Mitigation Strategies for Methicillin-resistant Staphylococcus aureus

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Muhammad Ifham Naeem[1], Muhammad Younus[2], Qamar un Nisa[3], Muhammad Zishan Ahmad[4], Tayyaba Akhtar[5], Nimra Arshad[6], Maria Asghar[3] and Muhammad Aeraf[7]

ABSTRACT

Staphylococcus aureus (S. aureus) is a spherical Gram-positive bacterium that is naturally non-motile. It is a pathogen of virulent nature that causes various skin and soft tissue infections in humans. Although it was easily treatable through the use of easily available antibiotics like methicillin this relief was short-lived as the bacteria started gaining resistance against the antibiotics. These bacterial pathogens were called methicillin-resistant Staphylococcus aureus or MRSA. MRSA defends itself against attacks of antibiotics by various mechanisms including modification of the target, efflux of drug and blocking the penetration of antibiotics. Additionally, it also codes a blaZ gene that manufactures the beta-lactamase enzyme. This enzyme renders the beta-lactam antibiotics useless against bacteria. This phenomenon is alarming as it means that antibiotics are now becoming useless for curing diseases and hence there is a need for the development of mitigation measures to control the prevalence of antibiotic-resistant bacteria. The administration of antibiotics is also problematic because it cyclically leads to antibiotic resistance. As the new antibiotics are being developed the bacteria are also developing resistance against them. Such problems necessitate a focus shift of researchers from antibiotics towards new treatment options that have no vulnerability towards resistance and will remain effective throughout usage. Some of the remedies that have been presented by researchers as alternatives to traditional antibiotics include nanoparticles, nanotechnology delivery systems and plant-based extracts. All of these alternatives need extensive research to thoroughly comprehend their action mechanism. Once completely explored these remedies can be exploited to their full potential for gaining the best results with minimum consequences.

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[1]KBCMA College of Veterinary and Animal Sciences, Narowal, Sub-campus UVAS Lahore, Pakistan.
[2]Department of Pathobiology, KBCMA College of Veterinary and Animal Sciences, Narowal, Sub-campus UVAS Lahore, Pakistan.
[3]Department of Pathology, University of Veterinary and Animal Sciences-Lahore.
[4]Department of Pathology PMAS-Arid Agriculture University Rawalpindi-Subcapmus Khushab.
[5]Department of Epidemiology & Public Health, University of Veterinary and Animal Sciences-Lahore.
[6]National Institute of Food Science & Technology, University of Agriculture, Faisalabad.
[7]Department of Microbiology, University of Veterinary and Animal Sciences-Lahore.
***Corresponding author:** afhamnaim4@gmail.com

1. INTRODUCTION

Staphylococcus aureus (S. aureus) is a pathogenic Gram-positive bacterium with a sphere shape and natural non-motility. It belongs to the genus of staphylococcaceae. It has an average size of 1 µm in diameter (Ondusko and Nolt 2018). S. aureus is a pathogen of virulent nature that colonizes different parts of its human hosts to produce life-threatening ailments. Additionally, S. aureus also prevents the initiation of immune responses of both endogenous and adaptive nature which can lead to the induction of human infection of either locally bound or systemic type. It is the widespread and leading etiologic agent causing infections of skin and soft tissues including problems like endocarditis, bacteremia and osteomyelitis (David and Daum 2017). The commensal or frequent extant of this bacteria symptomlessly in several portions of the body of humans including mucous membranes, glands of the skin, nasal epithelial cells, and the gut of well folks (Ogston 1881). Direct contact, usually through the touch of the skin surface with the skin of a colonized or infected person, is the core transmission method for the spread of S. aureus. Another alternative mode for transmitting S. aureus occurs through contact with contaminated surfaces and objects which can play a significant role in its spread from infected to healthy populations (Miller and Diep 2008). The data from reports of prevalence have shown that twenty percent of the population were constant nasal carriers of S. aureus while thirty percent had a recurrence of infection (Ogston 1882).

S. aureus is one of the major infections caused by communal bacteria in both humans and animals (Chang et al. 2003; Stryjewski and Corey 2014). S. aureus can colonize for a short or long period. It may even be treated spontaneously with the existing options of remedies. However, S. aureus is famous for its potential for antimicrobial resistance. Around 30% of the global population is infected with S. aureus asymptomatically and enduringly also by the MRSA (methicillin-resistant S. aureus). High-intensity of infection and severe condition of symptoms may cause high morbidity and fatality. This may result in a further increase in the cost of healthcare (Schmidt et al. 2015). MRSA colonization in infections also appears in several types of animals like horses, cats, dogs, cattle and birds (Weese 2004; Šťástková et al. 2012). Latest studies regarding the prevalence of S. aureus have reported a high colonization rate for MRSA bacteria in infected humans that tend to live in close contact with the animals (especially infected ones) (Weese et al. 2006). The re-emergence of infections with S. aureus occurs commonly even after complete treatment of infected hosts with antibiotics due to the hindrance in protective immune response development. Hence, S. aureus has seen a rapid rise in its ranks to become one of the major agents causing several health-relevant diseases (Gill et al. 2019).

Penicillin is an effective remedy to defend patients against S. aureus. However, recently it has become a short-lived relief due to the development of antibiotic resistance in bacteria. It started showing up in disease surveillance reports during the era around the 1940s that antibiotic resistance in bacteria can develop by the gene mutation phenomenon of the blaZ gene also known as the β-lactamase encoding gene. This gene helps the bacteria to resist the action of the antimicrobial drugs by producing the β-lactamases enzymes that cause the β-lactam ring disruption of the penicillin, hydrolytically, rendering it ineffective (Kardos and Demain 2011).

Various researchers have provided reports of the trends regarding antimicrobial resistance (Chambers and DeLeo 2009; Vanamala et al. 2021). There has been a proposal regarding the widespread administration of penicillin being the sole reason for the emergence and development of MRSA rather than the introduction of methicillin (Harkins et al. 2017).

MRSA or methicillin-resistant S. aureus is a new strain of S. aureus that was identified and isolated during the era of 1960s. It happened within a year's time after the first introduction of methicillin by Beecham at the clinical level (Harkins et al. 2017). Since that time the incidence and prevalence of MRSA infections

has increased at a global level dramatically. An alternate study regarding the prevalence of MRSA infections claimed the number of infections going up each day, especially in developed countries. This trend indicates the prevalence of bacteria in communities despite good well-being practices and the communal (Miller and Eells 2008). The infection of MRSA is still a notable risk for the population as 60 to 80% of colonization happens in case of hospital-acquired infections in well-developed countries with sufficient resources (Williams et al. 2009). A recent meta-analytical study of inpatients in the US reported that there are admissions of approximately 4 million S. aureus infection patients each year. Simultaneously, infections of MRSA increase the fatality rate (~19,000) of the US population in hospitals, each year (Klevens et al. 2007).

ABSTRACT

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The administration of antibiotics is also problematic because it cyclically leads to antibiotic resistance. As the new antibiotics are being developed the bacteria are also developing resistance against them. Such problems necessitate a focus shift of researchers from antibiotics towards new treatment options that have no vulnerability towards resistance and will remain effective throughout usage.

Some of the remedies that have been presented by researchers as alternatives to traditional antibiotics include nanoparticles, nanotechnology delivery systems and plant-based extracts. All of these alternatives need extensive research to thoroughly comprehend their action mechanism. Once completely explored these remedies can be exploited to their full potential for gaining the best results with minimum consequences.

2. MRSA-ASSOCIATED RISK FACTORS

Risk factors associated with MRSA may lead to fatality, hospitalization for a long period or admission to of a patient in the unit for intensive care, open wounds, an overdose of antimicrobial drugs, hemodialysis, the addition of drugs to treatment enhancing the toxicity profile, and placement of a urinary catheter for an extended amount of time. Identification of MRSA colonization during hospitalization of infected patients can reduce the danger of the development of infection or its spread to others (Ayliffe 1997). An impact of this MRSA infection is an increase in resistance against multiple antibiotics. This trend limits the options of therapeutic management options in the treatment of MRSA and its relevant infections. MRSA has also been discovered as an agent of poor infection control and its rapid resistance development towards almost all antibiotic therapy options in case of severe infections. The antibiotics mostly prescribed for the treatment of MRSA infections are aminoglycosides, fluoroquinolones and erythromycin.

Vancomycin is still considered as a crucial weapon necessary for the defence against the infection of MRSA (Cuny et al. 2010).
Another cause of the development and spread of antibiotic resistance is the misuse of antibiotic drugs. On the other hand, the world is facing this challenge due to the lack of suitable innovative antimicrobial drugs that can act effectively against resistant bacteria (Yeaman and Yount 2003).

3. BLOCKED PENETRATION

The mechanism of diffusion transports drug agents across a cell membrane by porin, diffusion through the bilayer of lipids and automatic uptake by bacteria. The minute hydrophilic pieces of antibiotics (β-lactams and fluoroquinolones) can easily cross the outermost membrane of the bacterial cell only through the porins passage. The reduction in the number of porin passages leads to the reduction in the amount of β-lactam and fluoroquinolone antimicrobial drugs that enter the cell. This phenomenon of under-dosing at the cellular level leads to the development of resistance against these classes of antibiotic drugs (Yeaman and Yount 2003).

4. EFFLUX PUMPS

Antibiotic inflow in the bacteria during the administration of drugs that act by passive diffusion. On the other hand, efflux devices of the bacteria tend to pump out the antibiotics that are bioavailable within the bacterial cell. The reduction in concentration of the antibiotic drug within the bacteria is unable to achieve the objective of stopping the bacterial populace growth (Yeaman and Yount 2003). These efflux pumps are always present in the cytoplasmic membrane of the bacteria. On the other hand, particular porins are present on the outermost surface of the bacterial cell. These efflux pumps can precisely target the antibiotics. The efflux system pumps drain the substances of toxic nature out of the cell to maintain a suitable environment internally. Many of these efflux pump systems are carriers of multiple drugs. On the other hand, they are also responsible for the efflux of toxic metabolites along with the externalization of antibiotics including fluoroquinolones, macrolides and tetracyclines. The drug efflux mechanism is significantly notable the Gram-negative bacteria (Dˇzidi´c et al. 2008; Soto 2013).

5. MODIFICATION OF TARGET MOLECULE

The modification of the target site often results in a spontaneous mutational modification of a gene present on the bacterial chromosome. This mutation can effectively differ the adhesion capability of antimicrobial drugs. Modifications in the ribosomal subunit 30S or 50S indicate the emergence of resistance towards the antimicrobial drugs that act by inhibition of protein synthesis in bacteria (Tenover 2006). Similarly, PBP adaptation favours the Gram-positive bacteria for developing antibiotic resistance. However, the production of β-lactamases enzyme is still an important mechanism of resistance progression in Gram-negative bacteria (Hiramatsu et al. 2001).

6. HERBAL MITIGATION

The mitigating impact of *C. latifolia, A. officinalis, T. vulgaris* and *Z. jujuba* has been considered for studies by several scientists. Animals that were administered with *T. vulgaris* and *Z. jujuba* presented a decrease in scores of gross lesions of both lungs and heart. On the other hand, *C. latifolia*

administration led to decreased gross lesions but only in the lungs. Development of gross lesions in the tissues of the host due to the virulence of bacteria. MRSA release toxin substances that can lead to various blood issues including hemolysis in RBCs, adhesion of RBCs in the tissue walls and hindrance against phagocytosis by macrophages (Otto 2014). The reduced score of gross lesions for lungs denotes the importance of the role played by extracts of these plants in preventing infections with MRSA in the systems of in-vivo nature. In the beginning, *S. aureus* circulates in blood vessels and, later on, it starts adhering to the extracellular matrix constituents, of the blood hence leading to the formation of thrombi, or host cells of endothelium and initiation of the cell colonization process (Niemann et al. 2004). *S. aureus* can also interact with cells of the endothelium in blood vessels (Peacock et al. 1999), the matrix of extracellular spaces (Flock 1999) and platelets (Sullam et al. 1996; Kerrigan et al. 2002). Several *S. aureus* surface proteins have a high degree of selective permeability to plasma proteins and matrix. They have been proven to moderate the processes of attachment to these surfaces (Van Belkum et al. 2002). Another well-known feature of *S. aureus* is binding to host RBCs (red blood cells). This binding occurs when plasma proteins like fibrinogen are present in blood (Croize et al. 1993; Wilkerson et al. 1997). Isolation and calculation of bacterial load from the blood, throat, joint, lungs, and heart were undertaken as an experiment to indicate the persistency and adhesion of *S. aureus* in host tissues. The data from these studies has revealed a notable decrease in a load of bacteria in

(a) the throat region of infected people of the group treated with the *T. vulgaris*
(b) the lungs of the group that were given antibiotic-treatments
(c) blood and heart of all groups that were treated except the ones with *A. officinalis* and *Z. jujuba* administration
(d) joints in the group treated with *Z. jujuba* and *A. officinalis*.

The decreased laid of bacteria has been witnessed due to several reasons including bacteriostatic and bactericidal effects of the phytochemicals like flavonoids, and phenolic and alkaloid compounds found in crude plant extracts (Benariba et al. 2013). These findings are in exact alignment with the research done by Owais et al. (Owais et al. 2005). He reported that a decrease in load of bacteria was observed in the vital organs of mice post-treatment with extracts of *Withania somnifera L. Dunal*. Haematology of samples from infected hosts can be studied to obtain a good understanding of the stage of bacterial infection, its progress and the impact of treatment. Elevations in levels seen during tests of ESR, neutrophils, and lymphocyte TLC count are credible infection indicators for the body of the host. Once the patient is cured after effective treatment these levels quickly drop to normal range (Piper et al. 2010). In the past *S. aureus* was known to contain an enzyme hemolysin, which helped it in killing of host blood cells in a targeted manner. A decrease in Haemoglobin, PCV, Red Blood Cells and platelets was observed in an unattended group of infected hosts being studied. This might be explained by to lysis effect of enzymes on the RBCs of the host during the invasion of bacteria or due to the removal of iron from the body of the host to indirectly inhibit red blood cell formation. There is evidence that *S. aureus* has the capability of using haemoglobin as a source of iron for bacterial growth (Mazmanian et al. 2003; Pishchany et al. 2013). Among the group being treated except for the ones receiving *A. officinalis* all other groups being administered plant extracts displayed an improvement in their haematological parameters. The best improvement of ESR and lymphocyte count towards normal was seen in the group being treated with plant extracts from *C. latifolia, Z. jujube* and *T. vulgaris*. Additionally, the groups being administered *T. vulgaris* and *C. latifolia* extracts had their count of neutrophil and platelet pretty close to the counts of their negative control group counterparts proving their higher potential for limiting infection. During this study, Sur and Ganguly (Sur and Ganguly 1994) observed a comeback to normal in haematological parameters of the infected host post-treatment with root extracts from tea plants in the case of Ehrlich ascites

carcinoma-induced mice. Various other experiments have also proved the antimicrobial activity of *A. officinalis* through in vitro procedures (May and Willuhn 1978; Mazmanian et al. 2003; Zarei et al. 2013; Rezaei et al. 2015), although its effectiveness in the in-vivo system is still vague indicating the necessity for in vivo studies.

7. NANOTECHNOLOGICAL MITIGATION

For many years, efforts have remained prime work to increase the effectiveness of treatment of MRSA by increasing the bioactivity and efficiency of the therapeutic measures. First time in 1994, nanotechnology was used to treat MRSA and *S. aureus* infections. The arrival of nanoparticles gives small-sized particles, defensive inner environments and shapes to increase the activity of drugs in organs, tissues and cells of the infected host. The use of nanoparticles for treating diseases shows better therapeutic results as compared to the traditional way of treatment (Kesharwani et al. 2014; Kesharwani et al. 2015; Kesharwani et al. 2019; Pandey et al. 2019; Bapat et al. 2020; Singh et al. 2020). The approval of the use of nanotechnology in treating infections of MRSA and *S. aureus* was first given by the FDA in 1994. The major advantage of the use of NPs are their size range, usability shape, and formation of a protective environment which helps to enhance the drug activity in organs, tissues and cells of the infected host. The formation of these nanoparticles requires far more effort than other antibiotic preparations (Aldawsari and Singh 2020; Singh et al. 2020a). Some major properties of these NPs include improving the stability of drugs in blood serum, increasing their time of retention in blood circulation, and delivering the drug at a specific site for activities regarding the pharmacology of that drug at a specific time and rate (Kingsley et al. 2006; Singh et al. 2020b). Another astonishing property of NPs is that they can be phagocytosed by the cells of the host and help in the treatment of the intracellular infections of the bacteria (Onyeji et al. 1994). The first delivery vehicle of NPs was made for vancomycin and teicoplanin in 1994 against MRSA infection (Taylor 2013). Esmaeili et al. used PlGA NPs for an antibiotic named Rifampicin. The drug therapy for mycobacterium infection and leprosy with Rifampicin is still in use. Fusidic acid is also practised against MRSA contagions (Esmaeili et al. 2007). Duran et al. used the in vitro Rifampicin fabricated with NPs (20 to 60 um) antibacterial activity, this combination can sustain the bioactivity and cytotoxicity of Rifampicin against MRSA (Durán et al. 2008). As discussed earlier, the infections of MRSA can be controlled with proper use of antibiotics but it is still a challenge to get effective antibiotics to treat the infection of MRSA. The majority of antibiotic drugs are of hydrophobic nature which causes low bioavailability and solubility (Delcour 2009). This is the main reason why the majority of the antibiotic drugs that are administered lead to the appearance of severe side effects, toxicity in normal body cells and the emergence of drug resistance against multiple antibiotics (MDR) (Prestinaci et al. 2015). Another major problem is the traditional delivery system of drug transfer which does not have sufficient competency for treating bacterial infections completely. Such shortcomings made it necessary for the researcher to formulate a novel system of drug delivery or NDDS to improve the index of the therapeutic window for antibiotic drugs. It is suggested that the use of NDDS can lower the adverse effects and decrease bacterial resistance against antimicrobial agents. Many new methodologies have been introduced under the umbrella of nanotechnology to steal the spotlight in the medical field (Choudhury et al. 2019a; Choudhury et al. 2019b). The challenge of the traditional delivery system has been solved by using nanosized carriers called sas nanocarriers. The use of nanotechnology-based therapeutic agents has been implemented in the enhancement of treatment regimens against different diseases for example cancer (Gorain et al., 2018; Choudhury et al. 2019b; Kesharwani et al. 2019; Gorain et al. 2020). These nanocarriers have

remarkable properties which include increased therapeutic efficacy, increased circulation time for systemically administered drugs, and improved stability of serum their overall stability is also far better than the standalone drugs. Along with these benefits, this approach also decreases the adverse effects on normal cells, decreases the resistance of microorganisms against antimicrobial agents, and uses combined regimens of therapy for reaching specific sites according to the drug requirement. The antibacterial properties of nanomaterials depend on the following mechanisms:
(1) formulation of reactive oxygen species (ROS) through photocatalytic activity which in turn leads to the destruction of the components of cellular and viral nature,
(2) the constituents that make the membranes of the cell and cell wall,
(3) discontinuation in energy supply,
(4) blockage of enzyme production and suppression of DNA synthesis (Huh and Kwon 2011).

8. NANOPARTICLES OF INORGANIC NATURE

These are nanometric particles that are chemically inorganic and have various benefits. They are beneficial because of the peculiar physicochemical properties they display when compared with individual molecules, atoms, or bulk materials of the same type (Choudhury et al. 2017; Numan et al. 2021). Some particular inorganic nanoparticles for example oxide derivatives of metals and nanoparticles of metallic nature are thought to have some antibacterial activities. Examples of these nanoparticles are gold nanoparticles (AuNPs), nanoparticles of silver (AgNPs), titanium dioxide nanoparticles (TiO2 NPs), and nanoparticles of zinc oxide (ZnO NPs) (Choudhury et al. 2020). Nanoparticles of an inorganic nature have the property to adhere and accumulate on the cell wall of bacteria cell wall quickly, and then penetrate the cell through pores due to their size being smaller than the pores (Sánchez-López et al. 2020). The higher ratio of surface area to volume means that even small doses of inorganic nanoparticles can show higher levels of antibacterial activity as compared to free antibiotic drugs (Choudhury et al. 2020). Hence proved that the inorganic nanoparticles show bactericidal action by disrupting the structural and functional integrity of microorganisms.

9. METAL NANOPARTICLES

The immense use of MNPs as medicine has drawn the attention of researchers and several studies done to find out the mechanism of MNPs as antibacterial medicine and also their role against resistance (Huh and Kwon 2011). The properties of metal nanoparticles regarding their physicochemical nature are their size, charge, shape, zeta potential, morphology of surface, and structure of the crystal, which makes them significant and regulate their actions on the bacterial cells (Figure 1). Recent research work shows that MNPs act in three different ways which are stress of oxidation (Gurunathan et al. 2012), non-oxidative stress (Leung et al. 2014), and release of ions by the metal (Zakharova et al. 2015). Different metal nanoparticles have been utilized to assess their efficacy against MRSA for instance silver (Ag) and gold (Au) NPs (Lambert 2002; Morones et al. 2005; Nabikhan et al. 2010; Sobrova et al. 2012). According to commercial use of MNP applications, the most commonly used MNP is AgNPs which are used in cosmetics, nanomedical devices, and food products.
Besides the fact that they are less toxic the silver ions, the ability of these NPs to induce oxidative stress for long periods in eukaryotic cell lines and subcellular organelles, for example, mitochondria, shows that they could contribute to the early onset of some metabolic diseases for example neurodegenerative and cardiac diseases (Dos Santos et al. 2014; Strauch et al. 2017; Grzelak et al. 2018; Holmila et al. 2019). The reason for this toxicity is still not found out but many studies show that it is not the uncontrolled release of silver ions but the size of the particles causing toxicity. Besides the uncontrolled ion release, there are

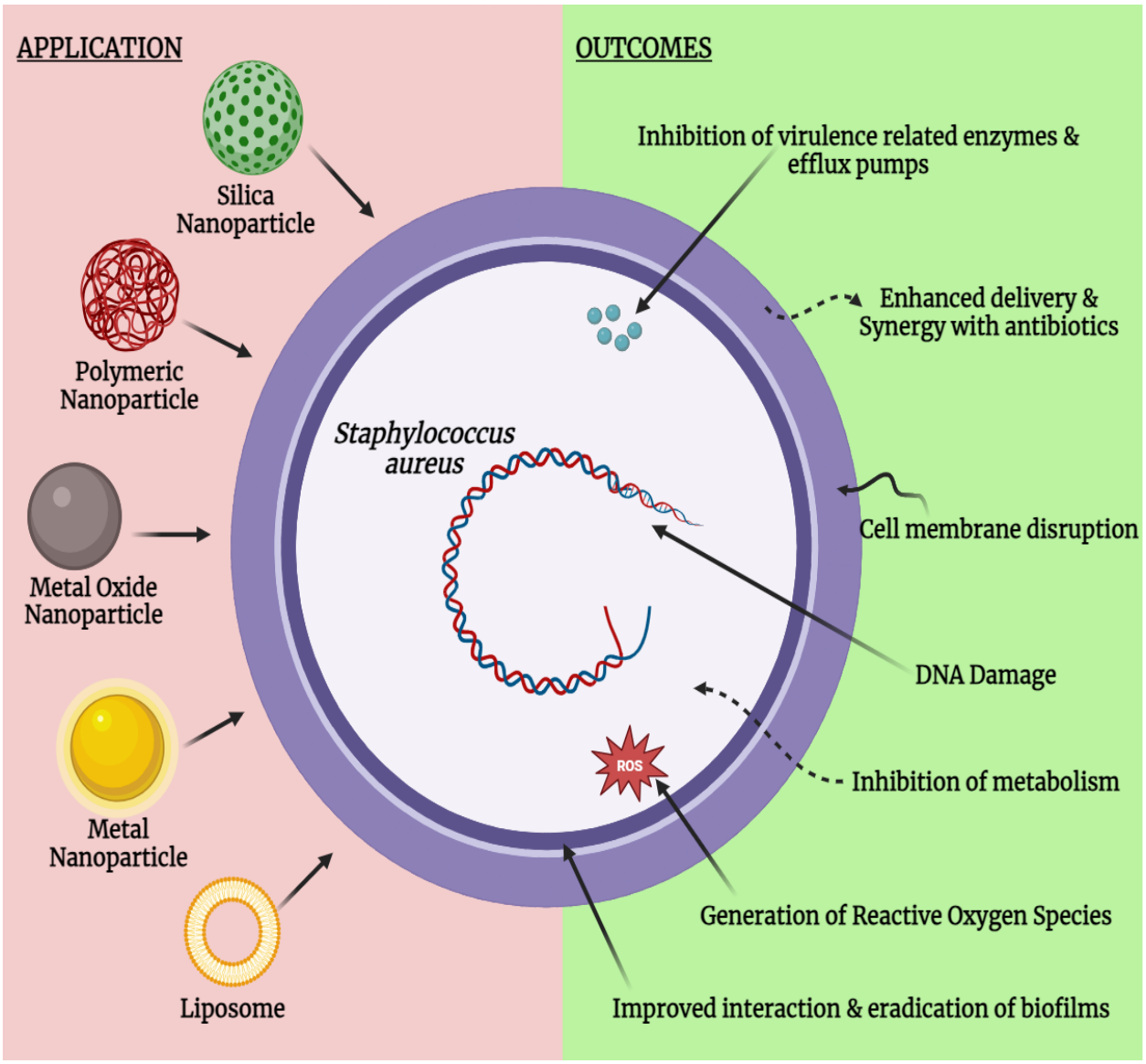

Fig.1: Nanotechnological mitigation of Methicillin-resistant *Staphylococcus aureus*.

different studies regarding AgNP toxicity and the animal modules used. Solvents employed during the particle synthesis are another major source of toxicity. As a result of this many researchers have now used the greener methods which results in a major reduction in the geno and cytotoxicity in the cell line by increasing the particle stability, the big example is the graphene (Strauch et al. 2017). The use of this particle in biomedicine, the lifetime matching i.e. the stability of the particle and the device function, to minimize the toxic events, is routinely applied in implants and topical applications. The less expensive alternatives of Au and AgNPs, are the zinc oxide (ZnO) and titanium oxide (TiO2) NPs which are seen to be used against MRSA, killed it under in vivo and in vitro conditions (Ansari et al. 2012; Rauf et al. 2017). In MRSA-associated skin infection, ZnO NPs have been used to reduce the burden of bacteria when used in murine models (Umamageswari et al. 2018) also one study shows the antibacterial activity of ZnO NPs against MRSA when used at a concentration of 1875mg/ml (Kadiyala et al. 2018). Another study revealed the bactericidal activity of these NPs and also their mechanism of action of these NPs which is through

inhibiting different pathways including amino acid synthesis in *S. aureus* (Roy et al. 2010). TiO2 NPs also show anti-MRSA activities in the disk diffusion method when used with different antibiotics including cephalosporins, glycopeptides, and azalides. TiO2 NPs form free radicals under UV photoactivation, which enhances their ability to kill MRSA (Wahab et al. 2014).

10. CONCLUSION

The development of methicillin resistance among bacteria has caused an alarm for the security of public health. This means that the antibiotics of today will soon be useless for the treatment of disease and hence there is a need for the development of alternate remedies. Other remedies that can be used effectively as a replacement for antibiotics include nanotechnology and herbal medicinal extracts. The main benefit of using these remedies is that they do not induce antibiotic resistance but reduce bacterial growth effectively. Additionally, these remedies do not have adverse effects that are usually seen during the administration of antibiotics, especially for an extended period. One important example of herbal remedies is the plant extract. On the other hand, an important example of nanoparticle remedies is nano-metals. These nanomaterials are usually prepared by finely ground metals and their derivative compounds. Some important examples of nano-metals include Gold and silver nanoparticles. Two important metal-derived nanoparticles are Zinc Oxide and Titanium Oxide.

These alternatives to antibiotics require further research and experimentation to understand their mechanism of action to exploit their full potential. These compounds can be extremely useful once their mechanism of action and methods of commercial preparation are thoroughly comprehended. These can help us in lowering the dosage of drugs, reducing dose frequency and lowering the required amount of antibiotics for treating patients. These effects will consequently lead to a lower toxic effect window, lesser cost of treatment and an overall reduction in prevalence of disease due to reduced transmission of antibiotic resistance.

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