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Review Article

A Short Review on Advances in Nanosystems Emerging as an Effective Approaches to Control Pathogenesis of *Staphylococcus spp*

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Abstract

Nanomaterials in drug delivery systems are emerging as a potential source of treatments. The bioavailability of nano-carriers depends upon various factors including their mode of administration, target specificity, availability of active compound and compatibility with biological system. Due to ingenious survival strategies many antibiotics become ineffective in the treatment of *Staphylococcus* spp. causing diseases. Though, nanosystems have been developed as an emerging approach to vanquish the obstacles for the treatment of *Staphylococcus* spp infections. Due to their encouraging and substantial outcomes, this review focused on the exploration of advances in nanosystems and their curing mechanism to control the infection of *Staphylococcus* spp. Several nanosystems are previously reported and compiled herein, which may use as a treatment of *Staphylococcus* causing diseases as well as inhibition of biofilm formation. Pathogenesis mechanisms such as immune clearance, membrane permeability and production of β-lactamase also described briefly in this review.

Introduction

The *Staphylococcus* is a gram positive facultative aerobic bacteria. It belongs to the family Staphylococcaceae and order Bacillales. It mainly reside on the skin and mucous membrane of humans and other animal. *Staphylococcus* is an opportunistic pathogen mainly colonize on human anterior nares and causes life threatening bloodstream infection like sepsis and endocarditis. It causes hospital-acquired infections mainly in soft tissue by confiscating the host defense and coagulation systems [1]. The infections creates high mortality rate despite of the proper treatment. *Staphylococcus aureus* is one of the most fatal bacteria, approx 20% to 50% mortality has estimated [2]. It causes inflammation and immunosuppression which leads to the disseminated intravascular coagulation (DIC), damage the endothelium layer and blocks blood stream as well as resulted as oxygen depletion in organs [3,4]. The adhesion process is the key step for the pathogenesis of *S. aureus* by secreting many toxins. They also secrete many factors like fibronectin binding protein A (Fnbp A), Fnbp B and teichoic acid which promote colonization at infection site and resist to immune response of the host [5]. The *S. aureus* develops resistance to β-lactams, daptomycin and glycopeptide antibiotics. Moreover, Methicillin-Resistant *Staphylococcus aureus* (MRSA) also develops an antibiotic resistance by over secreation of β-lactamases and reducing the efficacy of antibiotics.

Due to ingenious survival strategies many antibiotics are ineffective in the treatment of *S. aureus*. Therefore, deal with

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nanomaterials have developed as an emerging approach to vanquish the obstacles for the treatment of *S. aureus* infections. Nanosystems have ability to inhibit the biofilm formation, cell wall penetration, enhanced intracellular retention and improve antibacterial activity of the loaded antimicrobial agents [6]. However, several nanoparticles passively accumulates in targeted organs because of their own characteristics, such as nanosize, surface charge, and large surface area. While, modified nanomaterials could increase the membrane transportation by actively identify the receptors of host cells as well as bacterial cells. Currently, several microbicidal agents are conjugated with nanocarriers to increase the pharmacological activities against *Staphylococcus spp.* Therefore, nanosystems drug delivery advocated as an ideal weapon to control the pathogenicity of *Staphylococcus spp*.

Nanomaterials as chemical substances or biomaterials that are manufactured and used at a very small scale. Nanomaterials are develop to exhibit novel characteristics such as increased strength, chemical reactivity or conductivity as compared to the same material without nanoscale features. Due to their large surface area and easy surface modification, nanoparticles also used as nanocarriers to carry the drugs to targeted site in drug delivery system. Several metallic, magnetic, silica and carbon based nanoparticles have been designed for drug delivery applications [7,8].

This review describe the pathogenesis mechanisms of *Staphylococcus* such as immune clearance, membrane permeability and production of β-lactamase. We have compiled the several nanosystems which are previously known as a bactericidal agent for *Staphylococcus spp*. and their action mechanism also be summarized herein.

Pathogenesis mechanisms of Staphylococcus which causes infection

By immune clearance: In the bloodstream, Kupffer cells efficiently regulates *Staphylococcus* survivability by phagocytosis while sometimes the phagocytosis process has compromises then staphylococci certainly survive and multiply inside the cells. Thus, they release from intracellular niche and encounters by the peritoneal macrophages and bloodstream neutrophils [9]. An essential attributes of *Staphylococcus* requires to create infection and coordinate with timely expression of virulence factors along with relevant genes. Several reports are highlighted the genetic adaptation system 'accessory gene regulator' (Agr) or quorum-sensing system in *S. aureus* which requires for secretion of number of toxins and other soluble virulence factors [10]. It senses an auto inducing peptide (AIP) secreted by the *S. aureus* itself. The activation of Agr signaling occurs when AIP reaches a critical concentration due to high bacterial density. An active Agr system is essential for intracellular survival of *S. aureus* or inside the phagocytes cells [11].

By membrane permeability: The cell membrane permeability is another factor which directly relates to the bacterial survivability. Drug absorption is reduces when the energy metabolism of the bacteria is affected and creates a lower cell membrane permeability and leads to the drug resistance [12].

Long term exposure of drugs activates the efflux system which enhance the efflux of drugs and develop a drug resistance in the bacteria [13]. The efflux proteins exchanges takes place by electrochemical gradient formed by H^+ on both side of cell membrane [14]. Majorly, three multidrug-pumping proteins *viz*; QacA, NorA, and Smr present on the *Staphylococcus aureus* cell membrane (Foster, 2016). Among these, QacA is an important factor in MRSA [15].

By production of beta lactamase: The β-lactamase causes hydrolysis of β-lactam antibiotics and develops a lethal effect on bacteria by two mechanism (i) by binding to the penicillin binding protein which repress mucin synthesis in cell wall and leads to the cell wall disruption as well as bacterial lysis (ii) by trigger autolytic enzyme activity of bacteria [16]. Moreover, MRSA also develops an antibiotic resistance by over secreation of β- lactamases. It reduces the effect of antibiotics by hydrolysis of β-lactamase and resulted as inactivation of antibiotics. β-lactamase binds to the antibiotics and prevents them to reach the target site .

Action mechanism of nanomaterials to prevention of *Staphylococcus spp*. infection

Nano pharmaceuticals could efficiently administer to the human body by orally, intravenously, respiratory system and topically [17]. The size, shape, surface charge, chemical composition and hydrophobicity of nanosystems influences to the intestinal mucus. The mechanism of action is different with different set of nanomaterials for example liposome nanomaterials with PEG coating are easily able to penetrate in mucus layer than nanomaterials coated with chitosan. The negative charges presents on the surface of nanomaterial as well as mucus that causes repulsion and hydrophilicity of the mucus surface [18]. A previous study suggested that zinc oxide nanoparticles doped with digestive enzyme 'pancreatin' which shows potential antibacterial activity against Methicillin Resistant *Staphylococcus aureus* (MRSA). It induces the oxidative stress, membrane potential alteration and membrane damages. Their synergistic effects resulted as degradation of biofilm of pathogens through protease and amylase lipase activity of 'pancreatin'. The reduction of membrane potential leads to ROS generation and alters the homeostasis of the pathogen, oxidization of lipid content and resulted as disintegration of bacterial cell wall [19].

Metal nanoparticles

The metal nanoparticles exhibits potential antibacterial activity and helps to overcome resistance in pathogens. Their mechanism of action involves in metal ion release, cell wall and membrane disintegration, ROS generation, intracellular penetration and DNA damages [20]. Silver nanoparticles are widely accepted for their effective antibacterial activity by altering the cell wall protein, inhibits cell division, disrupt signal transduction and cause ROS production [21]. Recently our research team also reported the strong bactericidal activity of

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biogenic silver nanoparticles than their chemical counterparts [22] Figure 1.

The gold nanoparticles (AuNPs) shows promising results due to their high biocompatibility property [23]. Ultrasound-triggered nanosystem also used to treat MRSA infection by modifying polyethylenimine grafted bismuth oxybromide (BiOBr) nanoplates with

Fe3. [24]. Likewise, Zinc-doped Prussian Blue (ZnPB) had a great photothermal anti-MRSA activity.

Carbon based nanomaterial

Carbon Based Nanomaterial (CBN) including Graphene Oxide (GO), Reduced Graphene Oxide (RGO), Graphene Quantum Dots (GQDs), Carbon Quantum Dots (CQDs), Carbon Nanotubes (CNTs), and Carbon Nanofibers (CNFs) are also used as potent antimicrobial agent. Among these, GO have excellent chemical and mechanical properties and it can penetrate the cell membranes as well as leading cellular damages of the bacteria [25]. The CNB have high permeability which makes them efficient to penetrate the thick biofilm. At present, polymer-based nanocomposites also used as antibiotic carriers to treat intracellular MRSA. The diblock guanidinium polymer has been found efficient internalization in keratinocytes and inhibits the growth of intracellular MRSA [25]. Several other nanosystems are also have been reported for prevention and treatment of *Staphylococcus* spp. causing diseases listed in Table 1.

Advantages and disadvantages of nanosystems

Increase in antibiotic resistance in bacteria emerges as a greatest challenge to human health. Though, deal with nanomedicine plays a vital role in increasing the potency of existing therapies, by increasing stability and physiochemical properties of antibiotics, by biofilm internalization, prolongation of antibiotic release and targeted delivery of drug to the site of infection [58]. Size and surface potential of nanomaterials drives interaction with various component of the tissue and regulates intracellular uptake and biodistribution [59]. Hydrophobic property of nanomaterials helps in targeting the drugs to the targeted site and enhance the adhesion efficacy [58]. Nano-sized systems have ability to impede the instigation of resistance as well as vanquishing the resistance strategies of bacteria [60].

Despite of significant improvements in antibiotics delivery and stability, nanosystems also suffering from many drawbacks that limiting their efficient usage. Physical and chemical instability of nanoparticles, antibiotic leakage from liposomes due to incompatible physiological conditions and low loading capacity [62-72] are listed as major demerits of nanosystems. Several lipids sensitivity occurs due to high temperatures as well as fabrication techniques are very complex, expensive, and difficult to be scaled up [63].

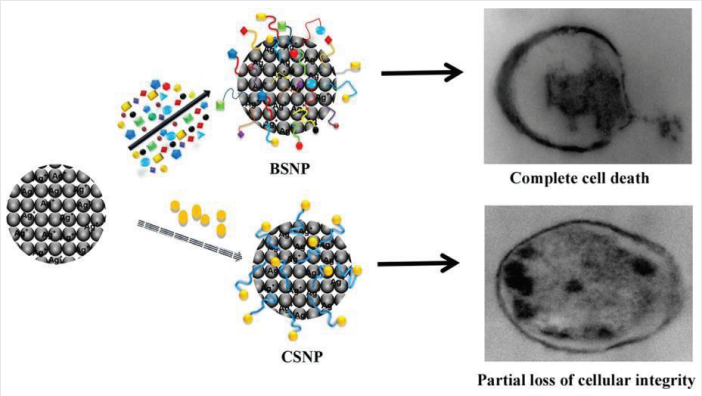

Figure 1: A comparative study of biogenic silver nanoparticles (BSNP) and chemical counterparts (CSNP) against *S. aureus*. Image adopted from Kumari, et al. [22].

Table 1: List of diseases caused by *Staphylococcus* spp. and their curing agents as nanomaterials.

Staphylococcus spp.	Diseases	Symptoms	Nanosystems as disease curing agent	References
Staphylococcus aureus	Epidermal and food borne diseases	Pimples , blisters on skin, nausea, vomiting, and abdominal cramps with or without diarrhoea	• Thyme oil nanoemulsion, • CuO/ZnO nanoparticles. • Parthenium hysterophorus Silver Nanoparticles. • ZnO and Yb (ytterbium) - doped ZnO nanoparticles. • CSNP-Cur (Curcumin loaded on positively charged chitosan nanoparticles). • Porphyrins and their self-assembled conjugates with Silver Nanoparticles. • Vancomycin+mesoporus Silica Nanoparticles (VMSNs). • Nanocomposite film (SA-CS@Cuo/ZnO) composed of Sodium alginate functionalized by Copper Oxide nanoparticles (CuONPs) and Zinc oxide nanoparticles (ZnONPs). • Fungal chitosan encapsulated Gynura procumbens mediated AgNPs (GP-AgNPs). • Sphingobium sp. MAH-11 mediated synthesis of AgNPs. Guar gum/Gelatin/Silver nanocomposite (GG/G1/Ag-N-composite). • Celery seed oil nanoemulsion. • Calamansi lime EO nanoemulsion.	He, et al. [26] Guan, et al. [27] Sivakumar, et al. [28] Navarro-Lopez, et al. [29] Ma, et al. [30] Shabangu, et al. [31] Fulaz, et al. [32] Rajkumar, et al. [33] Akter, et al. [34] Khan, et al. [35] Nirmala, et al. Liew, et al. [36] Li ,et al. [37]

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Methicillin-resistant *S. aureus* (MRSA)	Skin and soft tissue infections, pneumonia, osteoarticular infections, bacteremia, and endocarditis.	Skin erythema and separation seen in staphylococcal scalded skin syndrome	• Gelatin stabilized by photocrosslinking using riboflavin (vitamin B_2) as a photocatalyst, and carvacrol • Biguanide-Derived Polymeric Nanoparticles. • AgNPs synthesized by Desertifilum sp. (D-SNPs). • Vancomycin+mesoporus Silica Nanoparticles (VMSNs). • Elecrtospun Chitosan (CS)/poly (vinyl alcohol) (PVA) nanofibres (CPNFs) loaded with Cefadroxil monohydrate (CFX). • Oleylamine based zwitterionic lipid (OLA) with biodegradable polymer chitosan (CHs) formed pH-responsive VM (vancomycin)-OLA-LPHVs (lipid-polymer hybrid) 1 nanovesicles. • Graphene (Gr)-based nanoformulation containing Curcumin and ZnO-NPs.	Li,et al [38] Hamida, et al. [39] Fulaz, et al. [32] Iqbal, et al. [40] Hassan, et al. [41] Oves, et al. [42]
S. epidermidis	Nosocomial bloodstream infections, cardiovascular infections, and infections of the eye, ear, nose, and throat.	Colonizes in the skin and mucous membranes of the human body	• Silver lignin based nanoparticle. • Triphala nanoformulation. • Tween-stabilized AgNPs. • Nanosilver. • Brassica oleracea mediated synthesis of AgNPs. • Citosan/rhamnolipid nanoparticles (C/RL-NPs). • Gold nanoparticles coated cotton fabric.	Slavin, et al. [43] Omran, et al. [44] Mazur, et al. [45] Swolana, et al. 020) [46] Arshad, et al. [47] Marangon, et al. [48] Boomi, et al. [49]
S. capitis	Prosthetic valve endocarditis		Silver and Gold nanoparticles	Amin et al. [50]
S. haemolyticus	Vascular catheter-associated infections	Endocarditis, sepsis, peritonitis, and urinary tract, wound, bone, and joint infections	• Carbon nanotubes (CNTs)–silver nanoparticles (AgNPs)-co-doped polylactic acid (PLA). • Satureja Montana L. essential oil nanoemulsion (SEONE). • Silver nanoparticles (DRAgNPs) by using *Durio zibethinus rind* aqueous extract • Rumex hastatus-AgNPs.	Gan et al. [51], Maccelli et al. [52] Sumitha et. al.[53], Rashid et al. [54]
S. lugdunensis	Osteomyelitis, arthritis, septicaemia, wound infections and aggressive endocarditis.	Infection on skin	ZnSe nanoparticle.	Darroudi et al. [55]
S. xylosus	Erythema nodosum	Infection on skin	Chitosen NPs	Orellano et al. [56]
S. sciuri	endocarditis, peritonitis, septic shock, UTI, pelvic inflammatory disease and wound infections	Infection on skin	Intrinsic oxidase-like nanoenzyme Co4S3/Co (OH) 2 hybrid nanotubes	Wang et al. [57]

Conclusion

The strategies highlighted in this review based on using different nanosystems to endure antibiotic resistance against *Staphylococcus* spp. several antibiotics and bioactive materials showed enhanced bactericidal activity when they were loaded with nanosystems. Zeta potential, particle size, and solubility are the important physico-chemical factors for drug delivery. This review will helps the readers to explore the different nanosystems which have preventive approaches to control the *Staphylococcus* spp. infection. Majorly, immune clearance, membrane permeability and production of β-lactamase employed in *Staphylococcus* pathogenicity. Description of pathogenesis mechanism of *Staphylococcus* and action mechanism of nanomaterial could provide a concept between interaction of nanosystems and pathogen in human body.

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