbial cell permeability, which resulted in the release of intracellular material considered the most common mode of action of these particles (Tsai and Su, 1999; (Mohamed *et al.,* 2024); Chung and Chen, 2008) demonstrated that disruptions in the structure of *S. aureus* and *E. coli spp.* Occurred through the binding of chitosan to microbial enzymes and nucleotides. Chitosan exerts antibacterial action against both types of Gram bacteria (positive and negative) bacteria, where the difference in cell membrane structure is the main determinant of how chitosan acts.

Nanoemulsion, surfactant molecules coating a thin oil diffusion in aquatic solution, the mean size of this emulsion (ranged from 0.1 to 600 nm) can be affected by the concentration and mechanical energy of this surfactant. Nanoemulsions save protection and stability to active compounds by encapsulating them (Machado et al., 2020). Several studies were done on the antimicrobial activities of nanoemulsions and showed how they amplify the effect of antimicrobial drugs; this antimicrobial action is controlled by the physicochemical structure of nanoemulsions (Gırgın and Nadaroglu, 2024).

Panchal et al. (2024) demonstrated that higher effect of copper-oxide nanoparticles as antimicrobials compared to common antibiotics. Due to the toxic effect of higher concentrations of metal nanoparticles, so they are applied in a limited form. Triphala and Chitosan nanoparticles could be the solution to overcome copper toxicity in cattle.

Conclusion

Bovine mastitis is a significant challenge for veterinarians and academics. Further research is necessary to effectively manage mastitis. Microbial mutations causing antibiotic resistance pose a significant concern in the treatment of infectious diseases like mastitis. Antibiotic resistance is a global topic, addressed by both pharmaceutical businesses and academic researchers. Nanomaterials can improve antimicrobial medicine efficacy and open up new possibilities for antibacterial agent development due to their unique physicochemical properties. Nanoparticles can operate as antibiotic transporters, potentially addressing antimicrobial resistance. Nanoparticles have been studied as effective nano-antibiotics and delivery strategies to prevent antimicrobial resistance, potentially overcoming antibiotic resistance. This chapter discusses the role of nanoparticles in controlling and treating bovine mastitis.

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