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Modification of silica nanoparticles for antibacterial activities: mechanism of action

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ABSTRACT

Opening up a new avenue for smart design of nanomaterials by antibacterial agents such as antibiotics, metal/metal oxide nanoparticles (NPs), and polymeric materials to achieve high efficiency against multidrug-resistant (MDR) bacteria as a vital affair in the case of chronic bacterial infections specifically diabetic foot ulcer, pneumonia, and pseudomonas infections. Silicon dioxide (SiO_2) NPs with a biocompatible and porous surface can be applied as a novel, efficient carriers for loading other antibacterial compounds having low biocompatibility or ineffective antibacterial activity against MDR bacteria. Recently, modification or functionalization of silica NPs by conventional antibiotics, metal/metal oxide NPs and biodegradable polymers have been investigated to increase the bactericidal and mechanical properties for wound dressings and bone cement. However, there is no clear comprehension of the advantages and disadvantages of these drug delivery systems, which this review has tried to address.

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Introduction

Uncovering the new therapies for hindering multidrug-resistant (MDR) microorganism especially bacteria is the vital issue in acute and chronic infections such as diabetic foot ulcer [1]. A variety of material and biomaterials in micro and nano scales have illustrated different anti-planktonic and anti-biofilm activities against MDR bacteria [2-6]. Many nanomaterials have unique properties suitable for loading, encapsulation, and passive/active delivery of therapeutic agents [7-9]. Examples include one-pot synthesis, large-scale synthesis, suitable loading capacity, site-directed delivery, thermal stability, and low cytotoxicity for silica NPs [10, 11]. However, silanol (Si–O–H) groups at the surface of NPs can interact with the phospholipids of the reticulocyte membranes and lead to hemolysis [12], for which, surface modification of mesoporous silica nanoparticles (MSNs) by biocompatible polymeric materials such as polyethylene glycol (PEG) would be a perfect solution [13]. For modification of these types of NPs, polymers, metal or metal oxide NPs and antibiotics may be helpful depending on the bacterial species to be targeted. As shown in Figure 1, non-porous and MSNs are produced by the microemulsion and Stober's methods, respectively. Other silica NPs, such as hollow MSNs and core-shell silica NPs, may be used to encapsulate and load antibacterial agents. Spherical, half-sphere, dumbbell-shaped, short rod-shaped, long rod-shaped, hexagonal, dodecagonal, radial wrinkle-like, and worm-like have been reported as essential morphologies of silica NPs [14-16]. For example, the tetramers, trimers, heterotrimer, dimer, and heterodimer can be prepared from one-patch silica NPs via the solvent-induced assembly method (Figure 2) [15]. In addition, at the same triangle/square ratio equal to 0.1 and different concentrations of mesitylene and ammonium hydroxide, the growth trajectories of

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single-particle for MSNs were differed [16]. Loading antibacterial or anticancer agents to the disease site without leakage and obtaining high local concentrations of the drug are essential factors designing an effective formulation [17, 18]. In this regard, the interlocked molecular structures of pseudorotaxanes, rotaxanes, β-cyclodextrin (β-CD)-modified polyethylenimine (PEI), and a macrocycle of cucurbit[6]uril would be the appropriate options to trap and release the therapeutic agents as caps on the pores of MSNs [19, 20]. External physical signals (ultrasound, magnetism, heat, and light) and chemical signals (antibodies, enzymes, redox, and pH) are main stimuli to design smart silica NPs [21-23]. According to the above description, this review has tried to discuss recent progresses and related challenges regarding novel ways for functionalization of silica NPs by antibacterial agents.

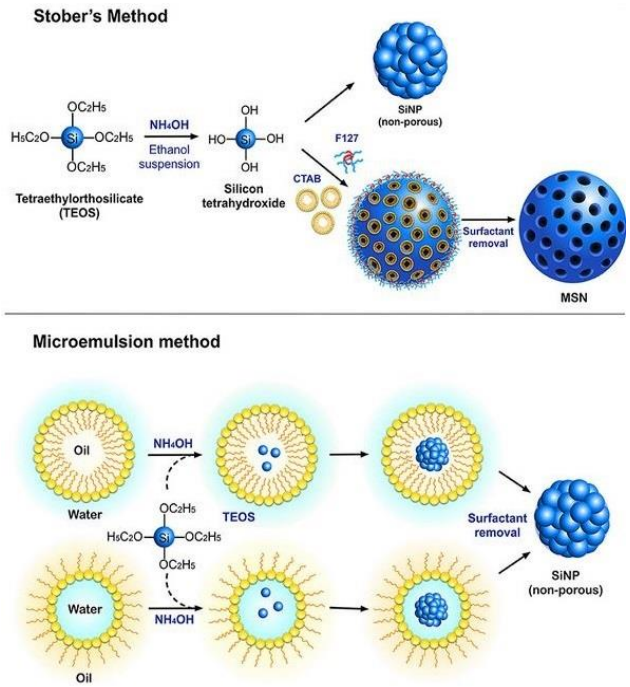

Fig. 1. Two main methods for synthesis of mesoporous and non-porous silica NPs (copyright under the terms of the Creative Commons Attribution License (CC BY) [10]).

Polymers

There are synthetic and natural polymers that can increase colloidal stability, biocompatibility, bioavailability, and biodegradability of silica NPs. For instance, a high molecular weight of PEG can augment hydrophilicity, biocompatibility, and blood circulation time by shielding the NP surface from aggregation and opsonization [24]. Silane-coupling agents and PEG crosslinkers are offered to obtain covalent conjugation of antibacterial compounds on the surface of MSNs. Organosilane coupling agents involving (3-aminopropyl) triethoxysilane, (3-mercaptopropyl) trimethoxysilane, methoxy-PEG-silane, and vinyltriethoxysilane can bind to a high content of silanol groups (Si-OH) on the surface of SiO_2 NPs followed by surface functionalization with organic polymers and antibacterial agents [25, 26]. Homogeneous dispersion of SiO_2 NPs in the matrix of the thin film of poly(butylene adipate-co-terephthalate) has been carried out by a solvent (chloroform) casting method. C=O, C-O, and C-H stretching bonds were characterized as the main functional groups in forming these nanofilms, which has an antibacterial effect on *E. coli* and *S. aureus* as inhibition zone diameters of 16.7 and 17.2 mm, respectively [27]. Improvement of the physical and thermal properties of SiO_2NPs-polymer also should be considered to obtain suitable therapeutic results in physiological conditions. Organic N-halamines as antimicrobial polymeric materials have exhibited potential bacteriostatic and bactericidal activities against Gram-positive and Gram-negative bacteria [28, 29]. Half hour exposure of *P. aeruginosa* and *S. aureus* to N-halamine-functionalized silica–polymer core-shell NPs showed excellent antibacterial effect for core-shell NPs with a mean size of 220 nm compared to 510 nm. For this study, the core-shell structure of NPs was prepared in three steps encompassing the synthesis of the 3-(methacryloxy)propyl trimethoxysilane-modified SiO_2NPs, coating with 3-allyl-5,5-dimethylhydantoin copolymers, and chlorination [30]. In another study, 3-(4′-epoxyethyl-benzyl)-5,5-dimethylhydantoin (EBDMH) was coated on the surface of amino-functionalized SiO_2NPs and then combined with poly(lactic acid) (PLA) to obtain PLA/EBDMH-SiO_2 nanocomposites, which around100% reduction after 3 hours was found for these NPs against *E. coli* and *S. aureus* [31].

Metal or metal oxide NPs

Producing reactive oxygen species (ROS) in colloidal solution has been reported as a significant

antibacterial mechanism for metal or metal oxide NPs [5, 32, 33]. These NPs can be formulated with MSN and non-porous silica NPs to increase antiplanktonic and antibiofilm activity. Silanized iminodiacetic acid-modified MSN was impregnated by Cu^{2+}, Zn^{2+}, and Cu^{2+}-Zn^{2+} to obtain photocatalytic activity against *E. coli* and *S. aureus*. CuO-MSN with 4.8 nm displayed bacteriostatic values of 100% and 85.87% at a CuO amount of 250 µg/mL against *S. aureus* and *E. coli*, respectively (Figure 3) [34]. Interaction between the surface roughness of NPs and growth inhibitory rate is the main factor, wherein a higher degree of roughness of NPs can result in a more antibacterial effect relative to the counterpart with a lower roughness [35]. Composite mesoporous CuO NPs (host) as template were used to prepare surface-rough MSNs (ghost), where surface roughness of MSNs were obtained by functionalization of the surface using (3-glycidyloxypropyl)trimethoxysilane (GLYMO) to provide covalent coupling of 4-hydroxyphenylboronic acid (4-HPBA). The diol groups related to carbohydrates on the bacterial membrane formed covalent bonds with boronic acid groups on the surface of MSNs. They led to a striking antibacterial impact on *Rhodococcus rhodochrous* and *E. coli* [36].

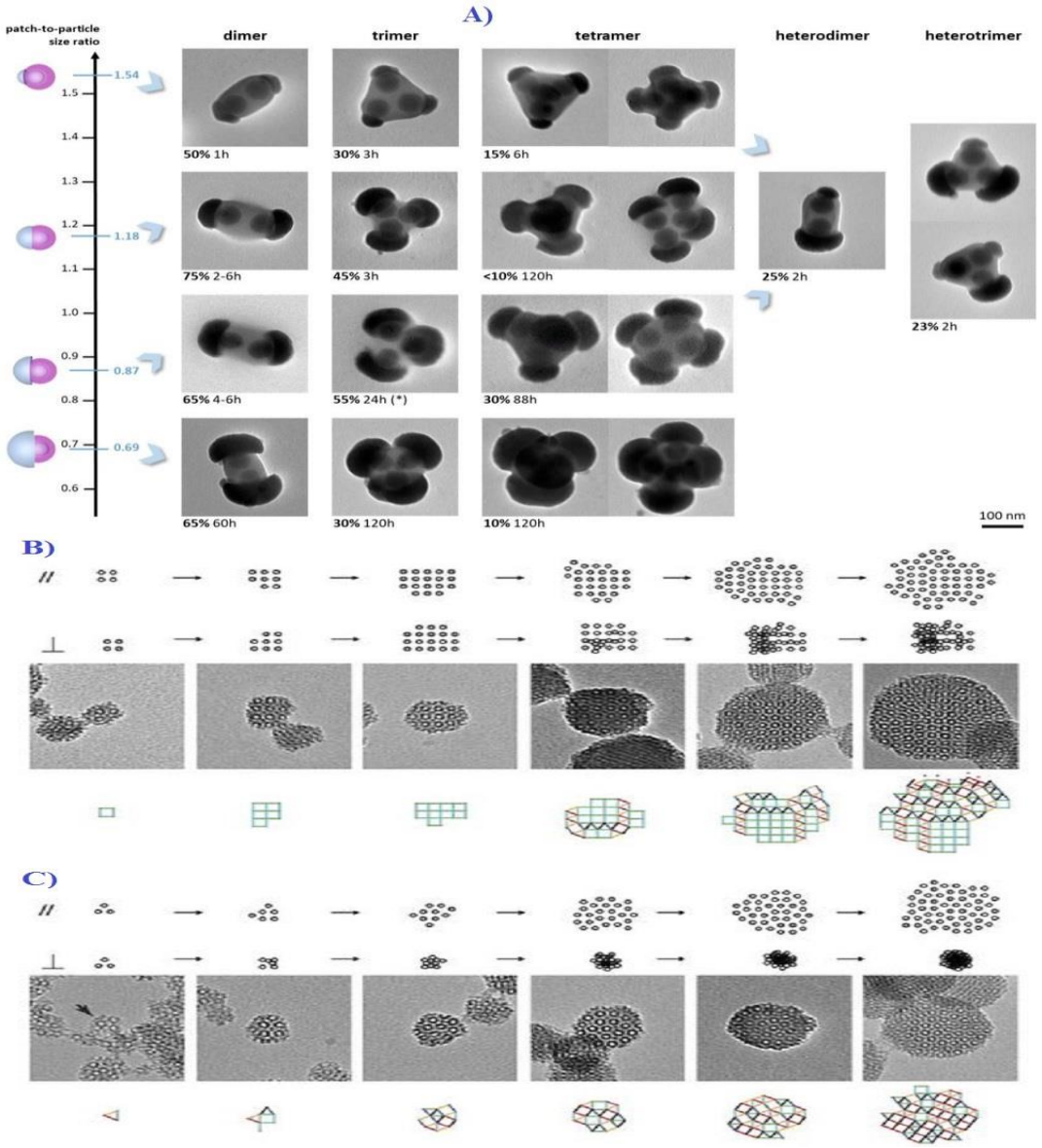

Fig. 2. Different morphologies of silica NPs; A) The tetramers, trimers, heterotrimer, dimer, and heterodimer shapes prepared from one-patch silica NPs via the solvent-induced assembly method (copyright under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/)) [15]. B and C) Different

concentrations of mesitylene and ammonium hydroxide at the same triangle/square ratio equal to 0.1 showed different growth trajectories of single-particle for MSNs (copyright under the terms of http://creativecommons.org/licenses/by/4.0/.[16]).

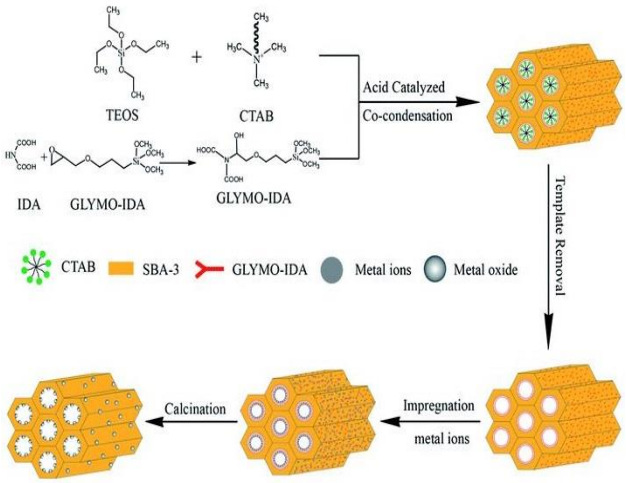

Fig. 3. The schematic image presenting the synthesis steps for metal and metal oxide NPs impregnated MSN. Silanized iminodiacetic acid (GLYMO–IDA), glycidyloxypropyltrimethoxysilane (GLYMO), cetyl trimethyl ammonium bromide (CTAB), tetraethyl orthosilicate (TEOS), modified MSNs (G-SBA), iminodiacetic acid, CuO and ZnO with 40 nm. copyright under a Creative Commons Attribution-Non Commercial 3.0 Unported License [34].

Antibiotics

Various bacteriostatic and bactericidal antibiotics can be used to functionalize NPs particularly metal/metal oxide and silica NPs to achieve synergistic effect against Gram-positive and Gram-negative bacteria [37]. Formulation of penicillin G-Ag@SiO_2 with a triangular shape showed a bactericidal effect on methicillin-resistant *S. aureus* (MRSA) and methicillin-sensitive *S. aureus* (MSSA) bacteria at a minimum concentration of 350 µg/mL and 20 µg/mL, respectively without cytotoxicity against the A431 cell line [38]. Covalent and non-covalent loading of antibacterial agents has been found to functionalize MSNs. For example, vancomycin antibiotic and lysozyme were loaded on MSNs by covalent and non-covalent binding. According to the results of in vitro and in vivo antibacterial tests, lysozyme-coated the carboxy-functionalized MSN demonstrated low cytotoxicity and a fivefold lower value of minimum inhibitory concentration (MIC) relative to the free lysosome. Promotions of peptidoglycans hydrolysis and membrane-perturbation were caused by interaction between lysosome-MSNs and bacterial envelope followed by increased local concentration of lysosome on the bacterial membrane and cell wall [39]. Silica NPs in two sizes of 100 and 500 nm were employed to load two antibiotics involving rifampicin and gentamicin respectively followed by incorporation in collagen type I to obtain hydrogel. Gentamicin-silica NPs_{500}-collagen showed significant antibacterial activity after 7 days against *P. aeruginosa*. Rifampicin-silica NPs_{100}-collagen had an antibacterial effect on *S. aureus* after 1 day [40]. Eradication of polymicrobial infections may be possible by loading multiple antibiotics on nanocarriers such as silica NPs to achieve main advantages including reduced side effects and the concurrent delivery of several antibiotics at the desired amounts to the infected site. For obtaining concurrent delivery of antibiotics toward Gram-negative and Gram-positive bacteria, two antibiotics of vancomycin and polymyxin B were loaded on carboxyl-modified and bare MSNs. Bare silica NPs revealed more loading of antibiotic 563 µg (161 µg vancomycin and 402 µg polymyxin B) per mg of bare silica NPs compared to carboxyl-modified NPs with 453 µg (156 µg vancomycin and 298 µg polymyxin B). The major antibacterial mechanism for these formulations was disruption of the cell membrane and cell wall [41]. Antibiotic-loaded MSNs also is suitable for increasing mechanical and antibacterial activity of bone cement. In this way, gentamicin was loaded on poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol)-based bone cement to increase the stability of bone cement structure after 6 months and extended-release of gentamicin [42]. MSNs also have employed to carry human defensin peptide of T7E21R-HD5 in order to growth inhibition of MDR *E. coli* in vivo via augmenting inner membrane permeabilization and the outer membrane penetration. Additionally, MSNs protected T7E21R-HD5 from degradation by intestinal protease and reduced intestinal inflammation via hindrance to the generation of inflammatory factors, including MMP-9, TNF-α, and IL-1β [43]. One major drawback of eradicating bacterial biofilm is the production of extracellular polymeric substances containing

nucleic acids, surfactants, lipids, glycoproteins, proteins, and polysaccharides by these bacterial communities [44, 45]. Therefore, disrupting these structures is an important factor for efficient penetration of antibiotics. Co-delivery of two antibacterial agents of peptide melittin and ofloxacin was carried out effectively by nanocomposites of MSNs capped by β-CD-modified PEI and adamantane-decorated MSNs containing a magnetic core capped by a macrocycle of cucurbit[6]uril. These nanocomposites exhibited the reducing biofilm biomass of *P. aeruginosa* PAO1 followed by eradication of bacteria with biocompatibility toward mammalian cell lines of 293T and NIH3T3 [20].

Green synthesis

Extracts or metabolites of plants, bacteria, fungi, lichens, and viruses can be exploited to produce metal, metal oxide, and silica NPs in various shapes and sizes [46, 47]. There are a variety of therapeutic effects such as anticancer, antimicrobial, anti-diabetic activities for medicinal plants [48, 49]. Phytosynthesis of NPs is a revolutionary method of preparing NPs in a simple, cost-effective and highly efficient manner for medical applications [50-54]. Periakaruppan *et al*. (2022) green synthesized silica *NPs* by *Punica granatum* leaf extract with excellent antibacterial activity against *Salmonella* and *E. coli* [53]. Silica NPs were functionalized with macromolecules of the leaf extract and these molecules also reduced silver ions (Ag^{+}) to form Ag NPs decorated on the SiO_2 NPs [55]. Additionally, *Citrus limon* extracts showed an ability to produce silica NPs by a size range of 20-57 nm and antibacterial activity above the value of 1.5 µg/mL against *Bacillus subtilis* [56].

Photodynamic Activity

MSNs could act as reactive oxygen species (ROS) generators and promote photodynamic activity, thus enact as antibacterial materials. These MSN, when incorporated into a matrix, could act as antibacterial membranes. Fluorinated MSN loaded with methylene blue could show photodynamic activity in the presence of light. These ROS generators were embedded on an electrospun polycaprolactam-zein membrane. These membranes also showed hydrophobic activity due to the presence of MSN on the surface which added to the low survival rates of the bacteria [57]. In another study by Tang *et al.*, (2019) glucose polymer incorporated silicon NPs were internalized by bacteria through ATP binding cassette transporter pathway. When irradiated at 660 nm, it led to the production of ROS by the photosensitizer chlorine e6 (a photosensitizer with low cytotoxicity and high efficacy). This study demonstrated that SiNP could target bacteria by with the help of glucose polymer such as poly[4-O-(α-D-glucopyranosyl)-D-glucopyranose] and due to the photodynamic activity both Gram-positive and Gram-negative bacteria could be killed [58]. MSNs could be used as an efficient multi-drug delivery system for a combination of hydrophobic drugs, and photosensitizers, whereby photodynamic sterilization could be achieved in multidrug-resistant biofilms. A pH sensitized amino-functionalized MSN was synthesized with curcumin as the photosensitizer, and the whole system was made positively charged thus penetrating the negatively charged *S.aureus* biofilm (Figure 4). The system was then irradiated with blue light-emitting diode (LED) light, whereby the bacterial viability was reduced by 98 % [59].

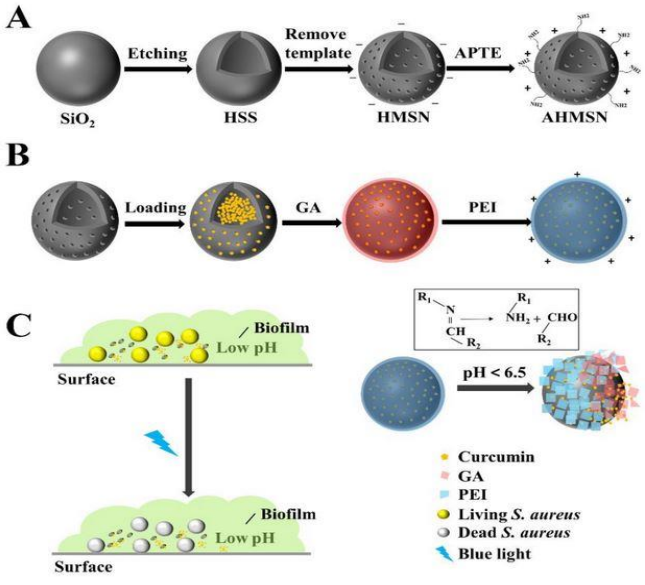

Fig. 4. Schematic image of amino-modified hollow mesoporous silica nanoparticles (AHMSN) loaded natural photosensitizer curcumin. Polyethyleneimine (PEI) and glutaraldehyde (GA) were applied to seal the AHMSN. copyright permission under under the terms and conditions of the Creative Commons Attribution (CC BY) license [59].

Conclusions

Silica NPs are a potent group of nanocarriers that has shown very efficient anti-microbial action and drug delivery. The mechanism of functionalizing silica NPs is the critical factor to be considered while applying it to biological systems (Figure 5). Green approaches for synthesizing silica NPs loading antibiotic for a controlled delivery would be a very effective solution for the silent pandemic of antibiotic resistance. In the post-Covid era, the problem of antibiotic resistance has to be tackled with such novel options. Since silica NPs have free silanol groups, which make them amenable to modifications, the porous nature which contributes to a higher payload of drugs makes it the best option for treating infections.

In addition to the shape and size of silica NPs, a higher roughness of silica NPs can result in more bacterial inactivation relative to a counterpart with low roughness. Removing polybacterial infections, particularly in the case of bacterial biofilms, may be possible by loading several drugs on silica NPs to obtain advantages, including reduced side effects of antibiotics and the simultaneous delivery of antibiotics at the desirable amounts to the infected site. Loading antibacterial agents to the disease site without leakage and obtaining high local concentrations of the drug are essential factors designing an effective formulation. This way, pseudorotaxanes, rotaxanes, β-CD-modified PEI, and cucurbit[6]uril may be suitable options to trap and release the drugs as caps on the pores of silica NPs. The main antibacterial mechanism for antibacterial agent-loaded MSNs is increasing inner membrane permeabilization and outer membrane penetration. MSNs are a desirable delivery system to protect defensin peptides such as T7E21R-HD5 from more degradation by the intestinal protease. Moreover, these NPs can reduce intestinal inflammation by blocking the generation of inflammatory factors like MMP-9, TNF-α, and IL-1β. It is worth noting that the main disadvantage of MSNs is a high density of silanol groups on their surface, which can interact with the membrane's phospholipids in the red blood cells leading to hemolysis. To solve this problem, surface modification of MSNs by biocompatible polymers such as PEG is more likely to be an appropriate strategy.

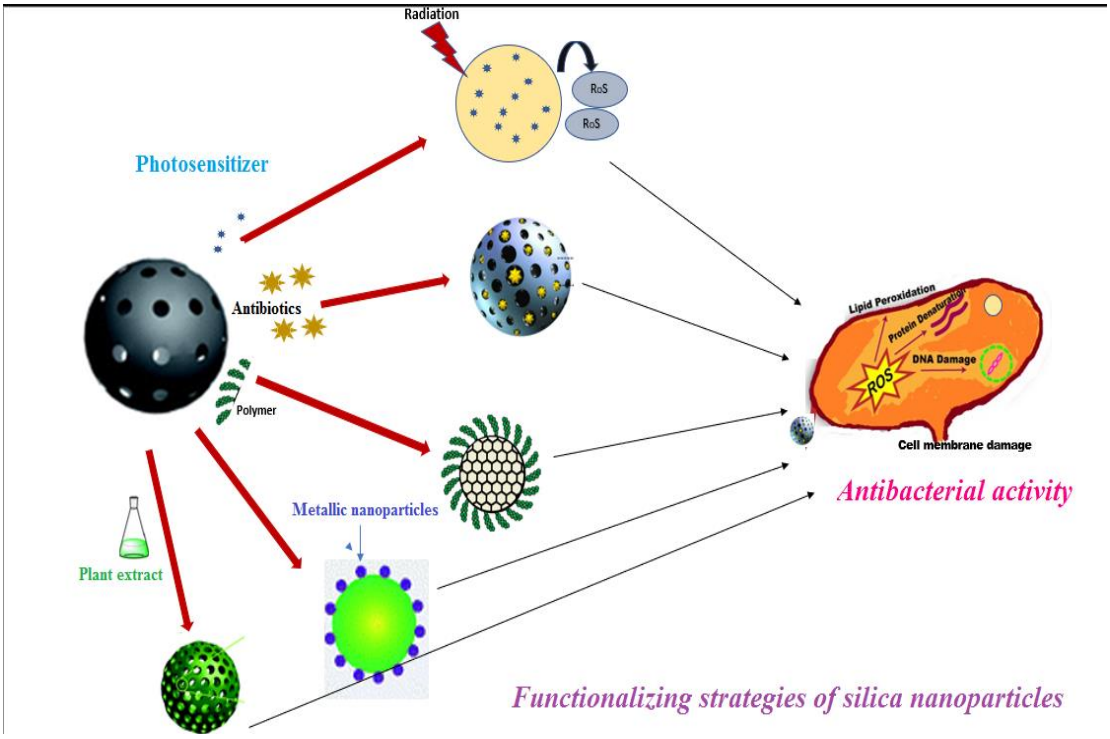

Fig. 5. Functionalizing mechanisms for silica NPs and how they inhibit bacterial growth [60].

Study Highlights

- The mechanism of functionalizing silica NPs is the critical factor to be considered while applying it to physiological conditions.
- Green approaches to synthesize silica NPs loading antibiotic would be a very effective solution for the silent pandemic of antibiotic resistance.
- Silica NPs have free silanol groups, which make them amenable for modifications.
- The porous nature of MSNs contributes to a higher payload of drugs.
- Surface modification of MSNs by biocompatible polymers such as PEG is more likely to be a suitable strategy.

Abbreviations

AHMSN: Amino-modified hollow mesoporous silica nanoparticles
GA: Glutaraldehyde
GLYMO–IDA: Silanized iminodiacetic acid
GLYMO: Glycidyloxypropyltrimethoxysilane
CTAB: Cetyl trimethyl ammonium bromide
LED: Light-emitting diode
MDR: Multidrug-resistant
MIC: Minimum inhibitory concentration
MRSA: Methicillin-resistant *S. aureus*
MSNs: Mesoporous silica nanoparticles
MSSA: Methicillin-sensitive *S. aureus*
NPs: Nanoparticles
PEG: Polyethylene glycol
PEI: Polyethyleneimine
ROS: Reactive oxygen species
TEOS: Tetraethyl orthosilicate

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Conflict of interest

The authors declare that they have no conflict of interest for this study.

Ethical approval

This article does not contain any studies with animals or human participants.

Authors' contribution

MA: conceptualization, preparing the first draft, and revising; ST and MN: revising of the manuscript.

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