

Review Article

Niosomal-Based Drug Delivery Platforms: A Promising Therapeutic Approach to Fight *Staphylococcus aureus* Drug Resistance

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Staphylococcus aureus, a prominent bacterial pathogen, presents formidable medical challenges owing to its rapid development of resistance. The emergence of multidrug resistant (MDR) S. aureus strains has become a pressing concern for healthcare systems, driving researchers to explore novel therapeutic strategies for managing infections associated with this pathogen. In this pursuit, niosomal-based platforms have emerged as promising candidates to effectively target S. aureus and fight conventional antimicrobial resistance. Niosomes comprise a bilayer membrane formed by nonionic surfactants, which can encapsulate both hydrophilic and hydrophobic drugs. These nanoparticles are known as vesicular delivery systems and have many advantages, such as low cost, less toxicity, and more flexibility and stability. Moreover, niosomes, being an effective drug delivery system, can directly interact with the bacterial cell envelope, thereby enhancing the pharmacokinetic activities of drugs at infected sites. A niosome-based delivery system can effectively treat S. aureus infections by destroying the biofilm community, increasing intracellular targeting, and enhancing the antibacterial activity. The main mechanisms of action of niosomes against resistant S. aureus strains involve the ability to resist enzymatic degradation, controlled release profile, and targeted drug delivery, which can provide an effective dosage of antimicrobial agents at the site of actions. In addition, niosomes have the potential to transfer wide-spectrum materials from different classes of antibiotics to nonantibiotic antimicrobial agents, such as natural compounds, antimicrobial peptides, and metallic nanoparticles. The combination of polymeric materials in the structure of a niosomal formulation could improve their bioavailability, loading capacity, and therapeutic efficacy for different applications. Furthermore, niosomes could find application in photodynamic therapy, offering a promising alternative to conventional treatments for eradicating drug-resistant S. aureus isolates. Finally, niosomal nanocarriers can be developed for delivering the drugs to desired sites by different routes of administration and could be considered a powerful strategy for overcoming the therapeutic obstacles caused by MDR S. aureus.

1. Introduction

Staphylococcus aureus is known as a seriously life-threatening agent for humans that bring enormous financial burdens to healthcare system budgets [1–3]. This pathogen is one of the major and continuous microorganisms causing a wide variety of diseases with high mortality rates in patients [4–6]. *S. aureus* can be a leading causative agent in various infections, including surgical site, respiratory tract, prosthetic joint, necrotizing pneumonia, and cardiovascular infections [7]. Methicillin-resistant *S. aureus* (MRSA) is a dangerous bacterial pathogen isolated from both community and clinical environments [8, 9]. In recent

years, chronic MRSA wound infections have become a big healthcare-associated problem that has detrimental effects on human quality of life [10–13]. According to the Centers for Disease Control and Prevention (CDC) report in 2018, the annual deaths caused by MRSA in the United States were estimated at 20,000 and this rate was higher than any other drugresistant pathogen [14]. The indiscriminate use of vancomycin in patients with MRSA infections has led to the emergence of vancomycin-resistant *S. aureus* (VRSA) and vancomycin-intermediate *S. aureus* (VISA) strains which have drastically increased therapeutic challenges in healthcare systems. VRSA is primary nosocomial pathogen that can cause invasive infections with considerable morbidity and mortality rates worldwide [15]. Also, patients infected by VRSA often require extensive treatment measures, leading to prolonged hospitalization, increased medical costs, and a higher risk of invasive infections. The rapid spread of multidrug resistant (MDR) *S. aureus* among patients also creates a great concern for public health, complicating treatment decisions for this pathogen significantly. Therefore, it is crucial to urgently develop novel treatments and alternative approaches to effectively combat resistant staphylococcal infections, particularly those caused by MRSA and VRSA strains [16].

Facultative intracellular parasitism, the ability to a form biofilm, and increasingly severe antimicrobial resistance are the reasons that cause S. aureus to become a successful human pathogen and challenge antibiotic therapy [17]. Furthermore, S. aureus employs several virulence factors, including adhesins, toxins, and immunomodulatory molecules, to evade the human immune system causing severe infectious diseases. For instance, protein A and clumping factor can inhibit opsonization and phagocytosis of S. aureus by host immune cells [18, 19]. Also, other staphylococcal virulence factors, including leukocidins, enterotoxins, proteases, hemolysins, and exfoliative toxins, play an effective role in dissemination of S. aureus during infection [20]. In addition, S. aureus has evolved several mechanisms to resist antimicrobial agents, including the production of drugdegrading enzymes, efflux pumps, and modifications of antibiotic targets [21]. Furthermore, S. aureus exhibits a high capacity to acquire resistance genes through horizontal transfer, leading to the emergence of resistant strains that pose significant challenges in treating infected patients [22].

However, various drawbacks, such as in vivo instability, low absorption, water insolubility, and no delivery to the target organisms, cause the failure of conventional dosage forms combating this superbug [23]. Therefore, developing nano-based drug delivery systems as an emerging and alternative pathway seems necessary for conquering therapeutic difficulty accompanied by *S. aureus* infections [24].

Vesicular drug delivery systems are composed of one or more concentric bilayer membranes that were first discovered by a British scientist in 1961 [25, 26]. The bilayer structure of these systems is formed by the self-assembly of amphiphilic molecules in an aqueous medium; thus, they can be utilized to incorporation of materials with a wide range of solubility [27]. Also, vesicular systems are gaining traction among researchers for several other advantages, including biocompatibility, flexibility of membrane components, simple formulation, biodegradability, and surface modification [28]. Numerous lipid-base vesicular systems have been prepared as novel formulation approaches to eradicating infectious diseases. Liposomes are the oldest type of lipoparticles that afford successful outcomes when transferring conventional medicine [29]. Also, the liposomal vesicular system could present several profits in delivering therapeutic agents for bacterial complications, including S. aureus infections [30]. However, due to some drawbacks of liposomes, like high cost, requirement of special methods for storage, and short half-life, scientist interest shifted toward other vesicular nanoparticles like niosomes [31, 32].

Niosomes are vesicular delivery systems, and since there is a nonionic surfactant in the component, they are called by this name. Alkyl glyceryl ethers, alkyl ethers, polyoxyethylene fatty acid esters, and sorbitan fatty acid esters are among these nonionic surfactants, which are used in niosomal formulations and can provide favorable properties for them [33]. The electrical neutrality of these amphiphilic molecules causes more compatibility and stability in niosomes, which can improve their pharmaceutical behavior. Also, enhanced permeability, negligible toxicity, biodegradability, and nonimmunogenicity are among the niosomal advantages resulting from the participation of nonionic surfactants in its composition [34, 35]. Cholesterol, an important membrane additive, could be included in the niosomal formulation because it positively affects entrapment efficiency, leakage, permeability, and rigidity [36]. The salient properties of niosomes in drug delivery are not limited to the items mentioned, and others include no special storage conditions, simple handling, osmotically active, structure flexibility, and high loading capacity [37]. Also, niosomal nanoparticles have great potential to encapsulate both hydrophobic and water-soluble drugs because of their vesicular structure. The lipid bilayers of these lipoparticles surround an aqueous core, which is suitable for hydrophilic compounds. While, the lipophilic layer allows the possibility of transporting hydrophobic compounds [32, 38]. However, niosomal applications in drug delivery systems can be limited due to some disadvantages such as aggregation, leakage of the entrapped drug, and timeconsuming preparation [39, 40]. The practical solutions to deal with these drawbacks include combination the proper proportion of ingredients (nonionic surfactants, cholesterol, charge inducer molecules, and hydration medium), alteration in the composition of loaded materials, and modification of preparation methods, which have a significant role in the efficiency of niosomes [31, 38, 41].

According to the numerous benefits, niosomal vesicular systems can be effective nanocarriers for pharmaceutical purposes, especially bacterial infections that could entail desirable consequences [42]. Numerous studies have demonstrated the tremendous potential of niosomal-based platforms as effective antimicrobial agents against various Gram-positive and Gram-negative bacteria and other pathogens. In this regard, the antibacterial activities of different niosomal formulations against Gram-positive bacteria, including S. aureus, Staphylococcus epidermidis, and Bacillus subtilis, were investigated, and the potential of niosomes as an effective antimicrobial delivery system was approved [43–45]. Also, in different studies, the efficacy of niosomal systems against Gram-negative bacteria such as Escherichia coli, Serratia marcescens, Pseudomonas aeruginosa, Acinetobacter baumannii, and Klebsiella pneumoniae was evaluated [44, 46, 47]. The results of these experiments indicate that niosomal platforms hold promise in preventing and eradicating serious infections associated with these microorganisms [38, 48]. Furthermore, diverse niosomal formulations have been successfully employed to deliver various compounds and their antibacterial effects have been proven [38]. In this review, we will discuss different aspects of



FIGURE 1: Mechanism of targeting bacterial biofilms by niosomes.

niosome usage for eradicating *S. aureus* and the management of related infections. Also, the superiority of niosomal-based delivery systems over conventional approaches will be emphasized.

2. Niosomes Delivery System against S. aureus Infections

2.1. Biofilm-Related Infections. S. aureus is widely recognized as a significant clinical pathogen due to its remarkable ability to form biofilms on both biotic and abiotic surfaces [12]. A biofilm is described as an aggregation of living bacteria in the surrounding extracellular polymeric substances (EPS) [49], which leads to bacterial survival in unfavorable conditions, such as excessive antimicrobial agents [50]. EPS plays a crucial role in biofilm formation and stability that its contribution to the development of antibiotic resistance is well known. EPS is a complex mixture of polysaccharides, proteins, lipids, and DNA that protects bacterial cells from environmental stresses by providing structural support [51]. Moreover, EPS can reduce the effective concentration of antimicrobial agents by preventing their diffusion into the biofilm structure, which can lead to the emergence of persistent infections. EPS can also act as a shield against host immunity responses that mediate bacterial resistance to immune clearance [52]. On the other hand, biofilms provide optimal conditions for the exchange of genetic material through horizontal gene transfer, leading to the acquisition of antibiotic resistance genes among the bacterial population [53]. Therefore, biofilm formation has undeniable role in the emergence of MDR S. aureus strains causing complicated infections that finding the effective treatment approaches against them is still challenging [12, 54].

Niosome nanoparticles can disrupt bacterial biofilm due to the facilitation of their penetration into the biofilm barrier. Indeed, niosomes interact with the cell wall of embedded bacteria, causing the accumulation of adequate drugs inside the cytoplasmic membrane. The mechanism of niosome–cell wall interaction is mediated by contact release, leading to the diffusion of niosome contents into intracellular space by creating a concentration gradient [55]. Also, the persistent drug accessibility in the biofilm matrix causes the efficient killing of biofilm-forming bacteria and eradication of existing biofilms, which could be provided through a sustained release profile of the niosomes (Figure 1) [38].

In addition, niosomal physicochemical properties including size, electrostatic surface charge, lipid composition, and bilayer rigidity/fluidity can affect the antibiofilm potential of encapsulated drugs [56, 57]. Several studies on the biofilm inhibitory and/or eradicating activity of different niosome-based platforms were investigated, and it was also suggested that niosomes could be an efficient drug delivery system for targeting bacterial biofilms. In this regard, a study found that minimal biofilm inhibitory/eradication concentrations (MBIC/MBEC) of S. aureus strains were more decreased by a lower concentration of niosomal vancomycin than the free drug [58]. Also, in another investigation, the significant antibiofilm activity of amoxicillin-loaded niosomes against S. aureus strains was proven, where niosomal formulations more reduced in colony-forming unit (CFU) counts of biofilm-forming bacteria at the same concentration of free drug [59]. The confirmatory study evaluated the antibiofilm effects of cefazolin-containing noisomes against S. aureus and MRSA isolates. The findings of this study demonstrated that encapsulated drugs can eliminate 1-, 3-,

and 5-day-old biofilm at lower concentrations than free antibiotics. In addition, drug-loaded niosomes reduced the biomass of formed biofilms and also dramatically decreased the MBEC value of tested isolates [60]. Furthermore, the effect of ciprofloxacin-loaded niosomes on biofilm destruction was confirmed by scanning electron microscope images, and it became clear that the density of the formed biofilms had significantly been decreased by niosomal antibiotic compared to that formed in treated culture with free antibiotic or untreated culture [61]. Additionally, an in vivo study showed that the antibiofilm activities of conventional drug could be improved by incorporating into niosomal systems. In this study, the antibiofilm potential of niosomal formulation against MRSA was proven, where cefazolin-containing niosome had an effective therapeutic role on chronic infected wounds by reducing CFU counts of biofilm-forming bacteria [60]. It is also reported that the ciprofloxacin encapsulated niosomes can be effective on the biofilm genotypic profile and inhibit biofilm formation via downregulating the expression of the biofilm-related genes [62].

The results of the study indicated that the attachment of *S. aureus* strains to bone plates was significantly suppressed through covering with niosomal drug. Thus, abiotic surface coating with vancomycin-loaded niosomes could prevent biofilm formation and also contribute to controlling biofilm-related infections. Also, regarding the noncytotoxic effects of the prepared formulation on normal human cells, niosome nanovesicles could be developed for further biomedical applications [63].

Overall, the authors of the reviewed studies presented niosomes as an appropriate carrier for antibiofilm agents that could treat conundrum infections caused by biofilmforming S. aureus isolates. Also, surface modifications could increase the antibiofilm potential of niosomes, which could be provided through altered niosomal composition or PEGylatation (polyethylene glycol). In this regard, the results of a study showed that preparation of norfloxacin niosomes with cationic agents could more efficiently decrease the biofilm formation due to further electrostatic attraction between positively charged niosomes and negatively charged biofilm [64]. Moreover, a study revealed that niosomal surface modification through PEGylatation (PEG-niosomes achieved a more positive charge on the surface) could enhance the antibiofilm activity of vancomycin-loaded niosomes against MRSA [65]. However, further research must be conducted to investigate the exact mechanism of niosome vesicular systems on biofilm and the effect of surface modifications on the antibiofilm activity of niosomes.

2.2. Ocular Infections. S. aureus is a common human colonizer and increases the risk for eye-associated infections, which causes this microorganism to become one of the primary ocular pathogens [66]. The review of the published studies shows that the high prevalence of antibiotic resistance among the S. aureus strains causing eye infections is an ongoing challenge in ophthalmology [67]. Topical ocular drug delivery is a favorable route to the eye due to several advantages, such as noninvasive, painless, simple utilization, and decreased adverse effects resulting in improved patient compliance. However, this type of medication transfer has left ophthalmologists facing several limitations, including tearing production, a short residency time, and less permeability across ocular tissues. Furthermore, the physicochemical properties of conventional therapeutic agents could cause their inefficiency in treating drug-resistant ocular infections [68].

Nanocarrier systems could improve topical drug delivery for the effective transfer of antibacterial drugs into ocular tissues, and in several studies, niosome-based platforms have been used for this purpose. In this regard, Khalil et al. [69] reported that the antibacterial efficacy of a conventional antibiotic significantly increased when loaded into a niosomal dispersion. Also, niosomal formulation had a remarkable therapeutic impact on S. aureus conjunctivitis compared to the commercial product (Orchacin®). Moreover, the physical stability and sustained drug release of formulated niosomes were approved [69]. In another investigation, a niosomal antibiotic formulation was synthesized for ophthalmic administration. It was proven that niosomes have more antibacterial activity compared to commercial formulation. According to the ocular irritancy and histopathology tests, synthesized niosomes could be endured by the ocular tissue and have great potential to serve as a safe treatment for bacterial conjunctivitis [70]. Moreover, niosomes, through improved ocular drug bioavailability, could be appropriate nanocarriers for overcoming ocular infections caused by resistant S. aureus isolates [71].

Chitosan is a linear polysaccharide derived from chitin and is a favorable material for niosome-based hybrid systems due to its unique biological properties, such as nontoxicity, biocompatibility, and biodegradability [72]. In another study, niosomal drugs were incorporated into chitosan, and a bioadhesive system for ocular drug delivery was performed. The results of the ex vivo study exhibited that chitosan-embedded niosomes could enhance drug permeation into corneal tissue through slow and sustained drug release. In addition, the dramatic antimicrobial efficacy of this hybrid system, especially against S. aureus, was confirmed [73]. Also, in another study, encapsulated niosomes were encrusted with cationic chitosan for bioavailability improvement of antibiotics at the ophthalmic site, and the result of microbiological susceptibility tests revealed significantly higher anti-S. aureus activity of the synthesized formulation in comparison to ZenoxTM (commercial eye drop). Overall, chitosan-coated niosomes exhibit enhanced interaction with bacteria due to increased surface electrical charge, making them a promising candidate for effectively treating bacterial conjunctivitis [74].

In situ gelling systems are favorable approaches to enhancing the therapeutic efficacy of conventional ophthalmic medications by improving the precorneal availability of the drug. The mechanism of these systems is an immediate sol-gel transition, which depends on different stimuli, including pH change, temperature alteration, and solvent exchange [75]. In this regard, vancomycin entrapped in niosomes was integrated into a pH-triggered forming gel system for ophthalmic application. The physicochemical stability, rheological properties, and biocompatibility of niosomal gel were approved. Also, the anti-MRSA activity of the prepared gelling system suggested that niosomal gel could significantly treat bacterial eye infections by enhancing the ocular retention of the drug [76]. Another study proposed the temperature-dependent gelling system containing antibiotic-loaded niosomes for ophthalmic drug delivery. Also, niosomal gels could develop as a thermoresponsive in situ gel for ophthalmic delivery since their outstanding features include physical stability, pseudoplastic flow behavior, facilitating gel formation, and prolonged precorneal residence time. Therefore, niosome in situ gelling systems hold great promise for ophthalmic purposes and can potentially serve as a viable alternative to conventional treatments [77].

2.3. Skin Infections. S. aureus is known as commensal skin bacterium that causes widespread bacterial skin and soft tissue infections in humans [78]. This bacterium is among the predominant pathogens that colonize burn wounds and cause chronic and life-threatening infections, particularly in immunocompromised patients [79]. Moreover, the rapid emergence of antibiotic resistance is occurring among S. aureus strains, which hamper the treatment of burn infections caused by this pathogen [80]. Additionally, impaired microcirculation in burn patients inhibits the distribution of systemic drugs into injured skin; this issue emphasizes the undeniable role of topical drug delivery in management of burn wound infections [81]. However, limited penetration to skin layers challenges the topical drug administration, and nano-based transdermal drug delivery could be a novel and high-potency systems for successfully controlling skin infections [82].

Niosome-based gel systems could facilitate the transdermal delivery of drugs and enhance the performance of antibiotics for treating burn wound infections. In this regard, a study showed that niosomal gel improved the permeation behavior of encapsulated drugs while providing controlled therapeutic activity and prolonged residence time. Also, prepared niosomal gel had better rheological characterization, physical stability, and antimicrobial effectiveness (against *S. aureus*) in contrast to conventional gel formulation. Therefore, the niosomal gelling system can be a powerful transdermal nanocarrier and may provide a new perspective for treating bacterial skin, particularly burn infections [83].

Silver sulfadiazine (SSD), a broad bactericidal agent commonly used for topical administration in burn wounds, can improve healing and re-epithelialize damaged skin. However, the administration of SSD causes many problems in treating burn patients due to several drawbacks of the conventional dosage form, such as poor aqueous solubility, not being biodegradable, and frequent dressing changes [84]. The niosomal gel system could accelerate wound healing by improving the release profile of SSD. Accordingly, in the study by Dharashivkar et al. [85], the SSD niosomal gel was considered for topical delivery and treatment of burn wounds. In this study, the microbiological analysis demonstrated more anti-*S. aureus* activity of niosomal SSD compared to the marketed dosage form. Moreover, an animal study showed that niosomal gel could enhance the angiogenesis and re-epithelialization of injured skin and could be introduced as an alternative strategy in transdermal drug delivery [85]. Also, due to the spreadability property of niosomal gel, this system could develop into a favorable woundhealing agent in patients [86].

As mentioned, chitosan polymer could be an ideal candidate for a niosomal hybrid delivery system. Chitosan gelembedded niosomes were presented as an antimicrobial hybrid system for local antibiotic delivery in burn infections [87]. Also, the bioadhesive property of chitosan is an important factor in wound dressing because it causes extended retention and better absorption of the drug at the site of application. Thus, incorporating niosomal drug into a chitosan polymer improves the pharmacokinetic profile of the encapsulated drug and can be an appropriate solution for topical therapy in bacterial wound infections, especially *S. aureus* [88].

Povidone-iodine (PVP-I) is an antiseptic agent used for topical wound dressing, which brings several problems, including uncontrolled release from skin bandages. It has been shown that encapsulation of PVP-I into niosomal carriers could be a suitable option for topical drug delivery by providing a better drug sustained release profile. Moreover, the anti-*S. aureus* potential of niosomal PVP-I offers a novel and promising for eradicating skin infections caused by antiseptic-resistant *S. aureus* isolates [89].

2.4. Intracellular Infections. Intracellular infections present a significant challenge for healthcare settings that are faced with the increasing occurrence of resistance to antibacterial agents [90]. As a facultative intracellular pathogen, S. aureus can invade immune cells and live there with the help of various virulence factors. Bacterial cleaning is a big trouble for the host immune system due to S. aureus preventing the combination of phagosome and lysosome [91]. Also, the intracellular survival of S. aureus in the immune cell niche is associated with persistent and relapsing infections that cause resistance to immune cell responses and antimicrobial agents [92]. Due to short time retention and also limited penetration in the subcellular space, conventional antibiotic therapy may lead to failure against intracellular infections [93]. It is proven that vesicular drug delivery systems improve the subcellular distribution of antimicrobial agents. Indeed, this system would facilitate the uptake by activated tissue macrophages through increasing the accumulating drug concentrations in infected sites [94]. Therefore, the nanovesicles could be appropriate for intracellular delivery by increasing drug distribution into infected cells. In this regard, in the study by Akbari et al. [95], the intracellular activity of niosomal drug against macrophages infected with S. aureus was assessed. Scanning electron microscopy showed that the drug-containing niosomes was tightly attached to the macrophage cell membrane and facilitated phagocytosis of the drug into the infected cells. In addition, the images of fluorescence microscopy showed that the number of engulfed drugs in niosomal form was much higher than the free form. Also, the significantly prolonged



FIGURE 2: Schematic illustration of different materials loaded into the niosomal delivery system.

intracellular distribution of antibiotics occurred when macrophage cells were incubated with niosomal formulation. Also, the reduction in bacterial CFUs indicates more significant intracellular activity of the antibiotic-niosome compared with the non-niosomal form. Moreover, the results of this study suggested that a niosome-based nanosystem could be developed as a safe strategy for recurrent latent infections [95]. However, further research and investigation of the mechanism of intercellular activity of niosomes are needed to support this claim.

3. Niosomal Systems for Delivery of Different Antibacterial Agents

Several experiments have been performed by using niosomal systems to deliver different antibacterial agents. The encapsulated materials in niosomal nanocarriers can be categorized into chemical antibiotics and nonantibiotic antimicrobial agents, including natural compounds, antimicrobial peptides (AMPs), metallic nanoparticles (MNPs), and photosensitizers (Figures 2 and 3).

3.1. Antibiotics. The niosomal vesicular system can deliver the encapsulated antibiotics inside bacterial cells by using bilayer fluidity and fusogenic properties, which aims to reduce dose-dependent adverse reactions and improve antibiotic therapy outcomes. In Gram-positive bacteria, the bilayer fluidity of niosomes induces intracellular drug release through interacting with peptidoglycan barrier and creating a concentration gradient. While the niosomes' fusogenic properties cause drug penetration into Gram-negative bacteria through fusion with the outer cell membrane [96]. The niosomal vesicles, apart from enabling massive drug release into bacterial cell, can shield antibiotics from enzymatic degradation and are employed as an appropriate way for dealing with drug resistance [38]. In recent years, various niosomal formulations for different pharmaceutical purposes, particularly antibacterial drug delivery, have been prepared by researchers. Also, the niosomes have been used as favorable nanocarriers for encapsulating different antibiotic classes, including β -lactams, fluoroquinolones, cephalosporins, and glycopeptides. In Table 1, all antibiotic classes loaded in the niosomal vesicular system are presented, and following, we will explain some classes that are taken for *S. aureus* infections.

3.1.1. β -Lactams. Amoxicillin, known as semisynthetic penicillin, has been among the most extensively prescribed to β lactam antibiotics since the 1970s [109]. This antibiotic irreversibly binds to penicillin-binding protein and inactivates cell wall synthesis, resulting in permeabilization and bacterial cell lysis [110]. The prevalence of amoxicillin resistance in S. aureus isolates is a global concern, and antibiotic incorporation in niosomal nanocapsules can be a successful therapeutic approach to eliminate drug-resistant infections. In this regard, the study by Shadvar et al. [59] has been performed on the loading of amoxicillin in niosome nanoparticles, and their antimicrobial effects against MDR strains of S. aureus were approved. The findings of this study indicated that amoxicillin-niosomes remarkably decreased minimum inhibitory concentrations (MIC) (two- to fourfold) for all MDR and MRSA strains. The time-kill and agar well diffusion assays also confirmed the antibacterial properties of the synthesized niosomal formulation, which were proposed as anti-MDR-S. aureus agent with negligible cytotoxicity [59]. Also, the lipid solubility of amoxicillin is a promising feature because its bactericidal activity could be increased in niosomal form by improving the bioavailability and half-life [111].

3.1.2. Fluoroquinolones. The fluoroquinolones represent an expanded class of broad-spectrum antibacterial agents that are effective for the prevention and treatment of a variety of



FIGURE 3: Mechanism of photodynamic therapy based on niosomes against S. aureus infection.

Gram-positive bacteria and also S. aureus infections [112]. Change in the trans-cellular transport is one of the main resistance mechanisms of S. aureus to this class of antimicrobial agents, and increasing the bacterial uptake of antibiotics by vesicular drug delivery can be a promising approach to cutting back fluoroquinolones resistance. Accordingly, in a study, the in vitro antibacterial activity of niosome encapsulated four fluoroquinolones including ciprofloxacin, gatifloxacin, levofloxacin, and norfloxacin, against 20 ciprofloxacin-resistant S. aureus strains (CRSA) was determined. All fluoroquinolones-loaded niosome reduced MIC against S. aureus (at least fourfold) and had more significant antibacterial effects than conventional antibiotics [99]. In addition, another study evaluated the inhibitory activity of niosomal ciprofloxacin preparations with two formulations against S. aureus clinical isolates. It also found that ciprofloxacin incorporated into niosomes with optimized formulation markedly decreased ciprofloxacin MIC (8-32-fold), and three of 45 CRSA isolates had lost their resistance phenotype [61]. Moreover, it has been proven that niosomal formulation decreases the MIC and sub-MIC values of ciprofloxacin against MRSA strains while restoring the efficacy of conventional drugs [62]. The results of these studies suggested that developing niosomal formulations could improve the potential of drug delivery in the bacterial cell and that niosome nanocarriers could prevent the rapid emergence of resistant fluoroquinolones, particularly among MRSA strains [113].

3.1.3. Cephalosporins. Cephalosporins are a large group of antimicrobial drugs classified into different generations, which have been introduced for clinical administration since 1964. Cephalosporins have played a significant role in treating various bacterial complications, including skin and soft tissue infections, community-acquired pneumonia, bacteremia, and meningitis [114]. However, the administration of cephalosporins has been challenged since the increasing emergence of resistance to β -lactam antibiotics among *S. aureus* strains, resulting in a greater need to discover alternative antibacterial agents [115]. Also, variation in the drug

plasma level, adverse effects, and a short residence time in the site of action are the main problems associated with conventional dosage forms of cephalosporins [116]. It is also proven that niosomes could improve drug bioaccessibility by controlling release profiles, thereby preventing drug-induced side effects. Also, incomplete absorption of cephalosporins is a key factor in developing resistance to this class of antibiotics [117] and niosomal encapsulation could enhance the distribution of poorly absorbed drugs into target sites [118]. In addition, the ex vivo study revealed that the niosomal formulation has a high potential for oral administration through improved intestinal permeation of conventional drugs [100]. Moreover, niosomal encapsulation can be a favorable solution to shield cephalosporins from the β -lactamase enzyme, a main and adaptive resistance mechanism to cephalosporins in S. aureus strains [32, 119]. Also, the antibacterial potential of cephalosporins was dramatically increased by incorporating these antimicrobial drugs into niosomes and, thus, could be an ideal nanocarrier for medicinal agents [48, 101, 120].

3.1.4. Glycopeptides. Vancomycin is a glycopeptide antibiotic first presented in 1958, and it is administrated as a choice drug for treatment and prophylaxis of serious infections caused by S. aureus, particularly MRSA. Unfortunately, the susceptibility of MRSA strains to vancomycin is decreasing, and a review of the clinical literature indicates the high emergence of VISA and VRSA among patients [121]. However, niosome nanoparticles as a nano-based approach could have superior anti-S. aureus activity than conventional formulation. In this regard, Barakat et al. [58] showed that the presentation of vancomycin in a niosomal form causes an eightfold reduction in MIC of MRSA isolates compared to the free drug. Moreover, niosomes could improve the pharmacokinetics profiles of vancomycin via extended serum half-life and reduced concentration-dependent toxicity. Also, niosomal delivery systems that prevent enzymatic degradation could be proposed for combating vancomycin resistance in S. aureus [17].

	TABLE 1: Char	acteristics and consequences of diffe	erent antibiotics l	oaded in niosomal systems.		
Antibiotic class	Active compound(s)	Formulation(s) developed	Pathogen(s)	Result(s)	Model of study(s)	References
Macrolide	Azithromycin	Niosomal gel	S. aureus	High antimicrobial activity, enhancing drug skin permeation compared to the conventional gel, excellent viscoelastic, and rheological properties	In vitro, ex vivo	[83]
		Niosome	MRSA	Improving antibacterial action	In vitro	[67]
Rifamycin	Rifamycin S	Niosome, PEGylated niosome	S. aureus	Reduction in MIC value of free drug	In vitro	[98]
Sulfonamide	Sulfadiazine	Niosomal gel	S. aureus	Sustained release profile, increasing in diameter of inhibition zone, accelerated burn wound healing	In vitro, in vivo	[85]
		Niosome	S. aureus	Reduction in CFU of biofilm-forming strains, no cytotoxic effects for fibroblast cell	In vitro	[63]
		Niosomal gel	MRSA, MSSA	Increasing antibacterial efficacy of vancomycin, reduction in bacterial CFU in infected eye, prolonged the ocular residence time of drug	In vitro, in vivo	[76]
Glycopeptide	Vancomycin	PEGylated niosomes	MRSA	High antibacterial and antibiofilm activities, good biocompatible feature, treatment of bacterial skin infection	In vitro, in vivo	[65]
		Niosome	S. aureus, MRSA	Reduction in MIC, MBIC, and MBEC values of free drug	In vitro	[58]
<i>β</i> -lactam	Amoxicillin	Niosome	S. aureus	High antimicrobial activity against MDR strains, reduction in CFU of biofilm-forming bacteria	In vitro	[59]
		Niosome	S. aureus	High intracellular antimicrobial activities	In vitro	[95]
	Ciprofloxacin	Niosome	MRSA, CRSA	Enhancing the antibacterial and antibiofilm potentials compared to free drug	In vitro	[61]
		Chitosan-coated niosomes	S. aureus	Increasing in diameter of zone inhibition, enhancement of drug permeation in corneal	In vitro, ex vivo	[73]
	Ciprofloxacin, gatifloxacin, levofloxacin, norfloxacin	Niosome	S. aureus	Reducing the MIC of fluoroquinolone against drug-resistant strains	In vitro	[66]
Fluoroquinolone	Moxifloxacin	Niosomal chitosan gel	S. aureus	Improving the antibacterial efficacy of drug, rheological, and bioadhesive properties	In vitro	[88]
	Ofloxacin	Niosome	S. aureus	Increasing antibacterial effect, improving ocular bioavailability of drug, no ocular irritancy	In vitro, in vivo	[20]
		Niosomal chitosan gel	S. aureus	Significant antibacterial activity, sustained release pattern, mucoadhesive characteristic	In vitro, in vivo	[74]
	Lomefloxacin	Niosome	S. aureus	Treatment of ocular infection with no signs of irritation or inflammation	In vitro, in vivo	[69]
	Cefdinir	Niosome	S. aureus	Improving skin permeability, increasing antibacterial activity of drug	In vitro, ex vivo	[100]
	Cefotaxime	Niosome	S. aureus	Enhancing the inhibitory effect of drug	In vitro	[101]
Cephalosporin	Cephalexin	Niosome	S. aureus	Prolonged drug release, decreasing in the MIC value of drug	In vitro	[48]
	Cefazolin	Niosome, chitosan-coated niosomes	S. aureus	Accelerating skin regeneration and bacterial infection elimination	In vitro, in vivo	[102]

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Antibiotic class	Active compound(s)	Formulation(s) developed	Pathogen(s)	Result(s)	Model of study(s)	References
Tetracycline	Doxycycline	Niosomal gel	S. aureus	Significantly increasing the antibacterial efficacy of free drug, good physical stability, pseudoplastic flow behavior	In vitro	[77]
Aminoglycoside	Streptomycin	Niosome	S. aureus	Antimicrobial and antibiofilm activities, negligible cytotoxicity against the human foreskin fibroblasts	In vitro	[103]
	Gentamicin	Niosomal gel, niosomal chitosan gel	S. aureus	Synergistic antibacterial activity with curcumin, suitable gelling, and rheological characteristics	In vitro	[104]
Chloramphenicol	Chloramphenicol	Niosome	S. aureus	Sustained release pattern, treatment of bacterial conjunctivitis, increasing the diameter of inhibition zone	In vitro, in vivo	[105]
Fusidane	Fusidic acid	Niosomal gel	Ι	Enhancing drug skin permeation, excellent spreadability, and rheological features	In vitro, ex vivo	[86]
Lincosamide	Clindamycin	Niosome	S. aureus	Decreasing in the MIC value of the free drug	In vitro	[106]
Oxazolidinone	Linezolid	Niosomal gel	MRSA	Improving skin permeation, high antibacterial activity, no skin irritation	In vitro, ex vivo	[107]
Carbapenem	Meropenem	Niosome	MRSA, VRSA	Antibiofilm and antibacterial activities, downregulating the biofilm gene expression	In vitro	[108]
MRSA, methicillin-resistant Si minimum biofilm inhibitory c Staphylococcus aureus.	<i>aphylococcus aureus</i> ; PEG, polyeth oncentration; MBEC, minimum b	tylene glycol; MIC, minimum inhibitory co iofilm eradication concentration; MDR, mu	oncentration; CFU ultidrug resistant; 0	. colony-forming unit; MSSA, methicillin-sensitiv CRSA, ciprofloxacin-resistant <i>Staphylococcus aure</i>	re Staphylococcus aur us; VRSA, vancomyc	eus; MBIC, in-resistant

TABLE 1: Continued.

TABLE 2: Ad	vances in niosome-based formulations for d	elivery of natural compounds and their e	fficacy against S. aureus and other pathoge	ens.	
Natural compound(s)	Formulation(s) developed	Pathogen(s)	Result(s)	Model of study(s)	References
Ajwain essential oil	PEGylated niosome	Staphylococcus aureus, Escherichia coli	Reduction in MIC value of ajwain essential oil, no toxicity for human fibroblast cells, good cell transfection	In vitro	[129]
Tea tree essential oil	Niosomal gel	S. aureus, Candida albicans	Increased antibacterial properties in comparison with conventional gel, excellent spreadability, and release profile	In vitro	[130]
Myrtle essential oil	Niosome	S. aureus, Staphylococcus epidermidis, Serratia marcescens, Bacillus subtilis	Enhancing antibacterial activity of free drug	In vitro	[44]
Lippia citriodora essential oil	Niosome	S. aureus, E. coli	Increasing the diameter of the inhibition zone, antioxidant activity	In vitro	[131]
Rosmarinic acid	Niosomal gel	S. aureus, Propionibacterium acnes	Significant antimicrobial activity, reduction in CFU of pathogen in infected skin, no skin irritation	In vitro, in vivo	[132]
Berberine	Niosomal gel	S. aureus, Pseudomonas aeruginosa, B. subtilis, C. albicans	Increasing antimicrobial activity of free drug, good release profile	In vitro	[43]
Thymol	Niosome embedded collagen/calcium scaffold	S. aureus, E. coli, P. aeruginosa	Sustained-drug release from composite scaffolds, improving cell viability against human fibroblasts, high antibacterial potential	In vitro	[133]
Propolis	Niosomal gel	S. aureus, C. albicans	Lower MIC value of niosomal formulation compared to ethanolic solution of propolis, enhancing drug deposition in skin layers	In vitro, ex vivo	[134]
Trans-ferulic acid	Niosome	S. aureus, E. coli, Acinetobacter baumannii	Improving the MBC value of drug, increasing the viability of HFF cell line, antioxidant activity	In vitro	[47]
Glycyrrhiza glabra, Hedera helix extracts	Niosomal temperature and pH stimuli system	S. aureus, E. coli	Enhancing the drug antibacterial potential with reduction in MIC and MBC values, good cell transfection	In vitro, in vivo	[135]
	Niosomal gel, niosomal chitosan gel	S. aureus, E. coli	Sustained release profile, suitable gelling and rheological characteristics, the synergistic activity with gentamycin	In vitro	[104]
Curcumin	Niosomal gel, niosomal chitosan gel	S. aureus, P. aeruginosa	Decreasing the MIC and MBC values of curcumin, the synergistic activity with copper/silver nanoparticles, high antibiofilm potential	In vitro	[136]
Coconut oil	Niosome	S. aureus	High inhibitory effect against MDR strains	In vitro	[137]
Mangosteen extract	Niosome incorporated in alginate/pectin hydrogel	S. aureus, S. epidermidis	Increasing antibacterial activity of free drug no toxicity for fibroblasts and red blood cells, good physical characteristics	In vitro, in vivo	[45]
Tannic acid	Niosome	S. aureus, E. coli, P. aeruginosa, Klebsiella pneumoniae	Downregulating the biofilm gene expression, controlled inhibition of bacterial growth	In vitro	[46]
PEG, polyethylene glycol; MIC, minin	num inhibitory concentration; CFU, colony-formi	ing unit; MBC, minimum bactericidal concenti	ation; HFF, human foreskin fibroblast; MDR, n	multidrug resistar	it.

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As was already said, surface functionalized with PEGylation could enhance the performance of niosomal drug delivery system. Applying PEG polymeric materials to nanoformulation structures could improve loading efficiency and decrease drug leakage [122]. Moreover, the PEGylation could inhibit the recognition and cleaning of niosomes by the host immune system and subsequently enhance their bioavailability. Indeed, by preventing the adsorption of blood proteins on niosomes, the PEG polymers could reduce opsonization and phagocytic uptake. Also, nanoparticle PEGylation, as passive targeted drug delivery, effectively enhances the antibacterial activity of niosomal systems. In this regard, the result of the study showed that PEG niosomes have a significant in vivo antibacterial efficacy against MRSA skin infection mouse model, compared to bare niosomes [65]. Besides passive drug targeting, conjugation of PEGylated nanoparticles with target ligands could provide favorable therapeutic indexes of drug administration in desired tissues and could be suggested as a beneficial solution for inadequate distribution of antibacterial drugs into infected sites [123].

3.2. Natural Compounds. Natural compounds are derived from various sources, including animals, plants, and microorganisms, and can play significant pathological roles against different diseases [124]. These compounds are gaining the attention of scientists due to their numerous pharmaceutical applications, particularly antibacterial activity [125]. Regardless of their high potential therapeutic effects, the biological activity of natural compounds is limited because of weak solubility, poor bioavailability, and instability during storage [126]. As a result, the nanodrug delivery system has been deemed an appropriate tool for overcoming the abovementioned drawbacks, which cause success delivery of natural compounds in suitable doses [127]. Furthermore, finding auxiliary, cost-effective, and potent antibacterial agents to overcome the antibiotic resistance of the S. aureus strain is crucial due to its high prevalence in healthcare settings and food [128]. In this manner, researchers have formulated niosomes with various natural compounds, effectively enhancing their anti-S. aureus activities. All advances in the formulations of niosomal nanocarriers for encapsulating natural compounds are summarized in Table 2.

3.2.1. Essential Oils. Essential oils are natural hydrophobic liquids composed of various chemical classes, including phenols, aldehydes, alcohols, ketones, and esters [138], which have detrimental effects on a wide range of bacteria. Due to the hydrophobic matter, the essential oils could merge with the cytoplasmic membrane, resulting in leakage of cellular contents and bacterial death [139]. However, these compounds are volatile and highly unstable [140], and in combination with niosomal nanocapsules, the stability of essential oils could be increased through gradual release. Moreover, it has been found that essential oil-loaded niosomes may be suitable for wound disinfection applications due to their anti-S. aureus efficacy, good intracellular transfection, and lower cytotoxicity for human skin fibroblasts [129]. In another study, the topical gel was prepared with encapsulation of tea tree oil into vesicular systems (niosome and liposome), and also the homogeneity, spreadability, and

antibacterial efficacy against *S. aureus* were approved [130]. Moreover, lippia citriodora oil-loaded niosomes with anti-*S. aureus* and antioxidant activities have a high potential for food industry application as a natural preservative. Therefore, niosomal encapsulation of bioactive compounds could be a novel approach for controlling *S. aureus* food-borne outbreaks [131].

3.2.2. Propolis. As a sticky compound, honeybee propolis has strong and broad-spectrum antibacterial activities through different mechanisms, including increasing cell membrane permeability, disrupting cytoplasmic membrane potential, inhibiting protein synthesis, and interfering with bacterial cell division [141]. Also, the highly potent antimicrobial ability of propolis is associated with diversity in its chemical composition, which mainly comprises flavonoids (e.g., apigenin), phenolic (e.g., artepillin C), and aromatic acids (e.g., ferulic acid). Moreover, artepillin C shows high antibacterial effects against MRSA, and the synergistic anti-MRSA activity of apigenin with β -lactam antibiotics was also proven [125]. Nevertheless, the low physical stability and sticky resinous nature of propolis pose several challenges in its application. In this context, a niosomal-based system could play a valuable role in the development of propolis processing. Notably, the antimicrobial potential of propolis was significantly improved through its formulation into niosomal gel, which could be an ideal candidate for bacterial and fungal wound dressing [134].

3.2.3. Curcumin. Curcumin (Curc) is a polyphenolic herbal compound that has displayed antibacterial activity by inhibiting biofilm formation and virulence factor production [142]. The reports indicate that nanoparticulate drug delivery systems have effective role in improving the therapeutic properties of curcumin, especially its antibacterial ability [143, 144]. In this regard, it was shown that Curc niosome gel had increased inhibitory effects on S. aureus in contrast to free Curc (ethanol solution). Also, the synergistic antibacterial activity between Curc and gentamicin was approved when simultaneously incorporated in niosomes. Moreover, a thermoresponsive in situ gel system based on niosomal Curc was proposed as a favorable platform for intravesical instillation due to its excellent properties, including short gelation time, good rheological behavior, gel erosion kinetics, and sustained release profile [104]. However, in the study, Curc (with/without Rose Bengal)-loaded niosome nanoparticles did not show any antibacterial effect on S. aureus which may be due to the low concentration of Curc loaded into nanoformulation or antagonistic effects between loaded drugs [145].

3.2.4. Mangosteen. Mangosteen extract (ME) is derived from a tropical plant (*Garcinia mangostana*) which contains outstanding medicinal benefits such as anti-inflammatory, antioxidant, and antibacterial properties [146]. The phytochemical compounds contained in ME affect Gram-positive bacteria by inhibiting peptidoglycan synthesis [147]. The results of study conducted by Pooprommin et al. [45] showed that incorporating niosomal ME into a hydrogel scaffold provided consistent

growth inhibition of *S. aureus* and *S. epidermidis*. Furthermore, synthesized niosomal platforms can be considered for wound healing applications due to their hemocompatibility, no skin irritation, and biocompatibility [45].

3.3. Antimicrobial Peptides. AMPs are cationic amphiphilic molecules with 10-50 amino acid residues. These peptides have high antimicrobial capacity against broad-spectrum infectious bacteria via different mechanisms such as membrane permeabilization, inhibition of cell wall formation, and disruption of intracellular processes. Lipid-based delivery systems are attractive for transporting AMPs and their protection from proteolytic degradation [148]. However, cholesterol in liposomal membranes might have a detrimental effect on AMPs encapsulation [149], and results in the study suggested that niosomes could be more suitable carriers for AMPs than liposomes due to better encapsulation efficiency. Also, the high stability and cost-effectiveness of niosomes offer an alternative approach for incorporating AMPs in nanostructured materials [150]. In the study, the in vitro inhibitory effects of melittinloaded niosomes against MRSA and VISA were found, and it is demonstrated that S. aureus skin infection is limited after administration of melittin nanoniosomes [151]. In another study, the niosomal gels with α -/ β -defensin significantly treated MRSA-infected wounds, and the high ability of niosomes for effective delivery of AMPs was approved [152]. The niosomal gel could increase the transdermal absorption of AMPs through their protection against chemical and thermal degradation [153]. Also, in separate studies, the anti-S. aureus activity of niosomes-encapsulated nisin and lysostaphin was found that could be effective strategies for treating infectious diseases [150, 154].

3.4. Metallic Nanoparticles. Recently, MNPs have been gaining popularity for their strong antibacterial activity. The possible antibacterial mechanisms of action of MNPs include disruption of enzymes in the respiratory chain, excessive generation of reactive oxygen and nitrogen mediators, and disruption in metabolic activities, protein synthesis, and repair systems [155]. Also, these nanoparticles have been highlighted as potential strategies to treat MDR infections due to the low risk of bacterial resistance to MNPs [156]. However, cytotoxicity, nonbiodegradability, and low bioavailability are major challenges in the development and clinical application of MNPs. Combining MNPs with vesicular vehicles, including niosomes, could be a favorable approach to tackling MNPs drawbacks [157]. In this regard, the study demonstrated that the antibacterial effect of MNPs against S. aureus was significantly enhanced when synthesized MNPs were loaded into niosome nanoparticles. Also, the strong antibiofilm activity of MNPs in niosomal form was approved that niosome-loaded MNPs reduced the expression level of biofilm-forming genes compared to free MNPs [158]. Moreover, in another study, Curc and MNPs simultaneously incorporated into niosomal system that synthesized hybrid system had more antibiofilm and antibacterial effects against S. aureus in contrast to non-niosomal forms [136]. Furthermore, it is shown that the chitosan composites based on niosomes and MNPs were highly effective against Gram-positive and -negative pathogenic bacteria, particularly *S. aureus*, and the synthesized niosomal composite had wound-healing properties [159]. Thus, the coformulation of MNPs into niosomes could be developed in clinical nanomedicine, and this hybrid delivery system could be highlighted to eradicate MDR infections.

3.5. Photodynamic Therapy. Photodynamic therapy (PDT) is an efficient approach for treating microbial infections with widespread antibiotic resistance. PDT consists of lightabsorbing molecules known as photosensitizers (PS), which can eliminate pathogens by generating reactive oxygen species. Lacking induction of resistance is a promising advantage of PTD that could be used to avoid the emergence of MDR pathogens [160]. However, the development of PTD may be hindered by the hydrophobic matter of many PSs, whereas lipid-based nanoparticles as a prominent PS delivery system could resolve the mentioned drawback [161]. It has also been proved that niosomal incorporation could enhance the antimicrobial photobiological activities of PSs by improving their poor water solubility [162], and niosomes could be proposed as promising nanocarriers for the clinical development of PDT (Figure 3).

4. Conclusion

S. aureus, being a dangerous human pathogen, is responsible for causing a wide range of diseases, posing numerous concerns for healthcare systems. The spread and dissemination of MRSA and VRSA strains, as highly virulent pathogens, are increasing worldwide that present significant challenges in medical settings. Due to the lack of effectiveness of the conventional treatments against MDR S. aureus isolates, it is urgently necessary to discover an alternative therapeutic solution for controlling infections caused by them. The niosomal drug delivery system can be developed as an effective strategy for reducing the problems related to antimicrobial resistance in S. aureus. The acceptable stability, cost-effectiveness, simple handling, and biodegradability are among the excellent features of these nanoparticles that significantly improve the therapeutic indices of loaded contents. Moreover, niosomes can be targeted to enhance the accumulation of drugs in the biofilm environment, thereby eradicating persistent infections. In addition, niosomes can prevent the induction of resistance in S. aureus strains by controlling the release of drugs and inhibiting their enzymatic degradation, which can be a helpful approach in managing S. aureus outbreaks. Niosomes, with their high encapsulating capacity, offer a powerful platform for delivering both synthetic and naturalbased drugs, thereby enhancing their pharmacokinetic properties, antimicrobial activity, and clinical efficacy. Also, the niosome-based vesicular systems have performed well in ocular delivery, and applying niosomal gelling systems could prove to be a novel therapeutic approach against complicated ocular infections associated with MDR S. aureus strains. Furthermore, the topical niosomal system could be beneficial for treating S. aureus skin infections, and chitosan-coated niosomes as a hybrid delivery system can be applied for wound healing. Moreover, optimization and surface modification of niosomal formulations could improve the ability of this delivery system for bacterial targeting. Generally, according to our findings, niosomes would be a successful drug delivery system for different biomedical applications, particularly in eradicating serious resistant infections caused by *S. aureus*.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

MRA and JH conceived and designed the study. JH contributed to comprehensive research and wrote the paper. JH, MRA, and ZC participated in editing the manuscript. All authors read and approved the final manuscript.

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