Chapter 03

Application of Nanotechnology in Combating Bovine Mastitis

Mona Mohamed Hassan Soliman*, Nagwa Sayed Ata, Amany Ahmed Arafa and Mai Mohamed Kandil

Department of Microbiology and Immunology, National Research Centre, Egypt
*Corresponding author: mona_nrc.micro@yahoo.com

ABSTRACT

Mastitis is considered the costliest illness on dairy industry and also adversely influences animal welfare. As treatment and prevention of mastitis depend intensely on antibiotics, there are increasing attention in veterinary and human medicine regarding the emergence of antimicrobial resistance. Diverse strains of bacteria, fungus, and algae are capable of causing mastitis. Bacteria are the main cause of bovine mastitis causing destruction to the udder parenchyma. Antibiotics are the main strategy for treatment of mastitis. In any case, long-term utilize of antibiotics in mastitis treatment has caused the emergence of resistant pathogens. Researchers have looked for alternative therapeutic ways to antibiotics for mastitis treatment. Researcher's efforts together with the innovative invention of nanotechnology are crowned with success in mastitis therapy and management. As a result, nanotechnology may become the principal sort of mastitis treatment in the near future. The current chapter will discuss the role nanoparticles in controlling mastitis in dairy cow herds.

KEYWORDS
Nanotechnology, Bovine mastitis, Nanoantibiotics, Drug delivery, Antibiotic resistance

Received: 22-May-2024
Revised: 12-Jul-2024
Accepted: 19-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Soliman MMH, Ata NS, Arafa AA and Kandil MM, 2024. Application of nanotechnology in combating bovine mastitis. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 19-26. https://doi.org/10.47278/book.CAM/2024.117

INTRODUCTION

Bovine mastitis (BM) is considered the most common and economically significant infectious illness that can affect dairy farms worldwide as it can raise treatment, labor, and culling expenses, which may lead to large financial losses (Kotb et al., 2021). Over 40% from the 1.489 million cows that are supposed to exist worldwide suffer from some form of BM (Zhylkaidar et al., 2021).

The average annual cost of failure resulting from BM is projected to be 147 per cow worldwide. Each cow experiences yearly losses of 11–18% due to culling and decreased milk output (Hogeveen et al., 2019). The United States losses billion-dollar annual costs as a result of declining milk supply and quality, which has a major impact on animal husbandry, growing veterinary care costs, and rising farm management expenditures (Hertl et al., 2014). Indeed, BM is significant ailment because of the disease's greater impact worldwide and also output expense (Shaheen et al., 2015).

Mastitis also affects the milk's quality, which has implications that extend outside of the dairy farm. Although BM was primarily a problem for dairy farmers and producers, worries about antibiotic residues, antimicrobial resistance, milk quality, and animal welfare have made it a problem for consumers and society as a whole (Hogeveen et al., 2011).

Traditionally, BM has been defined as inflammation of the mammary glands, mostly due to bacterial infection. There are 137 distinct pathogenic bacteria in BM, the most common ones being *Streptococcus* species, *Escherichia coli* (*E. coli*), and *Staphylococcus aureus* (*S. aureus*) (Elbayoumy et al., 2024).

The elevated incidence and increased treatment rate of such very costly and possibly deadly malady are alarming for both the dairy industry and policymakers. Preventive ways, immunization programs and treatment of diseased animals are all required for the control of bacterial diseases in BM. A number of treatment and prevention programs have been established, with varying fruitful rates (Sharma and Jeong, 2013).

In spite of the reality that antibiotics are still the most commonly used treatment for BM, worries concerning the emergence of antibiotic-resistant bacteria are growing. This chapter will discuss an overview of diagnosis, control, antimicrobial drug delivery and remedy of BM using nanotechnology.

History of Nanotechnology Application in Veterinary Field

Nanotechnology alludes to dealing with the structure of materials, chemicals, or components at the nanoscale level, generating particles between1.0 nm and 100 nm (Ianiski et al., 2021).

In 1959, Ricahard Feynman fist illustrated the idea of nanomaterials within the lecture Plenty of Room in the Bottom at Nobel Prize, suggesting that arranging the atoms the way we want would be possible (Feynman, 1960). Kroto et al. (1985) discovered the fullerenes while Iijima (1991) succeed in synthesis of carbon nanotubes, nanotechnology and nanoscience –

once considered as fiction – was viewed as a practical technology (Ferreira and Rangel, 2009).

In 1991, a preparation technique that included molecular atomic control was proposed (Ferreira and Rangel, 2009). Subsequently, several areas of activity made contributions to nanotechnology. Chemistry, science, atomic material field, computer technology, fabric science, and mechanical and electrical building were some of them (Roco, 2011). A new field known as nanomedicine has emerged as a result of growing interest in the therapeutic uses of nanotechnology (Ianiski et al., 2021).

According to Feugang et al. (2019), nanotechnology is expected to have a significant impact on the livestock business in particular in the twenty-first century. Commercially available veterinary medicine products nowadays include scientifically approved nanoparticle medicines (Underwood and Van Eps, 2012). That explains how nanotechnology practice is becoming more and more relevant to veterinary field. The study of nanoparticles holds great promise for the diagnosis, control, and treatment of BM.

Infection Diagnosis and Antimicrobial Resistance Detection Assisted by Nanotechnology

Detection of infection and antimicrobial resistance can be performed using nanotechnology. Conventional diagnostic techniques used for microbial illnesses need sample preparation and take a long period of time to readout, despite the fact that microorganisms exhibit high sensitivity and repeatability (Kaittanis et al., 2010).

Newly nanoparticles with known magnetic, electrical, luminescent, and catalytic features can quickly, accurately, and affordably detect antimicrobial medications as well as quickly judge if they are resistant or susceptible to them (Rosi and Mirkin, 2005; Jain, 2007).

Antibody-coated nanoparticles have been shown to be able to start the signals needed to count and do bioanalysis of extremely dangerous bacteria, including *E. Coli* O157:H7. This enables the very easy, rapid, and highly focused identification of a single bacteria in a lab environment in roughly 20 minutes (Look et al., 2010).

Research showed that in microarray-based systems, nanoparticles with specific Raman spectroscopic signatures could be utilized to identify antibiotic-resistant bacterial strains, as MRSA (Methicillin Resistant *Staph aureus*), from non-resistant isolates using single-nucleotide polymorphisms (Li et al., 2009).

Magnetic nanoparticles can be extremely effective and sensitive techniques for diagnosis of bacterial manifestations. With the use of super-magnetic iron oxide nanoprobes, *Mycobacterium avium* species, paratuberculosis (MAP) in milk and blood has been quantified quickly and extremely sensitive (Basu et al., 2004).

Moreover, recent advances in nanotechnology have made it possible to create pharmacological and biopharmaceutical diagnostics for microbial infection that are both quick and accurate, eliminating the need to prepare samples in opaque media like milk or blood (Grossman et al., 2004; Tully et al., 2006).

Every branch of medicine has undergone a revolution due to the emergence of new nanotechnology techniques, including diagnosis, vaccine development, and treatment. Recent diagnostic techniques for the precise and timely detection of mastitis have been made possible by the quick advancement of nanotechnology. Utilizing nano-biosensors, a special class of analytical methods for mastitis identification, is one of these primary diagnostic methods. A biosensor is a device that binds a physical nano-transducer with bioreceptors specific to the antigen or chemical that is under investigation (Driskell and Tripp 2009).

These sensors look for specific biological substances using electric impulses. Based on the target molecule's characteristics, the type of transductor used, the signaling and recognition system, and the nanoparticle used, there are many different kinds of biosensors (Martins et al., 2019).

Nanotechnology in Prevention and Treatment of Infectious Illnesses

Several researches have been done on the use of nanoparticles as new medicines, colloidal vaccine carriers, and adjuvants. Particulate systems exhibit a distinct similarity in size of microbes. The immune system may easily identify the microbe and nanoparticles as they are nearly similar in size to bacteria and viruses (Peek et al., 2008). Varied special vaccine carrier characteristics as size, chemical structure, charge, and surface features can also be modified to improve phagocytosis with mononuclear phagocytic system (MPS), which promotes the immunological presentation of antigens and the activation of antigen-presenting cells (APs) (Singh et al., 2007; Rice-Ficht et al., 2010).

Studies conducted in vivo investigated combinations of nanoemulsions containing proteins (as, recombinant *Bacillus anthracis* [*B. anthracis*] protective antigens) or entire viruses, such as the influenza virus, as possible vaccines (Myc et al., 2003; Bielinska et al., 2007). This vaccine can be delivered by mucosal routes and does not require cold storage, making it especially appropriate for immunization in many underdeveloped nations.

Effective Antimicrobial Medication Delivery using Nanoparticles

Liposomes: They are vesicles that are nano- to micro-sized, aqueous-cored and made of a phospholipid bilayer. Following the FDA's 1995 approval of Doxil as the first liposomal medication, liposomes have been investigated as a potentially effective therapeutically acceptable drug, protein, and enzyme delivery system (Lian and Ho, 2001; Torchilin, 2005).

Liposomes are widely used as antimicrobial drug delivery vehicles due to their lipid bilayer structure which resembles a cell membrane that readily fuses with the infectious microorganisms (Zhang et al., 2010).

Moreover, without undergoing chemical changes, lipophilic and hydrophilic antimicrobial medications may be

encapsulated and kept within the phospholipid bilayer and the aqueous core, correspondingly. The application of liposomes as antimicrobial drug delivery tools should take into account a number of factors, including the physico-chemical properties of lipids, the drugs to be loaded, the liposomes' particle size and polydispersity, surface charge (zeta-potential), stability in storage (shelf-life), repeatability, and viability in large-scale production (Lasic, 1998).

Increased in vivo stability was the outcome of conjugating liposomes with stealth compounds like polyethylene glycol, or PEG, on their surface. The platform can also be coupled with different targeted ligands, such as tiny compounds, aptamers, peptides, antibodies, and antibody fragments, for the purpose of targeted administration of antimicrobial medicines (Maruyama et al., 1990; Pinto-Alphandary et al., 2000).

Benzyl penicillin-encapsulating cationic liposomes was found to totally prevent the growth of *S. aureus* strain in one study, when compared to free medicines, with shorter exposure periods and lower drug concentrations (Kim and Jones, 2004).

Liposomal amikacin investigated changes in tissue distribution and notably prolonged half-life (tissue 63–465 h, blood 24.5 h) (Gangadharam et al., 1991). Extended blood circulation and improved localization were demonstrated by liposomal gentamicin and ceftazidime at the infection site (Bakker-Woudenberg et al., 1995). Significantly more intracellular MRSA infection was eliminated when vancomycin and teicoplanin-encapsulated liposomes were used (Onyeji et al., 1994).

Traditional antibiotics are not very efficient in treating cow mastitis, even though the bacteria are susceptible to them in vitro as the drugs are not well absorbed into the cells, especially by the phagocytes of the udder (Jain and Banerjee, 2008).

Antibiotics and other antimicrobial medications could be delivered utilizing liposomes and nanoparticles that can both protect the drug from the physiological milieu of bovines and help in its cellular uptake. Antibiotics have been added to polymeric nanoparticles, liposomes, and drug-loaded delivery vehicles, all of which have been shown to improve antibiotic intracellular delivery (Alving, 1988; Gruet et al., 2001).

Antibiotics from different families can be combined in nanoparticulate formulations (Müller, 1991). In order to prolong the release and prevent drug degradation. Because of all these qualities, using nanoparticles to treat bovine mastitis is a very suitable option. It has been demonstrated that solid lipid, metal, and polymeric nanoparticles are useful in the treatment and detection of bacterial infections causing mastitis in cows (Henry-Michelland et al., 1987; Spain et al., 2011; Mujawar et al., 2013).

Examples of Nanomaterials used in Antimicrobial Dosage form

There is increase in using nanoparticles in the veterinary, pharmaceutical, and medical fields due to their unique characteristics. The most developing scientific field in the world is nanotechnology. Nanomaterials have special properties both physically and chemically, and due to its large surface area compared to volume, they can be used to treat illnesses like mastitis in dairy cows (Algharib et al. 2020).

A new study had assured that bacteria shouldn't acquire antimicrobial resistance against metal nanoparticles. Apart from treating microbes with nanoparticle materials, the nanoparticles can also be synthesized using bacterial cells or enzymes. Current research has explored the production of metallic nanoparticles, such as gold [Au] and silver [Ag], either extracellularly or intracellularly, utilizing enzymes or microbes to produce biosynthetic nanoparticles (Holmes et al., 1995; Saravanan and Nanda, 2010).

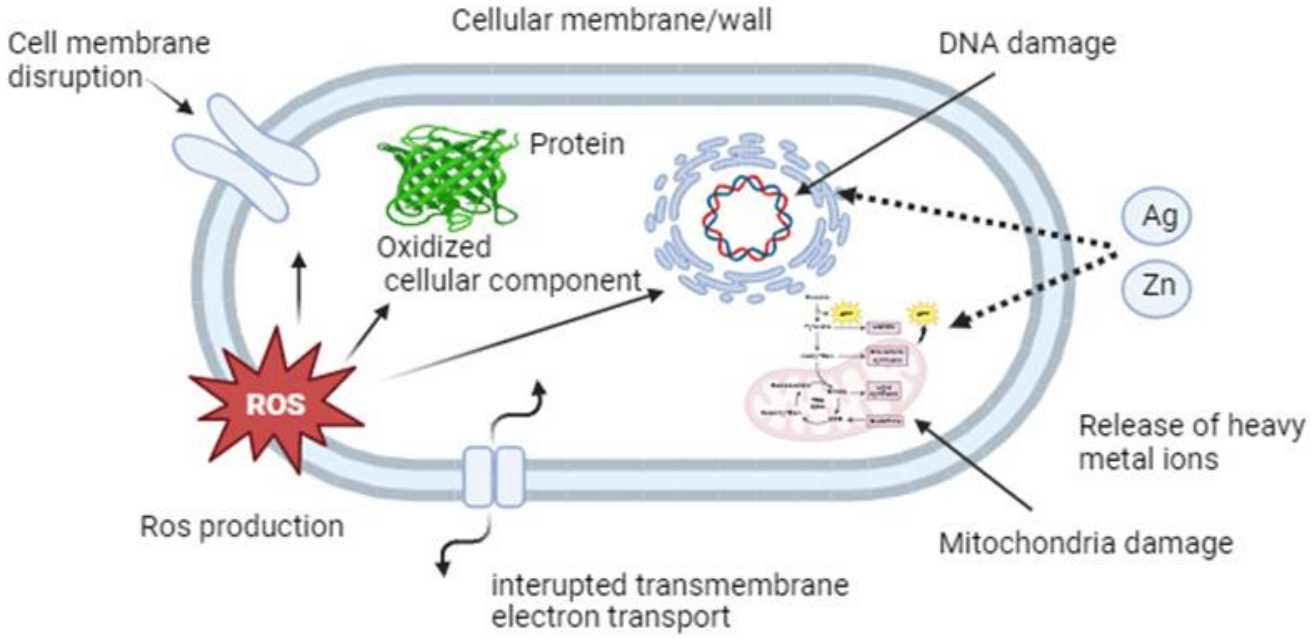

Fig. 1: Antimicrobial mechanisms of nanoparticles.

As seen in (Fig. 1), the antibacterial nanoparticles can destruct bacterial via a variety of methods as described by (Maness et al., 1999 and Rabea et al., 2003).

1) The generation of reactive oxygen species (ROS) via photocatalysis, which harms viral and cellular constituents.
2) Compromising the cell wall and membrane of the bacteria.
3) The transmission of energy is interrupted.
4) Reduction of DNA synthesis and the activity of enzymes.

Silver NPs

Silver (Ag) nanoparticles have been shown to be the most efficient against viruses, bacteria, and many other eukaryotic microbes among the varied kinds of metallic and metal oxide nanoparticles (Sharma et al., 2009; Chamundeeswari et al., 2010). Silver (Ag) nanoparticles release silver ions that boost antibacterial action while simultaneously gaining access to cell division and, the respiratory chain which ultimately cause cellular death (Klasen, 2000). The size of silver (Ag) nanoparticles has an inverse relationship with their antibacterial activity (Sondi and Salopek-Sondi, 2004; Raimondi et al., 2005). When silver (Ag) nanoparticles and antibiotics including amoxicillin, penicillin G, vancomycin, and erythromycin are used together, the antibacterial actions against both Gram-negative and Gram-positive bacteria are enhanced and work in concert, such as *E. coli* and *S. aureus* (Shahverdi et al., 2007; Fayaz et al., 2010). Moreover, green synthesized Ag NPs gave highly significant results against isolates of *Candida* species. and *Aspergillus* species isolated from mastitic cow milk (Hasanin et al., 2022).

Zinc Oxide (ZnO) NPs

Certain metal oxide nanoparticles, like zinc oxide, can withstand harsh manufacturing conditions and exhibit specific bacterial toxicity while having minimal impact on animal and human cells. The antibacterial activity of zinc oxide nanoparticles, or ZnO NPs, against important food-borne pathogens such enterotoxigenic *E. coli* and *E. coli* O157:H7 is being investigated as a potential medication carrier, and because they are biocompatible and relatively harmless to humans (Roselli et al., 2003; Brayner et al., 2006). In compared with silver nanoparticles (Ag NPs), it is more favorable in a number of ways, including cheap manufacturing expenses, UV-blocking properties, and a white look that contributes to light reflection characteristics that are helpful in sunscreen usage (Dastjerdi and Montazer, 2010). Additionally, it's thought that ZnO nanoparticles damage the lipids and proteins in the bacterial cell membrane, causing intracellular contents to seep out and the final death of the bacteria (Sawai, 2003).

Titanium Dioxide (TiO2) NPs

Of all the metal, metal oxide, and sulfur dioxide nanoparticles, titanium dioxide nanoparticles have been researched the most for photocatalytic antibacterial activity (Gelover et al., 2006). Strong antibacterial action is displayed by TiO2 nanoparticles when exposed to UV-A and near-UV beams. The required concentration needed to kill microbes is between 100 and 1000 parts per million. The strength of antimicrobial effect is dependent on the size, intensity, and wavelength of the light source of the TiO2 nanomaterials. According to a novel study, *E. coli* > *P. aeruginosa* > *S. aureus* > *E. faecium* > *C. albicans* is the decreasing order in which TiO2 nanoparticles' antimicrobial activity is recorded. The antimicrobial activity depends mainly on the density and the complexity of the cell wall or membrane of the targeted microbe. Furthermore, it was observed that the photocatalytic antibacterial efficacy of TiO2 nanoparticles was mostly dependent on the thickness of the cellular membrane or sheath structure of the microbe, and decreased in the following order: virus > bacterial wall > bacterial spore (Kühn et al., 2003). The generation of ROS, like peroxide and free hydroxyl radicals, is primarily responsible for the photocatalytic antibacterial action of TiO2 (Choi et al., 2007).

Gold (Au) NPs

By irradiating with the appropriate wavelengths, a range of nanoparticles, including near infrared light-absorbing gold (Au) nanoparticles, nanoshells, nanorods, and nanocages, have been employed to treat bacterial illness (Sekhon and Kamboj, 2010). Strong electrostatic attractions to the negatively charged cell membrane bilayer are the primary mechanism by which gold nanoparticles (Au NPs) exhibit antimicrobial activity (Johnston et al., 2010). To find selective antimicrobial effects, gold nanoparticles (Au NPs) conjugated with antimicrobial agents and antibodies have been studied. For example, gold nanoparticles (Au NPs) combined with anti-protein A-antibodies that target the bacterial surface, have been found to selectively destruct *S. aureus* (Pissuwan et al., 2010). Bacteria were efficiently harmed by the process of strong laser-induced hyperthermic actions that were followed by bubble arrangement around clustered gold nanoparticles (Au NPs). Strong antimicrobial agent effects by gold/drug nanocomposites, such as gold nanoparticles coated with antibiotics like streptomycin, neomycin, and gentamicin, have been reported in numerous studies against both Gram-positive and Gram-negative bacteria, as well as antibiotic-resistant strains (Grace and Pandian, 2007).

Chitosan

Many different types of bacteria, fungi, and yeasts can be inhibited by chitosan through various processes that are not all fully understood (Guarnieri et al., 2022). The most straightforward mode of action includes electrostatic interactions between the negatively charged microbial cell membranes and the positively charged NH3+ sites of chitosan. Intracellular

material is released as a result of the contact changing the microbial cell's permeability (Tsai and Su, 1999). Chitosan's binding to microbial enzymes and nucleotides can cause disruptions in the cell structure of *S. aureus* and *E. coli,* as demonstrated by Chung and Chen (2008). Chitosan displays antibacterial action in its polycationic shape against both Gram-positive and Gram-negative bacteria, with its mode of action differing based on the special cell membrane structure. While the negatively charged peptidoglycan and teichoic acidsare found in the cell wall layer of Gram-positive bacteria, chitosan directly interacts with these negatively charged structures in Gram-negative bacteria. These anionic structures include lipopolysaccharides and proteins (Nikaido and Vaara, 1985). There is no accurate information regarding on which bacteria the chitosan is more effective against. Indeed, some researchers as Chung et al. (2004) and Devlieghere et al. (2004) reported a more potent bactericidal effect on Gram-negative bacteria, whilst other writers (No et al., 2002; Fernandez-Saiz et al., 2009) showed a more potent effect on Gram-positive bacteria.

Nanoemulsion

An interfacial coating of surfactant molecules stabilizes a thin oil dispersion in water, forming nanoemulsions. The concentration, content, and mechanical energy of surfactants can affect the mean droplet size, which can range from 0.1 to 600 nm. By encapsulating the active compounds, nanoemulsions offer protection and stability to those compounds, as well as increasing the penetration power of the target compounds for more effective application (Machado et al., 2020). The antimicrobial activities of nanoemulsions have been highly studied in several studies, and the results show how effective they work to distribute and intensify the effect of antimicrobial drugs. For example, nanoemulsions including essential oils, as citral, have shown noteworthy antibacterial action. It has been found that the antimicrobial action of nanoemulsions are greatly affected by their configuration, underscoring the need of comprehending the physicochemical features of these systems (Gırgın and Nadaroglu, 2024).

Conclusion

The incidence of mastitis is incredibly increasing in farm animals as buffaloes and cows. To control mastitis, more strategic study in this area is needed. Veterinarians and mastitis researchers continue to face significant challenges due to bovine mastitis. When treating infectious disorders like mastitis, the emergence of antibiotic resistance caused by microbial variations poses a significant risk. Pharmaceutical corporations and academic researchers alike are addressing the global concern of antibiotic resistance development. The distinct physicochemical characteristics of diverse nanomaterials hold the potential to enhance the efficacy of current antimicrobial drugs and provide novel avenues for antibacterial agent development. It appears that using the characteristics of nanoparticles as antibiotic carriers appears to be one way to combat antimicrobial resistance. Numerous nanoparticles have been investigated as effective nanoantibiotics and antibiotic delivery systems that shield antimicrobial medications from resistance mechanisms. The importance nanoparticles in diagnosis, control, antimicrobial drug delivery and treatment of bovine mastitis was discussed in this chapter. Most significantly, using numerous independent and perhaps synergistic techniques on the same platform to boost antibacterial action is possible by nanoparticles and also can defeat antibiotic resistance. In an era where antibiotic resistance is growing, finding effective, safe, affordable, and tailored therapy for bovine mastitis necessitates interdisciplinary understanding and cutting-edge techniques from the fields of microbiology, immunology, biomaterials, polymers, and nanotechnology.

REFERENCES

Algharib, S. A., Dawood, A., and Xie, S. (2020). Nanoparticles for treatment of bovine Staphylococcus aureus mastitis. *Drug Delivery, 27*(1), 292-308.

Alving, C. R. (1988). Macrophages as targets for delivery of liposome-encapsulated antimicrobial agents. *Advanced Drug Delivery Reviews, 2*(1), 107-128.

Bakker-Woudenberg, I. A., Ten Kate, M. T., Stearne-Cullen, L. E. T., and Woodle, M. C. (1995). Efficacy of gentamicin or ceftazidime entrapped in liposomes with prolonged blood circulation and enhanced localization in Klebsiella pneumoniae-infected lung tissue. *Journal of Infectious Diseases, 171*(4), 938-947.

Basu, M., Seggerson, S., Henshaw, J., Jiang, J., del A Cordona, R., Lefave, C., and Basu, S. (2004). Nano-biosensor development for bacterial detection during human kidney infection: use of glycoconjugate-specific antibody-bound gold NanoWire arrays (GNWA). *Glycoconjugate Journal, 21*, 487-496.

Bielinska, A. U., Janczak, K. W., Landers, J. J., Makidon, P., Sower, L. E., Peterson, J. W., and Baker Jr, J. R. (2007). Mucosal immunization with a novel nanoemulsion-based recombinant anthrax protective antigen vaccine protects against Bacillus anthracis spore challenge. *Infection and Immunity, 75*(8), 4020-4029.

Brayner, R., Ferrari-Iliou, R., Brivois, N., Djediat, S., Benedetti, M. F., and Fiévet, F. (2006). Toxicological impact studies based on Escherichia coli bacteria in ultrafine ZnO nanoparticles colloidal medium. *Nano Letters, 6*(4), 866-870.

Chamundeeswari, M., Sobhana, S. L., Jacob, J. P., Kumar, M. G., Devi, M. P., Sastry, T. P., and Mandal, A. B. (2010). Preparation, characterization and evaluation of a biopolymeric gold nanocomposite with antimicrobial activity. *Biotechnology and Applied Biochemistry, 55*(1), 29-35.

Choi, J. Y., Kim, K. H., Choy, K. C., Oh, K. T., and Kim, K. N. (2007). Photocatalytic antibacterial effect of TiO2 film formed on

Ti and TiAg exposed to Lactobacillus acidophilus. Journal of Biomedical Materials Research Part B: Applied Biomaterials: An Official Journal of the Society for Biomaterials, *The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials, 80*(2), 353-359.

Chung, Y. C., and Chen, C. Y. (2008). Antibacterial characteristics and activity of acid-soluble chitosan. *Bioresource Technology, 99*(8), 2806-2814.

Chung, Y. C., Su, Y. P., Chen, C. C., Jia, G., Wang, H. L., Wu, J. G., and Lin, J. G. (2004). Relationship between antibacterial activity of chitosan and surface characteristics of cell wall. *Acta Pharmacologica Sinica, 25*(7), 932-936.

Dastjerdi, R., and Montazer, M. (2010). A review on the application of inorganic nano-structured materials in the modification of textiles: focus on anti-microbial properties. *Colloids and Surfaces B: Biointerfaces, 79*(1), 5-18.

Devlieghere, F., Vermeulen, A., and Debevere, J. (2004). Chitosan: antimicrobial activity, interactions with food components and applicability as a coating on fruit and vegetables. *Food Microbiology, 21*(6), 703-714.

Driskell, J. D., and Tripp, R. A. (2009). Emerging technologies in nanotechnology-based pathogen detection. *Clinical Microbiology Newsletter, 31*(18), 137-144.

Elbayoumy, M. K., Allam, A. M., Ghazy, A. A., and Nasr, S. M. (2024). Advances in Controlling Bacterial Mastitis in Dairy Cows. *Egyptian Journal of Veterinary Sciences, 55*(1), 1-21.

Fayaz, A. M., Balaji, K., Girilal, M., Yadav, R., Kalaichelvan, P. T., and Venketesan, R. (2010). Biogenic synthesis of silver nanoparticles and their synergistic effect with antibiotics: a study against gram-positive and gram-negative bacteria. *Nanomedicine: Nanotechnology, Biology and Medicine, 6*(1), 103-109.

Fernandez-Saiz, P., Lagaron, J. M., and Ocio, M. J. (2009). Optimization of the film-forming and storage conditions of chitosan as an antimicrobial agent. *Journal of Agricultural and Food Chemistry, 57*(8), 3298-3307.

Ferreira, H. S., and Rangel, M. D. C. (2009). Nanotechnology: general aspects and potential applications in catalysis. *Química Nova, 32*, 1860-1870. Available from: <https://www.scielo.br/scielo. php?script=sci_arttextandpid=S0100-40422009000700033>. doi: 10.1590/S0100-40422009000700033.

Feugang, J. M., Rhoads, C. E., Mustapha, P. A., Tardif, S., Parrish, J. J., Willard, S. T., and Ryan, P. L. (2019). Treatment of boar sperm with nanoparticles for improved fertility. *Theriogenology, 137*, 75-81. Available from: <https://pubmed.ncbi.nlm. nih.gov/31204016/>. doi: 10.1016/j. theriogenology.2019.05.040.

Feynman, R. P. (1960). There's plenty of room at the bottom. *Engineering and Science, 23*, 22–36. Available from: < https://resolver.caltech.edu/CaltechES:23.5.1960Bottom >.

Gangadharam, P. R., Ashtekar, D. A., Ghori, N., Goldstein, J. A., Debs, R. J., and Düzgünes, N. (1991). Chemotherapeutic potential of free and liposome encapsulated streptomycin against experimental Mycobacterium avium complex infections in beige mice. *Journal of Antimicrobial Chemotherapy, 28*(3), 425-435.

Gelover, S., Gómez, L. A., Reyes, K., and Leal, M. T. (2006). A practical demonstration of water disinfection using TiO2 films and sunlight. *Water research, 40*(17), 3274-3280.

Gırgın, H., and Nadaroglu, H. (2024). Exploring the Synthesis of Nanoemulsions and Assessing Their Antimicrobial Effects. *Pharmata, 4*(2), 49-57.

Goy, R. C., Britto, D. D., and Assis, O. B. (2009). A review of the antimicrobial activity of chitosan. *Polímeros, 19*, 241-247.

Grace, A. N., and Pandian, K. (2007). Antibacterial efficacy of aminoglycosidic antibiotics protected gold nanoparticles—A brief study. *Colloids and Surfaces A: Physicochemical and Engineering Aspects, 297*(1-3), 63-70.

Grossman, H. L., Myers, W. R., Vreeland, V. J., Bruehl, R., Alper, M. D., Bertozzi, C. R., and Clarke, J. (2004). Detection of bacteria in suspension by using a superconducting quantum interference device. *Proceedings of the National Academy of Sciences, 101*(1), 129-134.

Gruet, P., Maincent, P., Berthelot, X., and Kaltsatos, V. (2001). Bovine mastitis and intramammary drug delivery: review and perspectives. *Advanced Drug Delivery Reviews*, 50(3), 245-259. https://doi.org/10.1016/s0169-409x(01)00160-0

Guarnieri, A., Triunfo, M., Scieuzo, C., Ianniciello, D., Tafi, E., Hahn, T., and Falabella, P. (2022). Antimicrobial properties of chitosan from different developmental stages of the bioconverter insect Hermetia illucens. *Scientific Reports, 12*(1), 8084.

Hasanin, M. S., Emam, M., Soliman, M. M., Latif, R. R. A., Salem, M. M., El Raey, M. A., and Eisa, W. H. (2022). Green silver nanoparticles based on Lavandula coronopifolia aerial parts extract against mycotic mastitis in cattle. *Biocatalysis and Agricultural Biotechnology, 42*, 102350.

Henry-Michelland, S., Alonso, M. J., Andremont, A., Maincen, P., Sauzieres, J., and Couvreur, P. (1987). Attachment of antibiotics to nanoparticles: preparation, drug-release and antimicrobial activity in vitro. *International Journal of Pharmaceutics, 35*(1-2), 121-127.

Hertl, J. A., Schukken, Y. H., Welcome, F. L., Tauer, L. W., and Gröhn, Y. T. (2014). Effects of pathogen-specific clinical mastitis on probability of conception in Holstein dairy cows. *Journal of Dairy Science*, 97(11), 6942-6954. https:// doi.org/10.3168/jds.2014-8203

Hogeveen, H., Pyorala, S., Waller, K. P., Hogan, J. S., Lam, T. J., Oliver, S. P., and Hillerton, J. E. (2011). Current status and future challenges in mastitis research. In *Proceedings of the 50th Annual Meeting of the National Mastitis Council, 23-26 January, 2011, Arlington, USA* (pp. 36-48).

Hogeveen, H., Steeneveld, W., and Wolf, C. A. (2019). Production diseases reduce the efficiency of dairy production: A review of the results, methods, and approaches regarding the economics of mastitis. *Annual Review of Resource*

Economics, 11, 289-312. https://doi.org/10.1146/ annurev-resource-100518-093954

Holmes, J. D., Smith, P. R., Evans-Gowing, R., Richardson, D. J., Russell, D. A., and Sodeau, J. R. (1995). Energy-dispersive X-ray analysis of the extracellular cadmium sulfide crystallites of Klebsiella aerogenes. *Archives of Microbiology, 163*, 143-147.

Ianiski, L. B., Rodrigues, F. D. S., Stibbe, P. C., Weiblen, C., Pereira, D. I. B., Santurio, J. M., and Botton, S. D. A. (2021). Nanotechnology in veterinary medicine: a review. *Ciência Rural, 52,* e20210195.

Iijima, S. (1991). Helical microtubules of graphitic carbon. *Nature, 354*(6348), 56-58. Available from: <https://www.nature.com/articles/354056a0>. doi: 10.1038/354056a0.

Jain, D., and Banerjee, R. (2008). Comparison of ciprofloxacin hydrochloride-loaded protein, lipid, and chitosan nanoparticles for drug delivery. *Journal of Biomedical Materials Research Part B: Applied Biomaterials: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials, 86*(1), 105-112.

Jain, K. K. (2007). Applications of nanobiotechnology in clinical diagnostics. *Clinical Chemistry, 53*(11), 2002-2009.

Johnston, H. J., Hutchison, G., Christensen, F. M., Peters, S., Hankin, S., and Stone, V. (2010). A review of the in vivo and in vitro toxicity of silver and gold particulates: particle attributes and biological mechanisms responsible for the observed toxicity. *Critical Reviews in Toxicology, 40*(4), 328-346.

Kaittanis, C., Santra, S., and Perez, J. M. (2010). Emerging nanotechnology-based strategies for the identification of microbial pathogenesis. *Advanced Drug Delivery Reviews*, 62(4-5), 408-423.

Kim, H. J., and Jones, M. N. (2004). The delivery of benzyl penicillin to Staphylococcus aureus biofilms by use of liposomes. *Journal of Liposome Research, 14*(3-4), 123-139.

Klasen, H. J. (2000). Historical review of the use of silver in the treatment of burns. I. Early uses. *Burns, 26*(2), 117-130.

Kotb, E. E., M EL Sawah, A., E Kortam, L., A Abd El Fattah, O., and M Barghooth, W. (2021). Evaluation of using different adjuvants used for preparation of Staphylococcus aureus mastitis vaccine on the immune response. *Journal of Applied Veterinary Sciences*, 6(1), 9-17. https://doi.org/10.21608/ javs.2021.140065

Kroto, H. W., Heath, J. R., O'Brien, S. C., Curl, R. F., and Smalley, R. E. (1985). C60: Buckminsterfullerene. *Nature*, 318(6042), 162-163. Available from: https://garfield.library.upenn.edu/classics1993/A1993LT56300001.pdf. doi: 10.1038/318162a0.

Kühn, K. P., Chaberny, I. F., Massholder, K., Stickler, M., Benz, V. W., Sonntag, H. G., and Erdinger, L. (2003). Disinfection of surfaces by photocatalytic oxidation with titanium dioxide and UVA light. *Chemosphere, 53*(1), 71-77.

Lasic, D. D. (1998). Novel applications of liposomes. *Trends in Biotechnology, 16*(7), 307-321.

Li, M., Hu, B., Li, J., Chen, R., Zhang, X., and Chen, H. (2009). Extractive electrospray ionization mass spectrometry toward in situ analysis without sample pretreatment. *Analytical Chemistry, 81*(18), 7724-7731.

Lian, T., and Ho, R. J. (2001). Trends and developments in liposome drug delivery systems. *Journal of Pharmaceutical Sciences, 90*(6), 667-680.

Look, M., Bandyopadhyay, A., Blum, J. S., and Fahmy, T. M. (2010). Application of nanotechnologies for improved immune response against infectious diseases in the developing world. *Advanced Drug Delivery Reviews, 62*(4-5), 378-393.

Machado, G. T. P., Veleirinho, M. B., Honorato, L. A., and Kuhnen, S. (2020). Formulation and evaluation of anti-MRSA nanoemulsion loaded with Achyrocline satureioides: a new sustainable strategy for the bovine mastitis. *Nano Express, 1*(3), 030004.

Maness, P. C., Smolinski, S., Blake, D. M., Huang, Z., Wolfrum, E. J., and Jacoby, W. A. (1999). Bactericidal activity of photocatalytic TiO2 reaction: toward an understanding of its killing mechanism. *Applied and Environmental Microbiology, 65*(9), 4094-4098.

Martins, S. A., Martins, V. C., Cardoso, F. A., Germano, J., Rodrigues, M., Duarte, C., and Freitas, P. P. (2019). Biosensors for on-farm diagnosis of mastitis. *Frontiers in Bioengineering and Biotechnology, 7*, 186.

Maruyama, K., Kennel, S. J., and Huang, L. (1990). Lipid composition is important for highly efficient target binding and retention of immunoliposomes. *Proceedings of the National Academy of Sciences, 87*(15), 5744-5748.

Mujawar, L. H., Moers, A., Norde, W., and van Amerongen, A. (2013). Rapid mastitis detection assay on porous nitrocellulose membrane slides. *Analytical and Bioanalytical Chemistry, 405*, 7469-7476.

Müller, R. H. (1991). Colloidal carriers for controlled drug delivery and targeting: Modification, characterization and in vivo distribution. Taylor and Francis.

Myc, A., Kukowska-Latallo, J. F., Bielinska, A. U., Cao, P., Myc, P. P., Janczak, K., and Baker Jr, J. R. (2003). Development of immune response that protects mice from viral pneumonitis after a single intranasal immunization with influenza A virus and nanoemulsion. *Vaccine, 21*(25-26), 3801-3814.

Nikaido, H., and Vaara, M. (1985). Molecular basis of bacterial outer membrane permeability. *Microbiological Reviews, 49*(1), 1-32.

No, H. K., Park, N. Y., Lee, S. H., and Meyers, S. P. (2002). Antibacterial activity of chitosans and chitosan oligomers with different molecular weights. *International Journal of Food Microbiology, 74*(1-2), 65-72.

Onyeji, C. O., Nightingale, C. H., and Marangos, M. N. (1994). Enhanced killing of methicillin-resistant Staphylococcus aureus in human macrophages by liposome-entrapped vancomycin and teicoplanin. *Infection, 22*, 338-338.

Peek, L. J., Middaugh, C. R., and Berkland, C. (2008). Nanotechnology in vaccine delivery. *Advanced Drug Delivery Reviews, 60*(8), 915-928.

Pinto-Alphandary, H., Andremont, A., and Couvreur, P. (2000). Targeted delivery of antibiotics using liposomes and nanoparticles: research and applications. *International Journal of Antimicrobial Agents, 13*(3), 155-168.

Pissuwan, D., Cortie, C. H., Valenzuela, S. M., and Cortie, M. B. (2010). Functionalised gold nanoparticles for controlling pathogenic bacteria. *Trends in Biotechnology, 28*(4), 207-213.

Rabea, E. I., Badawy, M. E. T., Stevens, C. V., Smagghe, G., and Steurbaut, W. (2003). Chitosan as antimicrobial agent: applications and mode of action. *Biomacromolecules, 4*(6), 1457-1465.

Raimondi, F., Scherer, G. G., Kötz, R., and Wokaun, A. (2005). Nanoparticles in energy technology: examples from electrochemistry and catalysis. *Angewandte Chemie International Edition*, 44(15), 2190-2209.

Rice-Ficht, A. C., Arenas-Gamboa, A. M., Kahl-McDonagh, M. M., and Ficht, T. A. (2010). Polymeric particles in vaccine delivery. *Current Opinion in Microbiology, 13*(1), 106-112.

Roco, M. C. (2011). The long view of nanotechnology development: the National Nanotechnology Initiative at 10 years. *Journal of Nanoparticle Research, 13*, 427-445. Available from: <https://link.springer.com/article/10.1007/s11051-010-0192-z>. doi: 10.1007/s11051-010-0192-z.

Roselli, M., Finamore, A., Garaguso, I., Britti, M. S., and Mengheri, E. (2003). Zinc oxide protects cultured enterocytes from the damage induced by Escherichia coli. *The Journal of Nutrition, 133*(12), 4077-4082.

Rosi, N. L., and Mirkin, C. A. (2005). Nanostructures in biodiagnostics. *Chemical Reviews, 105*(4), 1547-1562.

Saravanan, M., and Nanda, A. (2010). Extracellular synthesis of silver bionanoparticles from Aspergillus clavatus and its antimicrobial activity against MRSA and MRSE. Colloids *and Surfaces B: Biointerfaces, 77*(2), 214-218.

Sawai, J. (2003). Quantitative evaluation of antibacterial activities of metallic oxide powders (ZnO, MgO and CaO) by conductimetric assay. *Journal of Microbiological Methods*, 54(2), 177-182.

Sekhon, B. S., and Kamboj, S. R. (2010). Inorganic nanomedicine—part 2. *Nanomedicine: Nanotechnology, Biology and Medicine, 6*(5), 612-618.

Shaheen, M., Ha, T. and Su, N. (2015). A treatise on bovine mastitis: disease and disease economics, etiological basis, risk factors, impact on human health, therapeutic management, prevention and control strategy. *Advances in Dairy Research, 4*, 1–10. https://doi.org/10.4172/2329-888X.1000150.

Shahverdi, A. R., Fakhimi, A., Shahverdi, H. R., and Minaian, S. (2007). Synthesis and effect of silver nanoparticles on the antibacterial activity of different antibiotics against Staphylococcus aureus and Escherichia coli. *Nanomedicine: Nanotechnology, Biology and Medicine, 3*(2), 168-171.

Sharma, N., and Jeong, D. K. (2013). Stem cell research: a novel boulevard towards improved bovine mastitis management. *International Journal of Biological Sciences, 9*(8), 818. https:// doi.org/10.7150/ijbs.6901

Sharma, V. K., Yngard, R. A., and Lin, Y. (2009). Silver nanoparticles: green synthesis and their antimicrobial activities. *Advances in Colloid and Interface Science*, 145(1-2), 83-96.

Singh, M., Chakrapani, A., and O'Hagan, D. (2007). Nanoparticles and microparticles as vaccine-delivery systems. *Expert Review of Vaccines, 6*(5), 797-808.

Sondi, I., and Salopek-Sondi, B. (2004). Silver nanoparticles as antimicrobial agent: a case study on E. coli as a model for Gram-negative bacteria. *Journal of Colloid and Interface Science, 275*(1), 177-182.

Spain, E., Kojima, R., Kaner, R. B., Wallace, G. G., O'Grady, J., Lacey, K., and Forster, R. J. (2011). High sensitivity DNA detection using gold nanoparticle functionalised polyaniline nanofibres. *Biosensors and Bioelectronics, 26*(5), 2613-2618.

Torchilin, V. P. (2005). Recent advances with liposomes as pharmaceutical carriers. *Nature Reviews Drug Discovery*, 4(2), 145-160.

Tsai, G. J., and Su, W. H. (1999). Antibacterial activity of shrimp chitosan against Escherichia coli. *Journal of Food Protection, 62*(3), 239-243.

Tully, E., Hearty, S., Leonard, P., and O'Kennedy, R. (2006). The development of rapid fluorescence-based immunoassays, using quantum dot-labelled antibodies for the detection of Listeria monocytogenes cell surface proteins. *International Journal of Biological Macromolecules, 39*(1-3), 127-134.

Underwood, C., and Van Eps, A. W. (2012). Nanomedicine and veterinary science: The reality and the practicality. *The Veterinary Journal*, 193(1), 12-23. Available from: <https://pubmed.ncbi.nlm.nih. gov/22365842/>. doi: 10.1016/j. tvjl.2012.01.002.

Zhang, L., Pornpattananangkul, D., Hu, C. M., and Huang, C. M. (2010). Development of nanoparticles for antimicrobial drug delivery. *Current Medicinal Chemistry, 17*(6), 585-594.

Zhylkaidar, A., Oryntaev, K., Altenov, A., Kylpybai, E., and Chayxmet, E. (2021). Prevention of bovine mastitis through vaccination. *Archives of Razi Institute, 76*(5), 1381. https:// doi.org/10.22092/ari.2021.356008.1764