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Treatment of mastitis caused by *Staphylococcus aureus* in cows with nanoparticles

Mostafa, S. Abdou[*]; Elsiefy, M.M.[**] and Nahla, A. Ebied [***]

[*]Department of Bacteriology, Animal Health Research Institute, Kafr El-Sheikh Branch, Agricultural Research Center (ARC), Egypt
[**]Department of Immunity, Animal Health Research Institute, Kafr El-Sheikh Branch, Agricultural Research Center (ARC), Egypt
[***]Department of Food Hygiene, Animal Health Research Institute, Kafr El-Sheikh Branch, Agricultural Research Center (ARC), Egypt

Review Article

Corresponding author:
Mostafa Abdou
E.mail: mostafaabdou152@gmail.com

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Abstract

One of the most significant zoonotic bacterial diseases is *Staphylococcus aureus (S. aureus)*, which may infect humans and animals, including dairy cattle worldwide. One of the most issues and financial burdens facing the dairy industry is *S. aureus* caused bovine mastitis, which has a detrimental effect on food safety, production, and animal welfare. Furthermore, it is difficult to cure with conventional medication due to its clever pathophysiology, which includes facultative intracellular parasitism, increasingly severe antibiotic resistance, and biofilm development. Therefore, the creation of nanoparticles is gaining momentum and becoming great instruments for overcoming the treatment challenge associated with *S. aureus* mastitis. In particular, inorganic nanoparticles, polymeric nanoparticles, solid lipid nanoparticles, nanogels, and liposomes seem to be particularly useful. This review focuses on the step-by-step advancement and limitations of nanoparticles in augmenting therapy for *S. aureus* mastitis. The most effective way to prevent new infections is to minimize or eliminate conditions that contribute to the spread of infection and conditions that allow bacteria to contaminate and penetrate the teat canals. First, the challenges of treating *S. aureus* with antimicrobial drugs are examined. Next, *S. aureus* mastitis is controlled. Furthermore, several dietary elements strengthen the animal's defenses against mastitis. Mastitis has decreased when the diet is supplemented with vitamins E and selenium, A and beta carotene, and copper and zinc components that are balanced to fulfill requirements. Second, the benefits of using nanoparticles to treat *S. aureus* mastitis are also outlined. These benefits include enhancing the intracellular penetration and accumulation of the medications that nanoparticles carry, lowering antimicrobial resistance, and avoiding the formation of biofilms. Thirdly, a range of nanoparticle kinds are presented for the purpose of suppressing *S. aureus* mastitis. Lastly, the challenges that still need to be overcome, as well as the potential applications of nanoparticles in the prevention of new infections and the management of *S. aureus* mastitis are covered. The readers will receive sufficient knowledge from this review of the difficulties facing the nanosystem to enable them to create and develop more effective Nano formulations to combat *S. aureus* infections.

Keywords: *Staphylococcus aureus; bovin mastitis; treatment; nanoparticles*

Introduction

One of the most deadly illnesses affecting dairy herds globally is bovine mastitis, which is typically brought on by a variety of bacteria **Ruegg, 2017; Tiwari *et al.*, (2013).** The most frequent pathogen among these bacteria is *S. aureus*, which is responsible for the most severe cases of mastitis **Monistero *et al.*, (2018),** and also it cause reproductive issues, a sharp drop in milk revenue, and costs associated with culling infected animals, replacing tainted milk with more expensive veterinary treatment **Botaro *et al.*, (2015).** *S. aureus* produces toxins in milk that have the potential to result in serious diseases **Johler *et al.*, (2013).** While **Kaczorektukowska *et al.*, (2022)** showed that Amoxicillin + Clavulonic acid and Gentamycin (100% each) were sensitive to *Staph aureus*, oxytetracycline (98.18%) and Amoxicillin (89.09%) were resistant to S. aureus. On antibiotic-resistant *S. aureus* isolated from mastitic milk, Cuo-Nps and Ch-Nps have inhibition zones **Orellano *et al.*, (2021).**
Cuo-Nps and Ch-Nps exhibit antibacterial efficacy against the isolated antibiotic-resistant *S. aureus*, which was isolated from mastitic bovine milk and showed resistance to multiple antibiotics **Hala *et al.*, (2024).**
Moreover, it has been connected to the subclinical, recurring, and clinical forms of bovine mastitis. Their capacity to remain intra cellular result in reinfection **Zhou *et al.*, (2018).**
The use of antibiotics is one of the main methods for managing mastitis. The treatment benefits are depends on severity of the condition, the medicine of choice, proper drugs use **du Preez, (2000).** Subsequently, they may revert to a more contagious wild-type phenotype, which increases the likelihood of further infections. Moreover, *S. aureus* develops a greater resistance to antibiotics when they are used often and for extended periods of time **Szweda *et al.*, (2014)**. In the last few years, concerns regarding treatment failure have received a lot of attention. Because of this, scientists have been working nonstop to develop new treatment strategies **Dehkordi *et al.*, (2011).** New role that nano carriers are playing in the management of cow mastitis and to help researchers understand how to shift their attention to the field of nano carriers in order to discover a novel approach to combat *S. aureus*-caused mastitis.

S. aureus therapy difficulty

The primary reasons for the treatment's failure are antimicrobial resistance and *S. aureus* ability to remain intracellularly within phagocytes. Numerous variables could be to blame for this, such as a decline in the rate at which routinely used antibiotics are retained in cells, a drop in the pace at which these drugs are absorbed intracellularly, or a decline in the effectiveness of these medications at the lysosomes' acidic pH. Acidic medications may also be ionic at neutral extracellular or cytoplasmic pH, which prevents them from dissolving across the lysosomal membrane. Antibacterial medication's activity is not always present in aqueous solutions due to all of these reasons. Consequently, in order to effectively treat *S. aureus* infections, more specific dose forms are required. If at all possible, these dosage forms should provide the following benefits: (1) broad phagocyte penetration and reserve within cells for an appropriate duration; (2) minimal or nonexistent metabolism within the cells; (3) increased activity against Staphylococci at an acidic pH; (4) distribution through the streak canal. How well antibiotics work to treat mastitis depends on a number of parameters, including their pharmacokinetics—the rate at which they are absorbed and distributed when administered intramarily, their penetration into milk when injected parenterally, and other considerations. **Prescott *et al.* (2000)** state that these properties are related to the kind of vehicle, organic bases given parenterally, even if the former's concentrations ionize in the latterless than those found in blood. Pharmacodynamics is yet another crucial element that must be considered. The antibiotics impede DNA synthesis, stop the formation of bacterial cell walls, and interfere with ribosome activity to stop protein synthesis, among other ways **Normark & Normark, (2002).** Positive therapy for an infected udder is challenging, if not impossible, because to the following reasons: certain bacteria can generate poisons and enzymes that damage udder tissue and facilitate the entry of germs; survival of

contenued undetected by neutrophils and preventing them from being phagocytosed; bacteria's survival and growth within the phagocytes; About half of the *S. aureus* strains that are isolated from sick cattle develop beta-lactamases, microabscesses, and glandular tissue atrophy at the site of infection. All these variables hinder the entry of antibiotics into fibrous membranes.

Therefore, antibiotic resistance in Staphylococci, especially *S. aureus* resistance to penicillin G, is one of the main problems with therapy **Olsen *et al.*, (2006).** Coagulase-negative staphylococci usually show higher resistance and the capacity to acquire multi-resistance in comparison to *S. aureus* **Pitk€al€a *et al.*, (2004).** According to **Haveri *et al.* (2005),** some researchers talked about the lack of correlation between the findings of susceptibility testing and the cure rates for mastitis.

Once *S. aureus* attaches itself to host tissues or prosthetic materials, it can spread and persist in a number of ways. Other characteristics of *S. aureus*, such as the production of an anti-phagocytic microcapsule and the creation of an abscess by the zwitterionic capsule, during infection, are essential in assisting the bacteria in avoiding human immunity **O'Riordan & Lee, (2004); Foster, (2005).** According to **Stephan *et al.* (2001),** *Staphylococcus aureus* has the ability to secrete both the extracellular adherent protein and the Staphylococci inhibitory protein, which can hinder neutrophil migration and chemotaxis release to the infection site. Furthermore, *S. aureus* generates leukocidins, which cause leukocytes to be destroyed by opening up cell membrane pores. *S. aureus* produces a variety of enzymes during infection, including lipases, elastases, and proteases, which change the bacteria's ability to assault, damage host tissues, and spread to new locations.

Treatment is made more difficult by *S. aureus* intracellular persistence in macrophages and the mammary epithelium. Furthermore, S. aureus can thrive and dwell in unique cell compartments such as the cytosol and endosome, which makes it difficult to remove them from the body and creates a reservoir where infections can recur. In addition, *S. aureus* small-colony variations (SCVs) are another kind that contributes to recurrent and persistent infection.

SCVs are often resistant to antibiotics and host defense systems after being able to "hide" in host cells in vitro; yet, they are changed to contagious type, which is likely to cause reinfection **Zhou *et al.*, (2018).**

For instance, it will be challenging to eradicate an infection without removing the prosthetic device if it is infected **Arrecubieta *et al.*, (2006).** One essential aspect of *S. aureus* pathogenicity is its capacity to create biofilms, and it has been linked to a number of syndromes, including mastitis, because of its capacity to delay phagocytosis, induce persistent antibiotic resistance, and, depending on the disease pattern, either increase or decrease inflammation **Thurlow *et al.*, (2011).** The dynamic process of biofilm formation makes it possible for planktonic cells to separate and colonize various surfaces after they quickly proliferated. This mechanism has a major impact on encouraging the microbial pathogen to exist in additional infection sites, which leads to the creation of new biofilms and the widespread spread of the infections. Recent research has demonstrated that mice's immune responses to *S. aureus* in biofilm form, which is used to produce acute mastitis in experiments, are more robust than those to **Gogoi-Tiwari *et al.* (2015)** planktonic cultures **Monistero *et al.*, (2018).** Recurrence of infection symptoms is caused by altered gene expression of adhesion molecules and toxins, as well as a quick multiplication that came after the separation process.

Thus, the development of biofilms is a significant contributor to the pathophysiology of *S. aureus*, and it is crucial to find alternative therapies that specifically target this component.

Benefits of using nanoparticles to treat *S. aureus* mastitis

It is envisaged that a new dosage form called nanoparticles will be employed intrammary to achieve the desired results.

Drug delivery methods using nanoparticles exhibit a variety of biological and functional characteristics **Garg *et al.*, (2015b; 2015c)**

To address the issues associated with conventional medication, they can be readily modified by adjusting the drug's dosage and

ratio as well as the components that are used in their manufacture, such as polymers, excipients, stabilizers, and others **Garg *et al.*, (2015d).**

Prevention of the growth of biofilms

Because the nanomaterials prevent the growth of biofilms, they have a substantial impact on the management of *S. aureus* infections. The glycocalyx, which possesses an anionic charge, is the principal constituent of biofilms. This enables it to interact with nanoparticles that are positively charged and able to pierce the dense biofilm **Kulshrestha *et al.*, (2017).**

The gold nanoparticles dramatically decreased the amount of biofilm that *S. aureus* produced, according to **Sathyanarayanan *et al.* (2013).** Triclosan, as an antibacterial drug in solution, kills *S. aureus* only outside the biofilm, according to **Liu, (2019).** However, loading triclosan into a micellar nanocarrier makes it easier for staphylococcal biofilm to penetrate and kill bacteria inside the biofilm.

-Improved parameters for intracellular delivery

Drug's absorption, distribution within cells, and therapeutic effect are all impacted by the different transport pathways. The nanoparticles respond to changes in PH, temperature, redox, and other environmental stimuli by releasing their payload through pores in their membranes. These nanoparticles stay intracellular for extended periods of time. In order to release the payload medicine at the appropriate location, we must synthesize on-demand release nanoparticles during the nanoparticle production process. The size, form, and synthetic chemistry of the nanoparticles, among other physical attributes, influence how well they are transported within cells.

The size of the nanoparticles has a big impact on how they behave in biological fluid and how much of them enter cells. It determines the nanoparticles' stability, toxicity, drug loading and release, and in vivo bio-distribution. The advantages of submicron versus micron size have been extensively studied; in other words, little particles are more effective than large ones at transporting medications to loci that are infected. For example, **Yuan *et al.* (2017)** shown that silver nanoparticles with a size range of 10 nm to 50 nm can be used to effectively cure goat mastitis caused by *S. aureus.* **Chithrani *et al.* (2006)** reported that the maximum cellular absorption of 50 nm-sized silver nanoparticles was observed in adipose-derived stem cells and mammalian cells **Ko *et al.*, (2015)**. Therefore, regulating the size of the nanoparticles is a viable strategy for intracellular drug delivery in the distinct *S. aureus* compartments.

Their form affects the pharmacokinetics of the payload medicine, biological behavior, phagocytosis by macrophages, and cellular uptake of the nanoparticles.

Variations in the charge of the nanoparticles affect the pattern of the endocytosis process. For example, the usage of positive or negative charge particles, such as carboxymethyl chitosan and chitosan hydrochloride, affects the cellular uptake of polymeric nanoparticles. In comparison to negative and neutral charge polymeric nanoparticles, positive charge nanoparticles have a higher rate of phagocytic uptake **He *et al.*, (2010).** Positive charge nanoparticles are believed to have a nonspecific adherence to normal tissue, making it more difficult for them to reach the diseased area. In contrast, negative charge nanoparticles may be preferred for delivering the treatment deeper into the tissue **Kim *et al.*, (2010). Miao *et al.* (2018)** state that in order to take advantage of the two opposing charges, we can create a type of nanoparticle that carries a positive charge in acidic inflammatory tissue and a negative charge in healthy tissue.

Furthermore, the functionalization of the nanoparticles' surface with "PEG, poloxamer, poloxamine polymers, and other" prevents the particles from being phagocytosed because these polymers make the particles more dispersed and less prone to aggregation, absorption of the protein on their surface, and ionic strength **Moghimi, (1999).**

Increased resistance to *S. aureus* small-colony variations (SCVs*).*

Since S. aureus infections are hard to treat with antibiotics and to eradicate with the immune system, SCVs have a significant role in the persistence of *S. aureus* infections' resistance

to treatment.
Because of this, a number of studies are attempting to use nanoparticles to increase the effectiveness of antibacterial medications against *S. aureus* SCV phenotypes. Mesoporous silica nanoparticles (MSNP) coated with rifampicin were employed by **Subramaniam *et al.* (2019)** as a nanocarrier technique to cure intracellular infection brought on by *S. aureus* SCVs. Because MSNP of two sizes, 40 nm and 100 nm, loaded with rifampicin increased the intracellular uptake of rifampicin by RAW 264.7 macrophages infected with *S. aureus* SCVs, more bactericidal action was demonstrated compared with rifampicin alone.

The development of various nanoparticle delivery methods to improve treatment for *S. aureus* infections.

It has been proven by multiple researchers that a variety of nanoparticles, both organic and inorganic, may have been employed in medical studies, particularly for illnesses related to cow mastitis. Nanoparticles can prevent the development of resistance to antibiotics through a variety of mechanisms, including killing bacteria, enhancing the effectiveness of currently available antibiotics by preventing their detection or degradation, and enabling targeted drug delivery to microorganisms so they can use the lowest concentration possible **Wong *et al.*, (2013).** Moreover, impeding colonization, biofilm formation, and bacterial adherence.
Certain nanocarriers can be conjugated or combined with a variety of antibacterial drugs to enhance their pharmacological activity against susceptible and resistant *S. aureus.* Therefore, medication delivery using nanoparticles is thought to be the best method for eliminating *S. aureus* infections. Additionally, this may lead to effective action against microbes. It is possible to boost both the intracellular concentration of antimicrobial medications and the efficacy of phagocytosis by adding specific macrophage ligands to the nanoparticles **Hua *et al.*, (2014).**

Liposomes

Nigatu *et al.* (2018) noted that liposomes may be modified to discharge the drug load at the desired site in reaction to the 39ºC temperature of the inflammatory area. Through modifications to the drug's pharmacokinetics and biodistribution, the liposomes enhance pharmacological efficacy while lowering toxicity. Although the stability of the lipid vesicles is limited due to their decreasing shelf life, they are safe to provide to youngsters as well. Furthermore, as mentioned by **Gabizon *et al.* (2006) and Allen and Martin (2004)**, its manufacturing is intricate and time-consuming.

Polymeric nanoparticles

One of the most effective nanoparticle therapies now being investigated as a potential delivery system for antibiotics is polymeric nanoparticles. Block copolymers, which contain two or more highly hydrophobic polymer chains, are used in the self-assembly process to produce polymeric nanoparticles, which are composed of (biocompatible and biodegradable) polymers.
Moreover, hydrophilic or hydrophobic medicinal compounds as well as macromolecules like peptides, proteins, and nucleic acids have been created to encase them in polymeric nanoparticles **Wang *et al.*, (2012).** Because of its various benefits, such as its low cost, nontoxicity, biodegradability, and biocompatibility, chitosan is used as a drug delivery vehicle. **Chakraborty *et al.* (2010)** reported that chitosan nanoparticles loaded with vancomycin and tagged with folic acid improved the vancomycin's transport across bacterial cell membranes, leading to a stronger bactericidal effect against vancomycin-resistant *S. aureus.* Additionally, chitosan nanoparticles loaded with tetracycline stopped S. aureus from penetrating cells, while chitosan nanoparticles loaded with Bacillus natto stopped biofilm development **Maya *et al.*, (2012); Jiang *et al.*, (2017).** PLGA (poly-lactic -co-glycolic acid) nanoparticles loaded with gentamycin not only acted as carriers of antibacterial drugs but also showed increased antibacterial efficacy against *S. aureus* by boosting the intracellular accumulation and dispersion of gentamycin **Imbuluzqueta *et al.*,**

(2010). Thomas *et al.* (2016) reported that PLGA nanoparticles loaded with ciprofloxacin and calcium phosphate loaded with levofloxacin and nafcillin sodium inhibited *S. aureus*'s ability to produce biofilms **Bastari *et al.*, (2014).** Moreover, **Turos *et al.* (2007)** showed that the anti-*S. aureus* infection treatment efficiency of ciprofloxacin was enhanced by glycosylated polyacrylate nanoparticles. Improved drug bioavailability and encapsulation efficiency, controlled payload release, and targeted drug release at the inflammatory and infected areas are further advantages of polymeric nanocarriers **Kumari *et al.*, (2010).**

On the other hand, reactive groups may influence the stability of the polymer as well as the pace at which the conjugation process progresses **Jijie *et al.*, (2017).**

SLNs (Solid lipid nanoparticles)

They have drawn interest as a possible therapeutic carrier for intracellular infections since they are biocompatible, biodegradable, and stable **Xie *et al.*, (2011). Xie *et al.*, (2014).** Another theory is that SLNs can serve as a substitute for liposome and polymeric nanoparticles. For example, studies by **Wang *et al.* (2012) and Han *et al.* (2009)** shown how SLNs loaded with tilmicosin could potentially prevent *S. aureus* mastitis. Furthermore, our previous studies **Xie *et al.*, (2017); Li *et al.*, (2019)** demonstrated that docosanoic acid SLNs loaded with enrofloxacin could successfully prolong the period of time that enrofloxacin accumulated and was stored inside the cell. In order to improve enrofloxacin's oral bioavailability, stability, and palatability, we most recently coated the SLNs with an enteric coating. According to studies by Kalhapure *et al.*, vancomycin-loaded SLN had a higher antibacterial activity against *S. aureus* than vancomycin that was free (2014). Furthermore, **Wang *et al.* (2015)** found that SLNs improved the antibacterial efficacy of florfenicol, lauric acid, and retinoic acid against *S. aureus.* **Silva and colleagues, (2015).** SLNs have several benefits, including as long-term stability, ease of manufacture, reduced toxicity, and the capacity to carry lipophilic and hydrophilic medicines.

Nanogels

Nanogels, which range in size from 20 to 200 nm, are a novel and imaginative type of three-dimensional cross-linked nanocarrier within the field of nanoparticles. These Nano-carriers are used in drug delivery to release pharmaceuticals via several methods, such as photo-isomerization at the target site, thermo-sensitivity, PH responsiveness, and enzyme responsiveness, among others. Compared to other drug carrier systems, nanogels are favored because of their remarkable biocompatibility and essential biodegradability, which make them a very promising option for drug delivery systems **Sultana *et al.*, (2013).** This prevents the organs from being overly filled with nanogels. Nanogels have no effect on the immune system since they are inert in the bloodstream and internal watery environments **(Rigogliusoa *et al.*, (2012).** Furthermore, nanogels can be administered in a variety of methods, such as "oral, nasal, parenteral, pulmonary, intra-ocular, and topical." As to **Soni and Yadav's (2016)** findings, nanogels are engineered to release the drug at the targeted site in a controlled and uninterrupted fashion with no adverse effects. The activity of bio-macromolecules in their natural habitat can be positively enhanced and maintained by the addition of nanogels. One technique to express nanogels is through polymeric micellar nanogels systems. According to **Sultana *et al.* (2013),** these systems exhibit superior stability across the surfactant micelle, slower patterns of dissociation, and a longer withholding period for loaded medications.

Many different types of nanogels are used to treat mastitis conditions; **Krishna *et al.* (2027),** for example, confirmed that nano copper gel is effective in treating clinical mastitis. Furthermore, red blood cell (RBC) nanogels have been shown to neutralize

Furthermore, research was done on dextran cross-linked polyacrylamide nanogels loaded with zinc nitrate as an antibacterial agent against MRSA **Malzahn *et al.*, (2014).** Silver nanoparticle loaded-dextran lysozyme nanogels demonstrated a stronger antibacterial impact against *S. aureus* **Ferrer *et al.*, (2014).** Additionally, *S. aureus* toxins are decreased by

PLGA nanoparticle-loaded RBC hydrogel **Wang *et al.*, (2015),** toxins connected to MRSA in the extracellular milieu and promoted macrophage phagocytosis of germs **Zhang *et al.*, (2017).**

Inorganic metal nanoparticles

Antibacterial and antibiofilm properties can also be attributed to metal nanoparticles. For instance, subclinical mastitis was treated with silver nanoparticles (AgNPs) **Dehkordi *et al.*, (2011).** They were thought to be an affordable substitute for an extremely expensive antimicrobial solution because of their bactericidal and fungicidal effects via a range of mechanisms, such as cell membrane damage, protein denaturation. The combined effects of antibiotics and AgNPs were also evaluated; for example, erythromycin and AgNPs were used to fight *S. aureus* **Kazemi *et al.*, (2014).**

Additionally, research has looked at the possible medical applications of selenium, a vital mineral with qualities. To halt the spread of MRSA infections, metal nanoparticles are the subject of extensive research **Hibbitts & O'Leary, (2018).**

Furthermore, violacein nanoparticles were discovered by **Berni *et al.* (2013)** to be more potent than common treatments in combating *S. aureus* in the setting of mastitis illness. It was believed at the time that violacein was a common bactericidal agent. **Yang *et al.*** found that amoxicillin nanoparticles worked just as well against *S. aureus* **(2009)**. Furthermore, according to **Garg and colleagues (2015a),** lasalocid has demonstrated notable efficacy against mastitis-causing microorganisms other than MRSA and its nano-sized form spreads more swiftly in the udder than its micro-sized form. Because they are easier to create in a range of shapes and forms, have antibacterial qualities, and enhance medication stability, metallic nanoparticles are therefore more beneficial. They do, however, have certain disadvantages, including the tendency to clump together fast, collect in the body after delivery, and release metal ions into the medium and cause cytotoxicity **Jijie *et al.*, (2017).** Reducing or eliminating the circumstances that cause teat end exposure through infection dissemination is the greatest strategy to prevent recurrence of *S. aureus* mastitis once it has been treated **Hala *et al.*, (2024).**

Conclusions

In dairy farming, staphylococcal subclinical mastitis is a complex disease that causes economic losses. The challenges associated with therapy include the quick acquisition of multidrug resistance, the potential for persistent, recurring infections due to biofilm formation, and facultative intracellular parasitism. Because of these, mastitis is a persistent problem and a subject of discussion for numerous research teams.

It is evident that giving too many or inappropriate antibiotics to dairy cows during treatment has a number of negative effects, including raising the risk of antibiotic resistance, lowering antibacterial activity, and lengthening the time needed to check and extend antimicrobial function **Oliver & Murinda, (2012).** Therefore, the need to overcome the shortcomings of conventional antibiotics is critical. The limitations imposed by antibiotics have been improved recently thanks to developments in nanoparticles with distinct physiochemical characteristics and functionalization **Yah & Simate, (2015).** In the past few years, a number of distinct nanoparticles have gained popularity for treating Staphylococcal infections. We have provided a quick overview of the most recent research in this field. These nanoparticles exhibit greater intracellular absorption than other conventional drug delivery methods; they also prolong the drug's intracellular accumulation and retention period, enhance its antibacterial activity, lower antimicrobial resistance, and prevent the formation of biofilms. Therefore, broadening our viewpoint to encompass the Nano world can aid in overcoming and addressing the therapy obstacles associated with *S. aureus* mastitis.

Prospects for treating mastitis in the future

We still need to do research and develop new, costly, yet safe Nano formulations that fight *S. aureus* mastitis in order to meet the therapeutic challenges associated with the illness. As was already mentioned, *S. aureus* can infiltrate tissues and reside there in certain

compartments. Therefore, the efficacy of the nanoparticles needs to be improved in order to effectively distribute the medication to the infected region and achieve colocalization between the pharmaceuticals and the intracellular *S. aureus* **Xie *et al.*, (2014).** To improve tilmicosin's capacity to treat *S. aureus* cow mastitis, our research team combined in-situ hydrogel technology with (SLN) technology to build a self-assembling tilmicosin nanogel **Zhou *et al.*, (2019).** Additionally, we are developing different nanogels compositions to treat cow mastitis in an effort to advance our research. Further study on stimuli-responsive nanogels is also needed to improve a topical nanogel counter to medical mastitis. Drug administration via nanoparticles has great potential, but there are some obstacles that need to be addressed, like the medication's quick bodily elimination and the loaded drug's premature release before the intended lesion, and the phagocytosis of the immune cells. These problems can be remedied by integrating nanomaterials with natural drug delivery systems, such as bacteria, red blood cells, platelets, and stem cells, which are believed to be smart drug delivery systems and covering nanoparticles with their cell membranes. They allow the medication to build up in the bloodstream and cross cell membranes for a prolonged amount of time in order to stop intracellular infection. Apart from these advantages, stem cells could offer a feasible method for tissue regeneration and increase the effectiveness of treatment for cow mastitis in the future. By neutralizing the bacterial toxin, RBCs can help lessen the harm caused by the bacterial infection. Our groups have recently produced widely applicable protocols for Nano-crystal Nano-suspension and SLNs, which will be beneficial for their use. It is feasible to get nanomaterials from the lab to the clinic, but it requires patience, work, and regulations.

Finally, there has been a lot of interest in creating Nano-robots that might be used for diagnostic and tissue restoration. However, these are cutting-edge research that have never been used before and could be eclipsed by artificial.

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