Chapter 7
Antimicrobial Metal-Based Nanomaterials and Their Industrial and Biomedical Applications

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1 Introduction

Nowadays, nanotechnology has presented great potentials in many arenas of science and technology. Indeed, nanotechnology is the study of extremely small structures [1]. It is the treatment of individual compounds into dimensional structures to yield materials with superior properties. Nanotechnology is widely used in target drug delivery [2], tissue engineering [3], sensors [4], water treatment [5] and other fields.

Owing to the extensive existence of drug-resistant pathogens as a serious health issue, there is growing interest in the employ of novel nanostructured materials, specifically metal-based nanomaterials (MNMs) as antimicrobials [6]. Thus, MNMs could aid as a substitute to antibiotics to control bacterial infections. In this regard, fabrication of metal compounds in nanoscale is very important.

The MNMs are classified to metals (e.g., Au, Ag, Ti, Zn, Cu), metal oxides (e.g., Fe_3O_4, TiO_2, ZnO, CuO, Ag_2O) and metal alloys (e.g., $ZnFe_2O_3$, $CuFe_2O_3$). They are synthesized by various methods such as chemical, physical and plant or microorganism-mediated biosynthesis. For example, Fe_3O_4 can be produced by co-precipitation method (chemical method) from iron (II and III) salts [7]; Ag can be synthesized by green synthesis of plants extract (gums, green tea, etc.) [8]. It is well known that the procedures and conditions for synthesis of MNMs can effect their physicochemical and biological properties. One of the important factors in MNMs

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is their particle size which influences the biological properties such as antimicrobial activities and toxicity.

The nanomaterials, specifically MNMs, have higher antibacterial activity than that those in microscale, as surface area in nanomaterials is very larger than their volume [9]. Actually, in the nanometer dimensions, some properties of the particles, e.g., thermal stability, reactivity, dissolution, are noticeably increased. In this chapter, the antimicrobial activity of MNMs is presented along with their applications in various arena from industrial to biomedical fields.

2 Antimicrobial Activity

Today, infectious illnesses are one of the chiefs led to disease and fatality in the world, and thus, there is the requisite for study on antimicrobial agents [10]. With an increase in resistance of antibiotics, a rising interest in developing new and effective antimicrobial agents has paramount importance [11]. Antimicrobial agents mention the materials that led to killing or inhibiting the microbes causing disease. Numerous antimicrobial agents are used for this purpose. In recent years, nanotechnology has been employed to prepare new antimicrobial systems and devices, capable of fighting opportunistic infections. Metal-based nanomaterials (MNMs) are able to identify bacterial cells from mammalian cells and can supply long-term antibacterial and biofilm inhibition [12].

Metal-based nanomaterials, e.g., Au, Ag, Si, CuO, ZnO, TiO_2, MgO, Fe_3O_4, Fe_2O_3, MgO, CaO, etc., have been applied in different fields to impart antimicrobial activity [6]. Because of dimensions, such as smaller size and the larger surface area to volume ratio of MNMs than bacteria, they provide strong and extended antimicrobial interaction with bacteria and biofilms at smaller dosages [13]. There are many physical and chemical factors such as size, zeta potential, shape and roughness that affect the antimicrobial activity of MNTs [14]. Changing these factors has a reflective effect on the antimicrobial activity of MNTs as presented in Table 1. Typically, smaller MNTs have higher antimicrobial activity. Nevertheless, some studies have demonstrated that size alone is not the most significant factor of the antimicrobial activity of MNTs [14]. Other parameters such as the media, the preparation process, the defense mechanism of the microbe and the physical features of the MNMs can also affect the microbicidal activity (Fig. 1) [15]. Actually, the logical reason for more toxic of the small MNMs than the large MNMs can be explained by increase the reactive oxygen species (ROS) production, which therefore can destruct and deactivate vital biomolecules [16, 17]. The precise mechanisms for antimicrobial activity of MNMs are still being studied. In general, three main possible mechanisms in this regard are [18]:

- Metal ions release that from dissolution of the metals from MNMs surface, react with the cell membrane and other cellular components.
- ROS generation on the MNMs surface that led to oxidative stress.
- Physical destruction of the cell membrane through the MNMs.

Table 1 Size, shape and antibacterial activities of the some of the metal-based nanomaterials

Metal-based nanomaterials	Size (nm)	Shape	Strain	Activity	Ref.
Au	8.4	Spherical	*A. baumannii, E. coli, P. aeruginosa, S. aureus*	MIC = 8 μg/mL	[20]
	50–100	Spherical	*E. faecium, S. oneidensis*	MIC = 32 μg/mL	
CeO_2	6	Square	*E. coli*	Z = ~0.2 mm	[21]
	7	NR	*E. coli*	MIC = 500 μg/mL	[22]
	15	Circular, ovoid	*E. coli*	Z = ~3.3 mm	[21]
TiO_2	12	Spherical	*E. coli*	MIC = 100 μg/mL	[23]
	17	Spherical	*E. coli*	MIC = 100 μg/mL	
	21	Spherical	*E. coli*	MIC = 100 μg/mL	
ZnO	12	Spherical	*E. coli*	Z = 31 mm	[24]
	19	Spherical-like	*E. coli*	MIC = 50 μg/mL	[25]
Ag	9	Spherical	*E. coli*	IC50 = 6.4 μg Ag^+/mL	[26]
	19	Spherical	*E. coli*	IC50 = 15.7 μg Ag^+/mL	
	43	Spherical	*E. coli*	IC50 = 40.9 μg Ag^+/mL	

MIC minimal inhibitory concentration; *Z* zone of inhibition; *LC50* lethal concentration; *NR* not reported

3 Applications

3.1 Industrial Applications

As discussed in the previous section, the MNMs show efficient antimicrobial effects against pathogenic microorganisms. Consequently, some of the MNMs, e.g., Ag, Au, ZnO, TiO_2, MgO, Fe_3O_4, etc., have got significant attention as antimicrobials fillers in industrial products such as antimicrobial coatings, food packaging and water treatment.

Antimicrobial food packaging: It is an imperative to evaluate the amount of the released antimicrobial materials from the package to foods/bioproducts during lengthy storage [27, 28]. There are many literatures published on the use of the

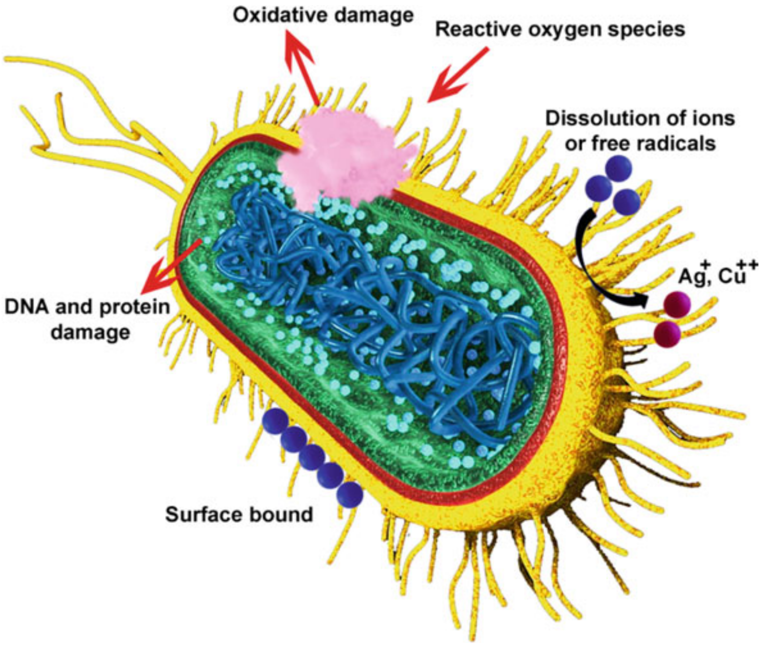

Fig. 1 Schematic of possible interactions and modes of toxicity when engineered MNMs interact with bacterial cells. Different nanoparticle forms are bactericidal through one or several of these mechanisms. DNA: deoxyribonucleic acid. Reprinted from [19] with permission from the publisher

MNMs as an antimicrobial filler for manufacturing antimicrobial packaging [27, 29]. In most of them, a polymer metric such as poly(vinyl alcohol), poly(ethylene glycol), poly(ε-caprolactone), natural polymers containing and MNMs is used [29, 30]. In general, the antimicrobial packaging can be fabricated by two main methods include: (i) Incorporation of antimicrobial agent into a polymer backbone by means of covalent or ionic bonds. (ii) Adsorption of antimicrobial agent on the polymer surface [29]. Numerous researchers have used Ag, Ag-Cu, CuO, ZnO and TiO_2 due to their great antimicrobial properties and high stability.

For example, low-density polyethylene/Cu film with antimicrobial activity was prepared by using solvent evaporation. The presence of Cu nanoparticles into low-density polyethylene improved the antimicrobial and mechanical properties [31]. Starch/poly(vinyl alcohol)/ZnO as an antimicrobial nanofilm was fabricated by the solution casting method. The antimicrobial, UV barrier and mechanical properties were enhanced by addition of ZnO nanoparticles [32]. In another work, montmorillonite/CuO nanocomposite was used for enhancing antimicrobial, optical and mechanical properties of chitosan film [33]. Recently, MNMs in combination of gums such as carboxymethyl guar gum and chewing gum used for the preparation of antimicrobial food packaging [34, 35].

Water treatment: Water contamination via toxic metal ions, dyes, pathogenic microorganisms, etc., is a serious issue for humans life. Consequently, the development of technologies for removing them from polluted water is an environmental challenge [5]. The use of antimicrobial MNs alone and/or in combination with synthetic/natural polymers is a facile method for the removal of contaminations from water [36]. Metal-based nanomaterials, i.e., Ag, TiO_2 and ZnO have been investigated for application in the disinfection of different waterborne illness-causing by microorganisms. One main problem in the use of antimicrobial MNMs alone is their low dispersion and instability in water. This problem can be solved by embedding and/or surface coating by polymers which give them great applications in water purification.

For example, Ag nanoparticles synthesized by *Penciillium Citreonigum Dierck* and *Scopulaniopsos brumptii Salvanet-Duval* fungi employed for pathogenic bacteria removal from wastewater [37]. Antimicrobial TiO_2/tragacanth gum nanocomposite was used for photocatalytic elimination of methylene blue dye from wastewater [38].

Animicrobial coating: Generally, antimicrobial activity of coatings can be categorized as biocidal or biostatic [39]. The agents that kill microorganisms are biocide, whereas the agents that inhibit growth of the microorganisms are biostatic [39]. Most of the antimicrobial coatings usually use biocides such as Ag, TiO_2, ZnO and Au as active agents. For example, in textile industry, these antimicrobial agents are incorporated into the polymer fibers during extrusion or attached to the surface of polymer fibers during finishing. Metal-based nanocomposites also are proposed to be used in different places (for instance, hospitals wall and ground) and devices (e.g., medical devices, doorknob, keyboard) that are prone to the microbial growth.

The antimicrobial textiles modified with MNMs such as Ag, Au, Cu, Ag–Cu, ZnO are reported by many researchers [40–44]. For example, chitosan/Au biomedical textiles fabricated via exhaustion method. Compared with Au nanoparticles or chitosan alone, the chitosan/Au coating demonstrated a better antimicrobial effect against bacteria [41].

Cosmestic: One of the industrial applications of MNMs is in cosmetic materials. Cosmetic products include sunscreens, soaps, shampoo, toothpastes and face creams. Sunscreens are the most common cosmetic products that protect against ultraviolet radiation [45]. They are usually divided into organic and inorganic agents. The MNMs such as ZnO, SiO_2 and TiO_2 are used as photo-stable and physical blocker agents in sun protection cream. Although, the MNMs are commonly found in cosmetics products, unfortunately, they are can be caused serious problems to the lungs. In recent years, several scientists studied the use of MNMs in cosmetic products [46]. For instance, Leong et al. synthesized the antimicrobial TiO_2 via modified sol–gel reaction for cosmetics applications. The azelaic acid was used for enhancing of antimicrobial activity of TiO_2. In another work, Spoiala et al. fabricated SiO_2/ZnO nanocomposite to be applied in cosmetic creams [47]. Antimicrobial and antioxidant ZnO nanoparticles synthesized by Adhatoda vasica leaf extract for use in cold cream formulation [48]. It was reported that cold cream containing ZnO displayed significant resistance against clinical skin pathogens [49]. Ag nanoparticles are also applied into toothpaste, shampoo and soap as preservatives and also in deodorants, lip products, wet wipes, face and body foams. Ag and Au nanoparticles have been implemented in day and night creams to provide the skin a fresher appearance [50].

3.2 Biomedical Applications

Bioactive MNMs represent an interesting alternative for the development of advanced biomaterials with antimicrobial properties, due to their good physicochemical and mechanical properties. The antimicrobial metal-based nanomaterials are widely used in biosensors, drug delivery, dentistry, tissue engineering, etc. This section represents a summary of recent development in the antimicrobial metal-based nanomaterials for biomedical applications.

Drug delivery: In general, drugs or biomolecules delivery to a target site (e.g., tumors and organs) is known as targeted delivery [51, 52]. Many efforts have been devoted to enhance the efficiency of MNM carriers for drug delivery. Numerous literatures studied the use of MNMs in target drug delivery, for example, Au/poly(lactic acid) nanocomposite for photothermally controlled drug delivery [53], graphene oxide/Ag for chemo-photothermal therapy [54], Fe_3O_4/glucose/Ag for light-responsive drug delivery [55], Ag/SiO_2/TiO_2 for doxorubicin drug delivery [56], poly(*N*-isopropylacrylamide-*co*-acrylamide)/SiO_2/Au for insulin delivery [57], Au/Au_2S for cis-platin delivery [58]. Table 2 summarizes the MNMs that have been studied for potential biomedical applications.

Biosensor: Biosensors are devices that associate the biological detecting to a detector or transducer. In general, three chief constituents such as a biorecognition part, a hold surface, e.g., MNMs and polymers, and a detector/transducer part exist in biosensors systems [59, 60]. Biosensors have been used in several clinical applications, e.g., glucose and cholesterol detection in patients. Biosensors based on antimicrobial MNMs and conducting polymers (polyaniline, polyfuran and polypyrrole) have been extensively used for detecting hydrogen peroxide, tyrosinase, glucose, cholesterol (Table 2).

Wound healing: Wound healing is a complex process involving a cascade of biological reactions in response to injury. The healing rate of acute wounds differs from chronic wounds, and it depends on the immunological status of patients [8]. It has to be highlighted that infection is a crucial and generally unsolved issue in wound healing. Therefore, the MNMs are good candidates for wound healing applications as they can inhibit or decline infections. For instance, at present, silver as a useful antibacterial agent is reemerging as a viable treatment option for burn wound treatment [61]. The combination natural polymers with antimicrobial MNMs to enhance the physicochemical and biocompatibility can offer a faster healing process [62]. In recent years, antimicrobial MNs/natural polymer nanocomposites have been investigated for wound healing, for instance, tragacanth gum/Ag,

Table 2 Antimicrobial metal-based nanomaterials that have been studied in biomedical applications

Metal-based nanomaterials	Size (nm)	Applications	Remarks	References
Au/Au_2S	20–80	Drug delivery	Drug release sensitive to near-infrared irradiation	[58]
Au/poly(lactic acid)	32.4	Drug delivery	The drug release rate could be tuned by controlling the intensity of near-infrared exposition	[53]
Chitosan-encapsulated ZnO quantum dots	Zn quantum dots 2–4	Drug delivery	Chitosan enhanced the stability of the ZnO quantum dots because of the hydrophilicity and cationic charge	[72]
WS_2/Fe_3O_4/mesoporous silica/poly(ethylene glycol)	WS_2/Fe_3O_4/mesoporous silica: 2.48	Drug delivery	In vivo synergistic therapeutic effect, effective inhibition of tumor growth is realized after the combined photothermal and chemotherapy delivered by $WS2/Fe_3O_4$/mesoporous silica/poly(ethylene glycol)/doxorubicin	[73]
Polyaniline/TiO_2/graphene oxide	17	Biosensor	Good selectivity and stability at 82% of the initial activity for 30 days maintained	[74]
Polypyrrole/Au	N.R	Biosensor	The biosensor showed only 40% loss of its initial activity after its 200 uses over 100 days, when stored at 4 °C	[75]

(continued)

Table 2 (continued)

Metal-based nanomaterials	Size (nm)	Applications	Remarks	References
Tragacanth/Ag	77.55	Wound dressing	The treated cotton fabrics showed good water absorption properties along with reasonable antibacterial effectiveness	[76]
Chitosan/poly(vinyl alcohol)/ZnO	ZnO: 50–100	Wound healing	Chitosan/poly(vinyl alcohol)/ZnO showed strong antimicrobial, wound healing effect, hemocompatibility and biocompatibility	[77]
Polyurethane/CuO	Thickness < 10 μm	Dentistry	Significant reduction of bacterial populations was demonstrated with 10% w/w CuO over a 4-h period	[78]
Poly(methyl methacrylate)/TiO_2	56–170	Dentistry	Poly(methyl methacrylate)/TiO_2 nanocomposite was successfully used for complete denture manufacturing	[79]
poly(ethylene glycol)/poly(lactic acid-co-glycolic acid)/Au	20	Photothermal therapy	Upon laser irradiation, the system releases the encapsulated drug with higher efficiency	[80]
Hydroxyapatite/poly(vinyl alcohol)/TiO_2	15	Bone tissue engineering	Hydroxyapatite/poly(vinyl alcohol)/TiO_2 nanocomposite leads to improved mechanical properties by achieving the initial mechanical strength up to 0.99 ± 0.19 MPa and enhanced in vitro bioactivity	[81]
Hydroxyapatite/TiO_2	TiO_2: 20, Hydroxyapatite: 100	Bone tissue engineering	SEM showed grains sizes of less than 1 μm and high granular interface quality, which are factors that favor cell attachment to granules and porous surfaces, ensuring good hydrophilic capacity and capillarity	[82]

N.R. not reported; *MNSs* metal nanostructures gellan gum/TiO_2, sodium alginate/acacia gum/ZnO, chitosan/TiO_2, chitosan/ZnO, chitosan/Ag, chitosan/poly(vinyl alcohol)/ZnO, CuO/TiO_2/poly(ethylene glycol) (Table 2).

Bone tissue: However, infections during or post scaffold transplantation are still challenging as they reduce the efficacy of bone healing. After the transplantation, infections may also be distributed to the scaffold from other sources of inflammation through bloodstream [63]. Implantation of a typically metallic orthopedic prosthetic is a common treatment for bone fractures [64, 65]. Many efforts have been made to change orthopedic implant materials. A recent investigation showed that nanotechnology might generally improve all materials employed for bone regeneration. Metal-based nanomaterials have displayed better properties related to their micron structure owing to their physicochemical, mechanical and biological properties. On the other hand, nanocomposites fabricated by MNMs and polymers or ceramic may become good alternative materials in bone tissue, in view of their better mechanical and biological properties [66]. Table 2 showed the nanometal-based composites in bone tissue engineering.

Dentistry: In spite of the notable advances obtained, biomaterials in dentistry accumulate microbial biofilms. Photogenic microorganisms are the main parameter of dental treatment defeat, creating secondary caries and infections which necessitate retreatment [18, 67]. Dental materials employed for the microorganism-induced illness treatment in the oral cavity are unable to hinder microorganism colonization and biofilm formation, while the combination of polymeric matrices and MNMs is capable of inhibiting microorganism proliferation [67–69]. Antimicrobial dental restorative nanocomposites improve the restorative treatment outcome and present an opportunity to extend their useful lifetime by reducing secondary caries caused by bacterial recolonization.

There are many literatures in which Ag, ZnO, TiO_2, CuO and other metal-based nanomaterials are utilized in dentistry (Fig. 2). For example, poly(lactic-*co*-glycolic acid)/Ag–Fe_3O_4 nanocomposite has been prepared via solvent casting and employed as a coating on implant surfaces [70]. In another work, poly(lactic-*co*-glycolic acid)/TiO_2 nanocomposites have also been used as growth factor sustained release systems for dental implants [71]. In addition, the structure of composite may also be employed as a reservoir for antibacterial and anti-inflammatory agents.

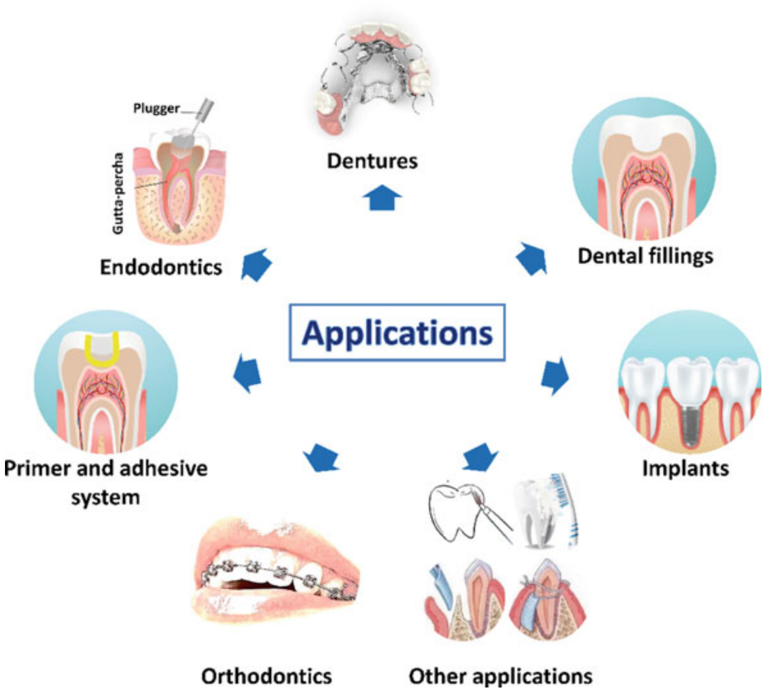

Fig. 2 Polymeric and inorganic antimicrobial nanosized fillers can be applied in various areas in dentistry, including endodontics, dental fillings, dentures, orthodontics, implants, periodontics and preventive dentistry as well as primer and adhesive systems [18]

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