Symposium - Review Article

Bio-inspired nanomaterials and their applications as antimicrobial agents

Abstract

In the recent decades, the interdisciplinary field of nanotechnology has expanded extensively. A variety of nanoparticles (NPs) have been used for a number of specialized applications. In this era facing a major problem of microorganisms developing antibiotic resistance, NPs are a lucrative option. Most physical and chemical processes of NP synthesis are associated with drawbacks and bio-inspired NPs have now become popular. This review summarizes the recent developments on the biosynthesis, characterization, and applications of NPs with particular reference to their use as antimicrobial agents. Reviewed here is the synthesis of gold and silver NPs (AgNPs) by a variety of biological forms and biomolecules as well as their effectiveness toward different fungal and bacterial pathogens. The use of gold NPs (bio-inspired by plants, fungi, and bacteria) and AgNPs, synthesized by carbohydrates (of plant, animal, and microbial origin), plant parts (bark, callus, leaves, peels, and tubers), fungi, and bacteria have been highlighted. In addition, the use of zinc oxide NPs (although not bio-inspired) as novel antimicrobial agents have also been discussed.

Key words:
Antimicrobial agents, bio-inspired, nanoparticles

Introduction

In the past few decades, the field of nanotechnology has developed extensively. Nanotechnology, in general, refers to the synthesis, characterization, and applications of materials that are in the nanometer range (1 m = 10^9 nm). Nanometric material properties differ from the bulk properties. This difference is due to the very small size and high surface area of the former. Such nanoscale structures are known to bridge the gap between bulk materials and the atomic and molecular structures. Nanotechnology is thus an interdisciplinary field that involves physical, chemical, biological, and engineering sciences. Nanomaterials can be broadly grouped into two main categories: (i) organic which include carbon nanoparticles (NPs) such as fullerenes and (ii) inorganic particles such as those of noble metals (gold, silver, and platinum), magnetic NPs (iron, cobalt, and nickel), and those of semiconductors (oxides of titanium, zinc, cadmium) to mention a few. NPs from each of these categories have been used for a variety of specialized applications as detailed in relevant reviews.[1-8]

Two major approaches have been used for the synthesis of metallic NPs. The "Top-down" approach begins with a suitable starting structure. This structure is decreased in size by employing a variety of physical or chemical methods. The "Bottom-up" methods involve the formation of nanostructures through the self-assembly in an atom-by-atom, molecule-by-molecule, or cluster-by-cluster manner. Biological synthesis of NPs, in general, involves this approach wherein, biomolecules mediate reductive processes and stabilize nanostructures. Most of the earlier studies on NP synthesis have involved the use of chemical or physical methods. These processes use high temperatures, apply radiations, include toxic chemicals, involve the generation of hazardous by-products, need specialized apparatus, and consume energy. On account of these issues, biological systems have emerged as effective alternatives

Access this article online	
Website: http://www.cysonline.org	**Quick Response Code**
DOI: 10.4103/2229-5186.94314	

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for the rapid, cost-effective, and "green" synthesis of NPs. In general, biological systems (plant and microorganisms) display a vast variety of biomolecules with reductive properties. These mediate a reduction of metal salts to nanostructural elemental forms. The nanostructures thus formed are capped by additional biomolecules present in the biological material. Microorganisms are constantly exposed to metals and often have inherent defense reductive mechanisms that mediate the synthesis of a variety of NPs. This property makes them some of the most lucrative bio-machines for the synthesis of novel materials. There are several reviews on bio-inspired nanomaterials with respect to their synthesis, the mechanisms involved, and applications in different fields.[9-19] However, a review on the applications of these bio-inspired NPs as antimicrobial agents is missing. The present review hopes to fill this void in the literature.

Nanoparticles as antimicrobial agents

Infectious diseases are major cause of mortality worldwide. The appearance of antibiotic-resistant pathogenic strains has been threatening public health globally. In some cases, microorganisms display multiple drug resistance. This has triggered a need for the development of novel therapeutic agents. With nanotechnology emerging as a forefront area in integrated science, the use of NP-based therapeutics for controlling pathogenic bacteria has emerged as an important alternative.

A variety of NPs have been explored for their antimicrobial properties. These include NPs of silica, silica/iron oxide, bi-functional Fe_3O_4-Ag NPs, titanium, copper and aluminum, and those of silver, gold, and zinc, as discussed in this review.[20-24] The NPs when studied as antimicrobial agents have not necessarily been synthesized through biological systems. Although there are a few dedicated reviews on the use of bio-inspired silver NPs (AgNPs) as antimicrobial agents,[15,18] the present review describes recent update on the antimicrobial properties of bio-inspired NPs. In the following sections, the synthesis and application of a variety of NPs of the two major noble metals (gold and silver) has been presented in a classified manner. In addition, the applications of ZnONPs (although not bio-inspired) have also been discussed as they are becoming popular as antimicrobial agents with regard to medical applications.

Gold nanoparticles as antimicrobial agents

Gold NPs (AuNPs) have been studied extensively as they display several unique features. They can be synthesized by relatively simple methods, exhibit good water solubility, and display excellent stability. In recent years, green approaches for the generation of AuNPs are on the rise and their antimicrobial properties have also been evaluated. There are a few reports on AuNPs mediated by plant material, fungi, and bacteria, as shown in Figure 1. The following section summarizes the reports on bio-inspired AuNPs and their antimicrobial activities.

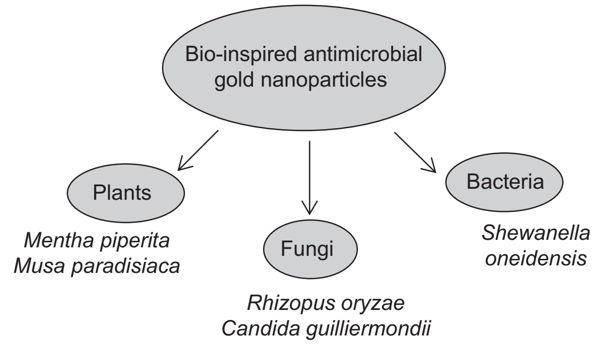

Figure 1: Summary of bio-inspired gold nanoparticles as antimicrobial agents

A few plant products have been applied for synthesizing antimicrobial AuNPs. For example, bioreduction of chloroauric acid ($HAuCl_4$) to Au^o by the plant extract of *Mentha piperita* (Lamiaceae) has been reported recently.[25] Amide groups in the extract were thought to be involved in the synthetic process. The NPs were 150 nm and exhibited strong antibacterial activity against *Escherichia coli*. AuNPs have also been synthesized by using banana peel (*Musa paradisiaca*) extract (BPE).[26] This simple, non-toxic, eco-friendly "green material" reduced $HAuCl_4$ to AuNPs. Dynamic light scattering studies revealed the average size of the NPs to be 300 nm. Fourier transform infra red (FTIR) spectroscopy indicated the involvement of carboxyl, amine, and hydroxyl groups in the synthetic process. The BPE-mediated NPs displayed efficient antimicrobial activity toward *Candida albicans*, *Shigella* sp., *Citrobacter koseri*, *E. coli*, *Proteus vulgaris,* and *Enterobacter aerogenes*. However, antibacterial activity was not observed with *Klebsiella* sp. and *Pseudomonas aeruginosa*.

A few microbial systems including fungi, yeasts, and bacteria have been used in the synthesis of antimicrobial AuNPs. A green method to synthesize nanogold-bioconjugate (NGBC) has been described.[27] The AuNPs (10 nm average diameter) were produced on the surface of *Rhizopus oryzae* by *in situ* reduction of $HAuCl_4$. The NGBC showed high antimicrobial activity against Gram-negative and Gram-positive pathogenic bacteria as well as against yeasts (*Saccharomyces cerevisiae* and *C. albicans*). The NGBC has been proposed as a promising candidate for obtaining potable water free from pathogens. Extracellular synthesis of AuNPs by a yeast (*Candida guilliermondii*) has also been described.[28] The biosynthesized NPs were 50 to 70 nm and displayed antimicrobial activity against five pathogenic bacterial strains. The highest efficiency was observed against *Staphylococcus aureus*. In another report, the metal-reducing bacterium *Shwanella oneidensis* brought about the reduction of tetrachloroaurate (III) ions to extracellular homogenous spherical gold nanocrystallites with an average size of 12±5 nm.[29] The particles were possibly fabricated by reducing agents present in the cell membrane and were capped by a detachable protein/peptide. The antibacterial activity of these AuNPs was assessed against *E. coli*, *S. oneidensis*, and *Bacillus subtilis*. However, these AuNPs were neither toxic nor inhibitory toward any of the test bacteria.

Cefaclor is a well-known second-generation antibiotic belonging to the β-lactam class of antibiotics derived from the fungus *Acremonium* (previously *Cephalosporium*). There is a report on a one-pot synthetic method for the development of AuNPs (52–22 nm) using this antibiotic.[30] The primary amine group of cefaclor acted as the reducing as well as the capping agent leaving the β-lactam ring available for antibacterial activity. The cefaclor-reduced AuNPs displayed potent antimicrobial activity against *S. aureus* and *E. coli* as compared with cefaclor or AuNPs individually. The minimum inhibitory concentration (MIC) values of cefaclor-reduced AuNPs were found to be 10 μg/ml and 100 μg/ml for *S. aureus* and *E. coli*, respectively. The AuNPs thus obtained were also coated onto polyethyleneimine-modified glass surfaces to obtain antimicrobial coatings (inhibiting growth of *E. coli*) suitable for biomedical applications. The antibacterial activity of these particles was through the combined action of cefaclor inhibiting the synthesis of the peptidoglycan layer and AuNPs generating "holes" in bacterial cell walls.

Silver nanoparticles as antimicrobial agents

An extensive literature survey has shown that AgNPs are the most popular inorganic NPs to be used as antimicrobial agents. There are a few reviews that summarize the green methods for AgNP synthesis.[15-18] This review will focus on the recent literature on bio-inspired NPs that have been tested for their antimicrobial activities. This literature has been classified in subsequent sections as (i) carbohydrate-mediated, (ii) plant-mediated, (iii) fungal biomass-mediated, and (iv) bacteria-mediated synthesis of AgNPs [Figure 2].

Carbohydrate polymer-mediated synthesis of silver nanoparticles and their antimicrobial activities

Plant- and animal-derived carbohydrates have been employed in the synthesis of AgNPs. Table 1 summarizes carbohydrate polymer-mediated synthesis and properties of antimicrobial AgNPs.

Plant-inspired synthesis of silver nanoparticles and their applications as antimicrobial agents

A variety of plant parts including barks, callus, leaves, tubers, and fruit peels have been used for the synthesis of AgNPs that display antimicrobial properties. *Cinnamon zeylanicum* bark powder (CBP) and powder extracts (CBPE) have been applied for this purpose. CBPE was more effective in the reduction of Ag^+ to Ag^o. The antimicrobial activity of the AgNPs was tested against *E. coli* (BL 12). The effective concentrations required to induce a 50% effect (EC_{50}) were found to be 11 ± 1.72 mg/l and MIC values were 50 mg/l.[35]

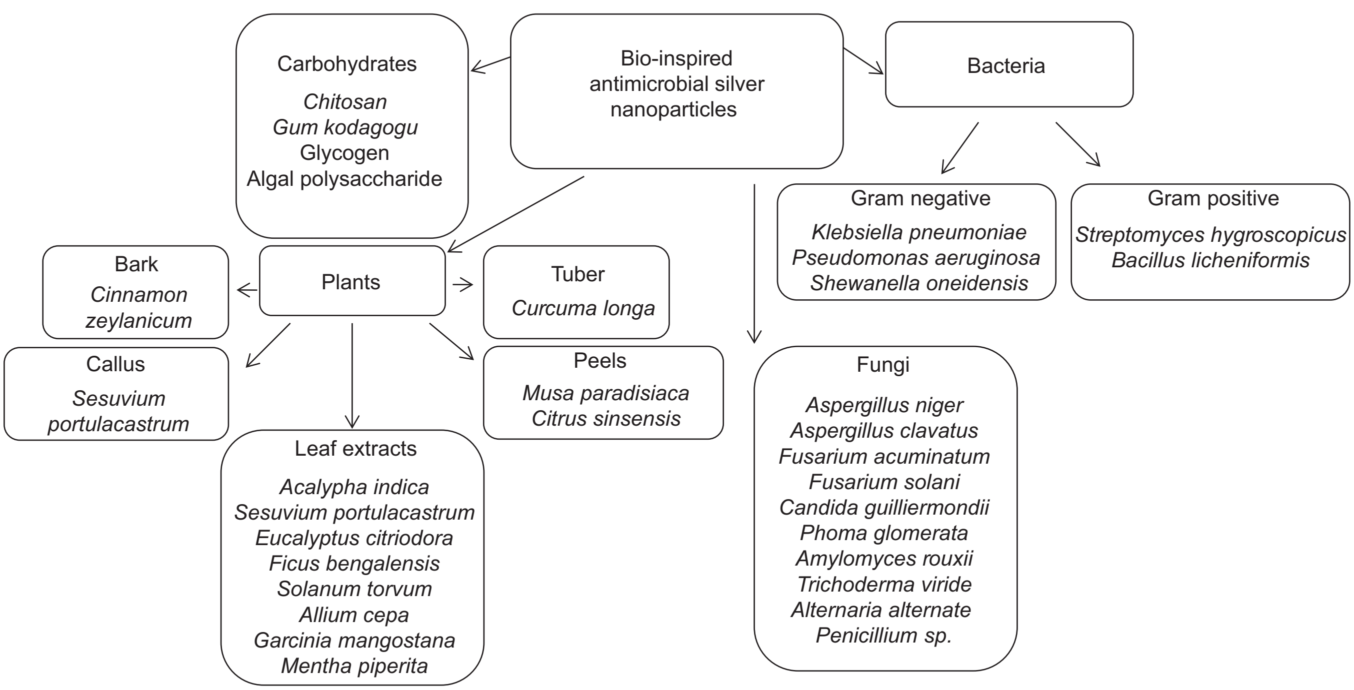

Figure 2: Summary of bio-inspired silver nanoparticles as antimicrobial agents

Table 1: Carbohydrate-mediated synthesis of antimicrobial silver nanoparticles

Carbohydrate and reference	Size (nm)	Mechanism of synthesis	Antimicrobial activity toward
Chitosan[31]	6-8	Hydroxyl, carbonyl groups	*E. coli, S. aureus, B. subtilis*
Gum kondagogu derived from *Cochlospermum gossypium*)[32]	19, 55	Hydroxyl, carboxyl groups associated with rhamnose, galactose, uronic acids, and peptides	*S. aureus, E. coli, P. aeruginosa*
Glycogen[33]	10	Hydroxyl groups	*C. albicans, E. coli, S. aureus*
Sulfated polysaccharide (Marine algae *Porphyra vietnamensis*)[34]	13	Sulfate moiety of polysaccharide, anionic polysaccharide as capping agent	Gram-negative bacteria

The callus and leaf extracts of the coastal sea marsh plant *Sesuvium portulacastrum* L have also been investigated for their ability to synthesize AgNPs.[36] The former was more effective in NP synthesis. The size of the NPs was between 5 to 20 nm. Proteins, flavones, and terpenoids were responsible for stabilizing the AgNPs. Among *P. aeruginosa*, *S. aureus*, *Listeria monocytogenes*, *Micrococcus luteus*, *Klebsiella pneumonia*, *Alternaria alternata, Penicillium italicum, Fusarium equiseti*, and *C. albicans* that were tested, highest zone of inhibition (ZOI) of 23 mm was formed against *S. aureus*. On the other hand, *M. luteus* was approximately three-fold less affected (8 mm ZOI). The ZOI obtained with *Penicillium* sp. was 18 mm and with *C. albicans,* it was 12 mm.

The aqueous leaf extract of *Acalypha indica*, an Indian traditional medicinal plant, was also able to rapidly (within 30 minutes) reduce ionic silver and stabilize AgNPs that were 20 to 30 nm in size.[37] These AgNPs showed effective antibacterial activity against *E. coli* and *Vibrio cholera*. The MIC values (lowest concentration at which no visible growth of the test pathogens was observed) for both the cultures were 10 μg/ml. The leaf extracts of *Eucalyptus citriodora* and *Ficus bengalensis* have also been successfully employed for the "green" synthesis of cotton fibers loaded with AgNPs.[38] These extracts that were rich in polysaccharides composed of p-menthane-3,8-diol, β-sitosterol, α-d-glucose, and mesoinositol reduced silver salts and stabilized AgNPs (average size of 21 nm). Cotton fibers loaded with NPs were also fabricated by the *in situ* reduction of silver nitrate into AgNPs. The biological synthesis of AgNPs using *Solanum torvum* leaf extracts has been reported recently.[39] The reduction of the $AgNO_3$ to AgNPs was completed in 60 minutes. Carboxylate groups in the biological material were important in the reductive process. The average size of the NPs was 14 mm. The growth of *P. aeruginosa*, *S. aureus*, *Aspergillus flavus,* and *Aspergillus niger* was inhibited by these bio-inspired NPs.

A rapid, convenient, and extracellular method for synthesis of AgNPs has been developed with the help of onion (*Allium cepa*) leaf extract.[40] The average size of AgNPs was 33.6 nm. The effect of AgNPs on the bacterial growth was monitored on the basis of optical density measurements. As the concentration of AgNPs was increased, there was a decrease in bacterial growth of *E. coli* and *Salmonella typhimurium*. Another simple eco-friendly mechanism for the biosynthesis of AgNPs has been reported by using leaf extracts of *Garcinia mangostana* (mangosteen).[41] Silver ions when exposed to leaf extract were reduced to AgNPs with an average size of 35 nm. Furthermore, these NPs were highly effective against a variety of multidrug-resistant human pathogens. For *E. coli*, the ZOI with AgNPs (20 μg/ml) was 15 mm and for *S. aureus*, it was 20 mm. In a recent report, the bioreduction of silver nitrate to AgNPs by the plant extract of *Mentha pipertita* has also been described.[25] The amide groups were involved in NP synthesis that were 90 nm in size. The synthesized AgNPs exhibited strong antibacterial activity against *E. coli* and *S. aureus*, the test cultures that were used.

Synthesis of AgNPs by *Curcuma longa* tuber powder and extract has also been described.[42] The tuber extracts were more efficient in AgNP synthesis. In the extract, the content of the reducing agents was large and these were easily available for the reductive process. *C. longa* tubers are known to be rich in terpenoids such as cineol, borneol, and in zingiberene, sabinene, a-phellandrene, sesquiterpines, and curcumin. These along with protein components were believed to play a role in silver nanoparticle biosynthesis. The minimum bactericidal concentration of these AgNPs for *E. coli* BL-21 strain was found to be 50 mg/l. Immobilization of AgNPs on cotton cloth showed better bactericidal activity when compared with polyvinylidene fluoride-immobilized cloth.

The use of fruit peels for the synthesis of AgNPs with antimicrobial activity has also been reported. Bio-inspired AgNPs were synthesized with the aid of BPE (*Musa paradisiaca*), a non-toxic, eco-friendly biological material.[43] Boiled, crushed, acetone precipitated, air-dried peel powder brought about a reduction of silver nitrate. Silver nanosized crystallites were obtained after short incubation periods. FTIR analysis indicated the role of different functional groups (carboxyl, amine, and hydroxyl) in the synthetic process. These AgNPs displayed antimicrobial activity against fungi such as *C. albicans* and *Candida lipolytica*. They were also antibacterial against *E. coli*, *E. aerogenes*, *Klebsiella* sp., and *Shigella* sp. Other bacteria such as *C. koseri*, *P. vulgaris,* and *P. aeruginosa,* however, did not display the characteristic zones of inhibition, indicating that these cultures were not inhibited by the AgNPs.

The aqueous extracts of *Citrus sinensis* (orange) peels for the synthesis of starch-supported AgNPs is also reported.[44] The antimicrobial activity of these NPs was tested against *B. subtilis* in the presence and absence of rifampicin. In the absence of rifampicin, a larger ZOI (20 mm) was obtained. However, in the presence of rifampicin, this was 17 mm. The starch associated with the NPs allowed lesser diffusion of the NPs, thereby explaining the observed results.

Antimicrobial activities of silver nanoparticles synthesized by fungi

Fungi have been used extensively for the synthesis of AgNPs. Table 2 summarizes the synthesis of AgNPs by a variety of fungi. The most frequent reports are on *Aspergillus* and *Fusarium* sp.

Bacterial synthesis of silver nanoparticles

A few Gram-negative bacteria have been used to synthesize antimicrobial AgNPs. AgNPs were synthesized by using *Klebsiella pneumoniae* and their antimicrobial activity against *S. aureus* and *E. coli* was evaluated.[58] The experimentation showed that the antibacterial activities of antibiotics such as penicillin G, amoxicillin, erythromycin, clindamycin, and vancomycin were enhanced in the presence of AgNPs against both the test cultures. With erythromycin, the highest synergistic activity was observed against the test *S. aureus* culture. In another study, the culture supernatant of *P. aeruginosa* strain BS-161R was effective in the simple and cost-effective green synthesis of AgNPs. [59] The reduction of silver ions resulted in mono-dispersed and spherical particles with an average size of 13 nm. The enzyme nitrate reductase and rhamnolipids present in the culture supernatant were thought to be responsible for the reduction and capping, respectively. The prepared AgNPs exhibited strong antimicrobial activity against *S. aureus*, *Micrococcus luteus*, *C. albicans,* and *C. krusei* at 8 μg/ml concentrations, suggesting a broad-spectrum nature of their antimicrobial activity. Another recent report describes the facile biosynthesis of small, spherical, nearly mono-dispersed silver nanocrystallites with average size of 4±1.5 nm by using the metal-reducing bacterium, *Shwanella oneidensis* MR-1.[60] Carbonyl, hydroxyl, amide, and carboxyl groups were involved in the synthetic process. Additionally, the antibacterial properties of these biogenic AgNPs were compared with those of chemically synthesized NPs (colloidal-Ag) and (oleate-Ag) on *E. coli*, *S. oneidensis,* and *B. subtilis*. The different chemical/biological coatings on the NPs significantly influenced their toxicity. The authors have suggested that such a strategy could in turn provide a means for adapting NPs for different applications or for altering their fate in biological and environmental systems.

There are a few reports on Gram-positive bacteria producing AgNPs. For example, the extracellular components of *Streptomyces hygroscopicus* resulted in the development of spherical AgNPs that were 20 to 30 nm.[61] Furthermore, the biosynthesized AgNPs significantly inhibited the growth of medically important pathogenic Gram-positive bacteria (*B. subtilis* and *Enterococcus faecalis*), Gram-negative bacteria (*E. coli* and *S. typhimurium*), and the yeast *C. albicans*. In another study, a strain of *B. licheniformis* was used to synthesize AgNPs.[62] These bio-inspired AgNPs were able to disrupt biofilms of two common bacterial pathogens, *P. aeruginosa* and *S. epidermidis,* a major cause of microbial keratitis. Observations in microtiter plate assays disclosed the potential of AgNPs in the effective inhibition of biofilm formation by these two cultures. The results strongly suggested the futuristic applications of AgNP-based contact lens care solutions, for biofilm-based human ocular problems.

Table 2: Synthesis of antimicrobial silver nanoparticles by fungi

Fungus and reference	Size (nm)	Mechanism of synthesis	Antimicrobial activity toward
Aspergillus niger (soil isolate)[45]	20	Nitrate reductase, protein	*S. aureus, E. coli*
Aspergillus niger (silver thread disposal site)[46]	3-30	Nitrate reductase	*S. aureus, E. coli, Bacillus* sp.
Aspergillus niger (mangrove sediment)[47]	5-35	70 kDa protein	Clinical pathogens
Aspergillus clavatus (*Azadirachta indica* stem endophyte)[48]	10-25	–	*C. albicans, Pseudomonas fluorescens, E. coli*
Aspergillus clavatus[49]	550-650	–	*S. aureus, Staphylococcus epidermidis*
Aspergillus oryzae var. *viridis*[50]	5-50	Organic content of dead cells	*S. aureus* KCCM 12256
Fusarium acuminatum (*Zingiber officinale*)[51]	13	Nitrate-dependent reductase	*S. aureus, Salmonella typhi, S. epidermidis, E. coli*
Fusarium solani[52]	3-8	–	*S. aureus, E. coli*
Candida guilliermondii[28]	10-20	–	*S. aureus*
Phoma glomerata[53]		–	*S. aureus, E. coli, P. aeruginosa*
Amylomyces rouxii[54]	20	–	*S. aureus, E. coli, Citrobacter, S. dysenteriae, P. aeruginosa, B. subtilis, Fusarium oxysporum*
Trichoderma viride[55]	5–40	–	Gram-positive and -negative bacteria
Alternaria alternata[56]	20-60	–	*Phoma glomerata, Trichoderma* sp., *C. albicans*
Penicillium (K1 and K10)[57]	10–100	–	*Bacillus cereus, S. aureus, E. coli, P. aeruginosa*

Table 3: Antimicrobial activities of ZnO nanoparticles

Type of ZnO, reference	Synthesis procedure	Antimicrobial activity
ZnO, MgO, TiO_2, CuO, CeO_2, Al_2O_3 [63]	Purchased from Nanoscale Materials Inc (KS)	*S. aureus, S. epidermidis, Streptococcus pyogenes, Enterococcus faecalis, B. subtilis, E. coli* K12
ZnO-Fe composites[64]	Gelatin based thin films	*S. aureus, E. coli*
ZnO-*Acacia concinna* surfactant [65]	Chemically synthesized (ZnO NaOH)	*Pseudomonas, Fusarium*
ZnO[66]	Chemically synthesized (Zinc acetate, aniline)	*S. aureus, E. coli, S. typhimurium, K. pneumoniae*
ZnO [67] Equiaxed Nanorods	Chemically synthesized (Zinc acetate, NaOH, Methanol, Polyethylene glycol as surfactant) Zinc nitrate, soluble starch, NaOH)	*S. aureus, E. coli*
ZnO [68] Mn doped ZnO	ZnO coprecipitation Zn^{2+}, Mn^{2+} in alkaline methanol	*E. coli, K. pneumoniae, Shigella dysenteriae, Salmonella typhi, P. aeruginosa, B. subtilis, S. aureus*
ZnO [69] in polystyrene films Polyvinylpyrrolidone gels	Methanolic KOH	*L. monocytogenes, Salmonella enteritidis, E. coli* (O157: H7)
ZnO [70]	Zn acetate in diethylene glycerol	*S. aureus, E. coli*

Other (non-bioinspired) inorganic nanoparticles as antimicrobial agents

Oxides of titanium, copper, aluminum, and zinc are some of the other inorganic nanoscale materials that have antimicrobial activity. An extensive literature survey has shown that most of these NPs have not generally been synthesized by using biological systems. Although the aforementioned variety of metal oxides have been investigated for their antimicrobial activities, ZnONPs have received particular attention in medical settings.[63] Similar to other metal oxides, these ZnONPs have also been synthesized chemically. ZnONPs have several advantageous features. They display photo-catalytic and -oxidizing capacities against biological and chemical species. They are stable under harsh conditions and can be fabricated at ambient temperature. The most important character is that they are generally regarded as safe. Table 3 summarizes the use of such chemically synthesized ZnONPs individually or in combinations with other agents in being effective as antimicrobial agents.

Conclusion

In conclusion, a variety of biological systems have been employed for the synthesis of NPs displaying antimicrobial properties. An important point that arises from the literature survey involved is that bio-inspired NPs of noble metals (silver, in particular) are very popular as antimicrobial agents. Most of the studies have involved the testing of antimicrobial properties against potential pathogens. However, these may also possess antimicrobial properties toward the normal flora. In the future, a possible line of investigation would be the development of nanomachines specifically destroying pathogenic microorganisms. However, it must be noted that there are a few constraints on the use of these NPs as antimicrobial agents. First, a dramatic increase in the prices of these noble metals worldwide would restrict their widespread use. Second, microorganisms are capable of developing resistance to metals through natural selection or horizontal gene transfer. Third, not all type of gold and AgNPs are antimicrobial in nature. There is thus a need to determine additional factors involved in the biosynthetic processes that make such nanoparticle preparations antimicrobial or non-antimicrobial. Another aspect is related to the use of crude extracts in the synthetic procedures. Components of these extracts should be tested for their detrimental effects on human health. It may thus be necessary to isolate and purify the components in the extract that mediate the synthetic process. It is also evident that apart from gold and AgNPs, oxides of other metals are less expensive, lucrative alternatives. There is scope for studies on the synthesis of such metal oxide NPs through biological routes and examination of their potential as antimicrobial agents.

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How to cite this article: Zinjarde SS. Bio-inspired nanomaterials and their applications as antimicrobial agents. Chron Young Sci 2012;3:74-81.
Source of Support: Nil, **Conflict of Interest:** None declared