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Antimicrobial nanomaterials against biofilms: an alternative strategy

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30 **Abstract**

31 Microbial adhesion to surfaces and the consequent biofilm formation under various
32 environmental conditions is a common ecological phenomenon. Although biofilms
33 play crucial beneficial roles in many processes, they can also cause serious problems
34 for food, biomedical, environmental and industrial sectors, leading to higher costs of
35 production and equipment maintenance, and negative public health and environmental
36 impacts. Biofilms are difficult to eradicate due to their resistance to conventional
37 antimicrobial applications. Consequently, attention has been devoted to new emerging
38 nanomaterials (NMs) for their remarkable antimicrobial function. Understanding the
39 inactivation mechanisms is the key to increase the efficiency of nanoparticles (NPs)
40 and enhance the feasibility of their application against various microorganisms under
41 different environments. In this paper, we review the activities of NPs as antimicrobial
42 agents. We also discuss the mechanisms and factors contributing to antimicrobial
43 properties of NPs. In addition, we describe some of the approaches employing NPs as
44 effective antimicrobial agent, and associated challenges and problems in developing
45 NPs as effective antibiofilm agents.

46 **Key words:** biofilm, biostatic nanoparticle-based coatings, antimicrobial, disinfection

47

48 **1. Introduction**

49 Adhesion of microbes to surfaces and the subsequent biofilms have been very
50 common in diverse environments. Biofilms are community structures of microbes
51 surrounded by a hydrated matrix composed of extracellular polymeric substances

(EPS), which is secreted by these indwelling microbes and mainly contain polysaccharides, proteins, lipids and nucleic acids, to protect or facilitate their growth in hostile environments (Flemming and Wingender 2010). Although important engineering implication in wastewater industries (Nicolella et al. 2000; Srivastava and Majumder 2008) and petroleum pollution elimination (Dos Santos et al. 2008), biofilms are problematic in infectious diseases (Hall-Stoodley et al. 2004), food (Simões et al. 2010), environmental (Inbakandan et al. 2013; Ren et al. 2014) and biomedical fields (Sihorkar V et al. 2001) because they are mostly detrimental to health, social manufacture and living activities (Davey and O'toole 2000; Beyth et al. 2015). Several researchers suggested that the importance of biofilm control is severely underrated (Simões et al. 2010; Pelgrift and Friedman 2013).

Under different environmental conditions, microbes colonize and develop biofilms on diverse surfaces including those of natural aquatic systems, water pipes, living tissues, tooth and medical devices (Donlan 2002; Markowska et al. 2013). Most microorganisms on earth live in various aggregates biofilm, such as bacteria, fungi, archaea, and viruses (Donlan 2002; Skraber et al. 2005; Wingender and Flemming 2011). Biofilm formation comprises a sequence of steps: formation of a conditioning film; transport of the microorganisms from the bulk liquid to adhesion surface; initial adhesion of microorganisms to the surface; biofilm growth; and biofilm maturation (equilibrium between the accumulation and detachment) (Fig.1) (Ferreira et al. 2010; Simões et al. 2010). Because of the complex matrix structure, biofilms are more tolerant to antimicrobials than planktonic cells (Khan and Khan 2016), and frequently

74 develop antibiotic resistance, thus being more difficult to control. As a result,
75 conventional approaches (e.g. mechanical cleaning, ultraviolet radiation, traditional
76 chemical antimicrobials) were utilized to counter biofilms. And some novel
77 approaches have been studied as potential strategies for biofilms control (Flemming
78 and Ridgway 2008; Simões et al. 2010; Chen et al. 2013), such as quorum sensing
79 inhibitors (QSIs) (Rasmussen and Givskov 2006), antimicrobial peptides (Park et al.
80 2011b), enzymes (Thallinger et al. 2013), nanomaterials (NMs) (Bakkiyaraj and
81 Pandian 2014; Qayyum and Khan 2016), biomimetic surfaces (Salta et al. 2010; Sun
82 and Qing 2011). However, many of these approaches have demonstrated a modest
83 antimicrobial efficacy and still have limitations in successfully controlling biofilms.

84 Among the above methods to biofilms control, nanotechnology is highly
85 promising and has received an enormous amount of attention for effective
86 antimicrobial ability (Li et al. 2008b; Bakkiyaraj and Pandian 2014; de Souza et al.
87 2014; Qayyum and Khan 2016). Nanoparticles (NPs) are particles possessing grain
88 sizes on the order of 1-100 nm (Buzea et al. 2007). NMs are highly reactive and
89 preferred over other antimicrobial agents mainly because of their surface area is
90 exceedingly large relative to their size. NMs possess antimicrobial and antibiofilm
91 properties against various bacterial, fungal and other microorganism species (Li et al.
92 2008b; Huh and Kwon 2011; Bakkiyaraj and Pandian 2014; Hossain et al. 2014;
93 Beyth et al. 2015; Qayyum and Khan 2016). Consequently, NMs could serve as an
94 alternative to inactivate microorganisms. Unlike the conventional chemical
95 antimicrobials, these antimicrobial NMs are cost-effective, easy-to-use, relatively

inert in water and are not strong oxidizers.

In this review the potentials of various NMs as antimicrobials for the biofilms control are described. The antimicrobial mechanisms of action and major applications of NPs are provided. The barriers for their full-scale application and the research needs for overcoming these barriers are also discussed. We also look at the potential impact of NMs on human and ecosystem health as well as any potential interference with treatment processes and provide directions for future research.

2. Antimicrobial and antibiofilm properties and application of NMs

The antimicrobial NMs discussed in this paper fall into three general categories: metals and metal oxides nanoparticles, naturally occurring antimicrobial substances, and carbon-based NMs. High surface area to volume ratios and unique physicochemical properties of various NMs are believed to contribute to effective antimicrobial activities. The major antimicrobial mechanisms reported in the literature are summarized in Fig. 2. These NPs interact with microbial cells through a variety of mechanisms including: 1) photocatalytic production of reactive oxygen species (ROS) that damage cellular and viral components, 2) compromising the bacterial cell wall/membrane, 3) interrupting transmembrane electron transfer, and 4) inhibition of enzyme activity and DNA synthesis (Maness et al. 1999; Rabea et al. 2003; Pal et al. 2007; Li et al. 2008b). The antimicrobial and antibiofilm activity of different types of NMs against different microbes are listed in Table 1 and Table 2. Moreover, Table 3 summarizes NMs with their antimicrobial mechanisms, as well as their current and potential uses. For future industrial scale application of NPs as effective antimicrobial

agents, we need a better understanding of the mechanisms of how NMs influence antimicrobial activity.

2.1 Silver nanoparticles (Ag NPs)

Nanoparticles of metal and metal oxides have been widely studied for their antimicrobial activities, such as silver (Ag), iron oxide (Fe_3O_4), titanium oxide (TiO_2), and zinc oxide (ZnO). Among them, silver nanoparticles are renowned for their influential antimicrobial activity, and have been the most widely used metal nanoparticles as an effective antimicrobial agent in various fields like medical, textile, and building industries. Silver has been used since ancient times for treating wide range of illnesses (Rai et al. 2009).

As previously stated, silver ions interact with sulfur-containing and phosphorus-containing groups of proteins of the cell wall and plasma membrane of bacteria, rendering them inactive and causing aggregation of these proteins (Hindi et al. 2009; Lara et al. 2009; Blecher et al. 2011; Knetsch and Koole 2011). Binding of silver ions to negatively charged parts of the membrane leads to perforation of the membrane, leakage of the cellular compounds, and cell death (Knetsch and Koole 2011). Some silver ions pass through the membrane into the cytoplasm of the bacterial cell, causing damage to protein and nucleic acid inside bacteria (Lara et al. 2010; Blecher et al. 2011). Once inside the cell, silver NPs target and damage bacterial DNA and respiratory enzymes, leading to loss of the cell's replicating abilities and ultimately cell death (Hindi et al. 2009; Rai et al. 2009). In addition, silver NPs attack the respiratory chain and cell division that finally lead to cell death,

140 while concomitantly releasing silver ions that enhance bactericidal activity (Blecher et
141 al. 2011; Huh and Kwon 2011). The generation of ROS on silver NPs was also
142 demonstrated (Hindi et al. 2009; Gordon et al. 2010; Lara et al. 2010).

143 Silver NPs show stronger antimicrobial activity than metallic silver, which is
144 mostly dependent upon the size, shape, and released silver ions (Ag^+) of the
145 nanoparticles (Knetsch and Koole 2011; Pelgrift and Friedman 2013). Ag NPs with
146 smaller size and larger surface area achieve increased ability to pass through cell walls
147 and membranes into the cytoplasm (Gordon et al. 2010; Blecher et al. 2011; Knetsch
148 and Koole 2011; Pelgrift and Friedman 2013). In a study by Pal et al. (2007),
149 triangular or truncated particles were found to be more effective in bacterial killing
150 activity than rods and spherical particles. In addition, there may be the formation of a
151 silver oxide layer on the nanoparticle surface and leading to the formation of Ag^+
152 reservoir (Knetsch and Koole 2011). Xiu et al. (2012) demonstrated that Ag NPs
153 morphological properties are indirect effectors that primarily influence Ag^+ release.
154 Therefore the antibacterial activity of Ag NPs could be controlled by modulating Ag^+
155 release, possibly through manipulation of oxygen availability, particle size, shape,
156 and/or type of coating.

157 Ag NPs have been shown to be effective against a variety of pathogens,
158 including viruses (Rai et al. 2009), fungi (*Candida albicans*) (Ghosh et al. 2010), and
159 many bacterial species, such as *Escherichia coli*, *Staphylococcus aureus*, *Bacillus*
160 *subtilis*, and *Salmonella typhi* (Pal et al. 2007; Shrivastava et al. 2007; Ghosh et al.
161 2010; Martinez-Gutierrez et al. 2010; Blecher et al. 2011). Moreover, Ag NPs are also

162 effective bactericidal agents regardless of the drug-resistance mechanisms against
163 multidrug-resistant *Pseudomonas aeruginosa*, ampicillin-resistant *Escherichia coli*
164 O157:H7, and erythromycin-resistant *Streptococcus pyogenes* (Lara et al. 2010). In a
165 recent study, Leid et al. (2012) showed that silver carbene complexes (SCC)
166 encapsulated in NPs were active against highly resistant bacterial strains, such as
167 methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug resistant
168 *Acinetobacter baumannii* (MRAB), and were active against the biodefence pathogens
169 like *Bacillus anthracis* and *Yersinia pestis*. In addition, Ag NPs have also been found
170 to augment the efficacy of other antimicrobial agents, such as penicillin G,
171 amoxicillin, erythromycin, and vancomycin (Shahverdi et al. 2007; Rai et al. 2009).
172 Microbes are also less likely to develop resistance against silver and Ag NPs, as their
173 broad range of targets would require multiple and simultaneous compensatory
174 mutations. As a result, silver can be used to arrest bacterial resistance to antibiotics
175 and enhance their efficacy (Knetsch and Koole 2011; Pelgrift and Friedman 2013).

176 Ag NPs have also been taken as an alternative strategy for microbial biofilms
177 control (Markowska et al. 2013). Several studies have also shown an important
178 activity of Ag NPs against microbial biofilms, but the precise mechanism underlying
179 their actions remains unresolved. Ag NPs have shown a broad spectrum of antibiofilm
180 activity against bacteria and fungi in disease infection and medicine fields. Roe and
181 his colleagues found catheters coated with bioactive Ag NPs to have significant in
182 vitro antimicrobial activity and prevented biofilm formation of *Escherichia coli*,
183 *Enterococcus*, *Staphylococcus aureus*, coagulase-negative staphylococci,

184 *Pseudomonas aeruginosa* and *Candida albicans* (Roe et al. 2008). Ag NPs
185 surface-modification exhibited strong antibiofilm activity against *Staphylococcus*
186 *epidermidis* RP62A (Taglietti et al. 2014). Nano-silver (25.2 ± 4 nm) was found to
187 effectively prevent the formation of *Pseudomonas aeruginosa* biofilms and kill
188 bacteria in established biofilm structures (4-log reduction in the number of
189 colony-forming units) (Martinez-Gutierrez et al. 2013). Habash et al. (2014) noted
190 that 10-nm Ag NPs were most effective than other sizes (20, 40, 60, and 100 nm) in
191 inhibiting the recovery of *Pseudomonas aeruginosa* biofilm cultures and showed
192 synergy of inhibition when combined with sub-MIC levels of aztreonam. Ag NPs (9.5
193 ± 1.1 nm) could effectively inhibit the growth of a planktonic *Streptococcus mutans*
194 clinical isolate and kill established its biofilms, suggesting that Ag NPs can be used to
195 prevent and treat dental caries (Pérez-Díaz et al. 2015). Compared to control, weaker
196 adherence and disintegrated biofilm formation of *Vibrio parahaemolyticus* Dv1
197 treated with a probiotic *Bacillus licheniformis* cell free extract (BLCFE) coated Ag
198 NPs were observed (Shanthi et al. 2016). Shahrokh and Emtiazi (2013) found that,
199 compared with industrial biocide E-265, low concentration of colloidal nanostructured
200 silver (40 ± 10 nm) (1-2 ppm) showed unique antibacterial and antibiofilm activities
201 against pathogenic strains. Silver nanowires did not show an antibacterial activity
202 against test organisms, but showed a promising property of a quorum
203 sensing-mediated inhibition of biofilm in *Pseudomonas aeruginosa* NCIM 2948 and
204 violacein synthesis in *Chromobacterium violaceum* ATCC 12472 (Wagh et al. 2013).

205 Ag NPs also have important anti-biofouling activity in water treatment and

206 maritime industries. Recently, one study revealed the anti-microfouling potential of
207 Ag NPs against sixteen different marine biofilm forming bacterial strains (Inbakandan
208 et al. 2013). Another study investigated the effect of Ag NPs on natural bacterial
209 communities, and results showed the increasing concentrations (0 - 2000 µg/L) of Ag
210 NPs caused a significant decrease in marine biofilm volume and biomass, affecting
211 the relative abundance of major bacterial groups in the biofilm community (Fabrega et
212 al. 2011). EPS and microbial community interactions in the wastewater biofilms play
213 important roles in controlling the antimicrobial effects of Ag NPs, the microbial
214 susceptibility to Ag NPs is different for each microorganism (Sheng and Liu 2011).
215 Fouling-resistant behavior of silver nanoparticle-modified surfaces against the
216 bioadhesion of microalgae has also been detected as EPS also can be produced by
217 microalgae. The Ag NPs coatings revealed a significant surface inhibitory effect
218 against the adhesion of the marine microalga *Dunaliella tertiolecta* and the freshwater
219 green alga by above 85% in both seawater and freshwater environments, and contact
220 killing was the predominant antifouling mechanism of Ag NPs-modified surfaces
221 (Ren et al. 2014).

222 *Candida albicans* is the most common pathogenic fungus isolated in clinical
223 practice. It has the ability to form biofilms and morphogenetic conversions between
224 yeast and hyphal morphologies contribute to biofilm development and represent an
225 essential virulence factor. Several researches have noted the antibiofilm activity of Ag
226 NPs against *Candida albicans*. Monteiro et al. (2011) evaluated the antifungal effect
227 of silver colloidal nanoparticles against *Candida albicans* and *Candida glabrata*

228 adhered cells and biofilms, and found that Ag NPs were more effective against
229 adhered cells than pre-formed biofilms with the exception of *Candida glabrata*, which
230 in both cases showed a reduction $\sim 90\%$, and the particle size of Ag NPs and the type
231 of stabilizing agent used did not interfere in the antifungal activity of Ag NPs against
232 *Candida* biofilms (Monteiro et al. 2012). Recently, Silva et al. (2013) reported that
233 silver nanoparticles showed a significantly greater effect on reducing *Candida*
234 *glabrata* biofilm biomass compared with *Candida albicans*. Lately, spherical silver
235 nanoparticles (1 nm) were reported to have a potent dose-dependent inhibitory effect
236 on biofilm formation of *Candida albicans*, with an IC_{50} of 0.089 ppm and CC_{50} of
237 7.03 ppm, mainly via cell wall disruption (Lara et al. 2015).

238 Antibiofilm properties of Ag NPs against multi-drug resistant (MDR) have been
239 also investigated recently. Chemically synthesized Ag NPs (20 $\mu\text{g/mL}$) can inhibit the
240 growth optimally and the formation of biofilm in the sensitive strain and the resistant
241 strain *Pseudomonas aeruginosa* with an inhibition rate of 67 % and 56 %, respectively
242 (Palanisamy et al. 2014). Treatment of catheters with gum arabic
243 capped-silver nanoparticles (GA-Ag NPs) at 50 $\mu\text{g/mL}$ resulted in 95 % inhibition of
244 bacterial colonization against the MDR biofilm forming of *Pseudomonas aeruginosa*
245 (Ansari et al. 2014). The Ag NPs (MIC 11.25 - 45 $\mu\text{g/mL}$) coated surfaces also have
246 effectively restricted biofilm formation of MRSA and methicillin resistance
247 *Staphylococcus epidermidis* (MRSE) isolated from wounds, arrested the bacterial
248 growth and prevent the glycocalyx formation (Ansari et al. 2015).

249 Green synthesis of NPs attract increasing attention of investigators recently

because of the potential toxicity problem of chemical NPs. Green NPs are synthesized using non-toxic reducing agents like plant extracts, enzymes and microbial biomass. Biologically synthesized Ag NPs exhibited a potential antibiofilm activity on biofilms formed by *Pseudomonas aeruginosa* and *Staphylococcus epidermidis* (Kalishwaralal et al. 2010). Kumar and Sujitha (2014) showed that Kocuran-functionalized silver glyconanoparticles could inhibit the biofilm development by *Staphylococcus aureus* and *Escherichia coli* through the damage of intact cell architecture. Biogenic silver nanoparticles with a mean size of ~ 6 nm (Bio-Ag⁰⁻⁶) not only exhibited excellent antibacterial performance but also could control biofilm formation and induce detachment of the bulk of *Pseudomonas aeruginosa* biofilms leaving a small residual matrix (Zhang et al. 2014). Significant antimicrobial and antibiofilm effects against *Pseudomonas aeruginosa*, *Shigella flexneri*, *Staphylococcus aureus*, and *Streptococcus pneumonia*, have been observed at lowest concentration of Ag NPs synthesized with a novel plant extract of *A. cobbe* in combination with antibiotics, and significant enhancing effects for ampicillin and vancomycin against gram-negative and gram-positive bacteria, respectively (Gurunathan et al. 2014). A green starch-stabilized Ag NPs was shown to be more effective against gram-positive and gram-negative pathogens as compared with acid-fast bacteria, disrupted biofilm formation and exhibited better antibacterial activity compared to human cationic antimicrobial peptide LL-37 (Mohanty et al. 2012). Significant biofilm inhibition by ELE-Ag NPs synthesized by using aqueous leaf extract of *Eucalyptus globulus* (ELE) was observed in case of *Staphylococcus aureus* and *Pseudomonas aeruginosa*,

272 respectively (Ali et al. 2015). The silicon tubes and polystyrene coverslips surfaces
273 with biogenic Ag NPs using tea extract demonstrated efficient antibiofilm activity, via
274 disrupting cell-cell adhesion in *Staphylococcus aureus* and *Escherichia coli* biofilm
275 (Goswami et al. 2015).

276 Given these properties, there are many diverse applications for Ag NPs,
277 including wound dressings, coatings on medical devices to prevent microbial
278 colonization, substitution of antibiotics and surgical masks, impregnated textile
279 fabrics, nanogels, and nanolotions (Ip et al. 2006; Leaper 2006; Li et al. 2006; Huh
280 and Kwon 2011; Knetsch and Koole 2011).

281 **2.2 Titanium nanoparticles (TiO₂ NPs)**

282 After the first report on a TiO₂ application for the photocatalytic purification of
283 water containing cyanide (Frank and Bard 1977), this material has been extensively
284 used on a variety of applications and products including air and water pollution
285 control systems and self-cleaning surfaces. When TiO₂ is irradiated with near-UV
286 light, this semiconductor exhibits strong photocatalytic oxidation, which is an
287 advanced oxidation process for the removal of trace contaminants and microbial
288 pathogens (Maness et al. 1999; Li et al. 2008b; Blecher et al. 2011; Huh and Kwon
289 2011; Qu et al. 2013; Hossain et al. 2014).

290 The photocatalytic antimicrobial activity of TiO₂ is attributed to the production
291 of ROS, including hydrogen peroxide (H₂O₂), superoxide radical (O₂•-) and hydroxyl
292 radicals (•OH), upon exposure to near-UV and UVA radiation (Choi et al. 2007b;
293 Hindi et al. 2009; Huh and Kwon 2011). When irradiated TiO₂ is in close proximity to

294 bacteria, the ROS damages membrane, DNA, and many other macromolecules of
295 bacterial cells. Damaged membrane structure (Maness et al. 1999; Huh and Kwon
296 2011), OH radical forming (Benabbou et al. 2007; Hossain et al. 2014), Fenton
297 reaction phenomenon (Gogniat and Dukan 2007), the oxidation/reduction of the
298 intracellular coenzyme A (Markowska-Szczupak et al. 2011), and the physicochemical
299 properties of TiO₂ particles (Huang et al. 2000; Markowska-Szczupak et al. 2011),
300 also contribute to microbe inactivation. There are two distinct phases during the
301 destruction of a bacterial cell. In the initial phase, the oxidative damage of cell wall
302 takes place, but cells still remain viable. As the photocatalysis progresses, the titanium
303 dioxide particles cause deleterious oxidation processes leading to cell death (Huang et
304 al. 2000; Desai and Kowshik 2009; Markowska-Szczupak et al. 2011). The kinetic
305 data show that the cell wall damage takes place in less than 20 min, followed by the
306 progressive damage of cytoplasmic membrane and intracellular components (Huang
307 et al. 2000; Markowska-Szczupak et al. 2011). TiO₂ NPs also have bactericidal effects
308 in the absence of irradiation, suggesting that they use other antimicrobial mechanisms
309 unrelated to photocatalytic ROS production, which is yet to be fully understood
310 (Adams et al. 2006; Choi et al. 2007a).

311 Inactivation of microorganisms depends upon several factors, e.g., concentration
312 of TiO₂, type of microorganism, intensity and wavelength of light, degree of
313 hydroxylation, pH, temperature, availability of oxygen, and ROS retention time
314 (Benabbou et al. 2007; Markowska-Szczupak et al. 2011; Hossain et al. 2014).
315 Moreover, bacteria inactivation rate can be increased with increasing dosage of TiO₂,

light intensity and contact time (Hossain et al. 2014). Other studies reported TiO₂ NPs' antimicrobial efficiency in the order of *Escherichia coli* > *Pseudomonas aeruginosa* > *Staphylococcus aureus* > *Enterococcus faecium* > *Candida albicans* and concluded that the order was mainly determined by the complexity and density of the cell membrane/wall (Kühn et al. 2003; Huh and Kwon 2011). Another study concluded that the diverse sensitivity of bio-particulates towards photocatalysis followed the following order: viruses > gram-negative bacteria > gram-positive bacteria > yeasts > filamentous fungi (Markowska-Szczupak et al. 2011). The TiO₂ photocatalysis shows a great potential to kill bacteria, but the use of this process is limited to the environment with sufficient UV light. TiO₂ doped by metals (Ag, Ni, Pt, Au, Ag, Cu, Rh, Pd) and oxides (ZnO, WO₃, SiO₂, CrO₃) or non-metals (C, N, S, P) can improve visible light absorbance of TiO₂ and increase its photocatalytic activity under UV irradiation (Li et al. 2008b; Markowska-Szczupak et al. 2011; Hossain et al. 2014). The addition of Ag to TiO₂ was found to significantly enhance antimicrobial activity (Vamathevan et al. 2004; Reddy et al. 2007b).

According to recent studies, TiO₂ also inactivates various microorganisms that are highly resistant to desiccation and UV radiation, which makes TiO₂ a promising agent for improving hygiene, and product safety in food industry and cosmetics (Reddy et al. 2007b; Muranyi et al. 2010; Huh and Kwon 2011). For example, antibacterial effects of TiO₂ on *Lactobacillus acidophilus* would also be used in orthodontic appliances, such as pit and fissure sealants, toothbrushes, dental implants, and screws (Choi et al. 2007b; Huh and Kwon 2011).

338 TiO₂ NPs have also been used as antibiofilm agent. Several researchers have
339 demonstrated the antibiofilm activity of TiO₂ NPs against bacteria and fungi.
340 *Streptococcus mitis* from the oral cavity causes endocarditis and other systemic
341 infections. Khan and co-workers showed that TiO₂ NPs can control the growth and
342 biofilm formation activities of *Streptococcus mitis* ATCC 6249 and Ora-20, and
343 increase in super oxide dismutase activity, suggesting its potential use as alternative
344 antimicrobial agents for oral hygiene (Khan et al. 2016). Natarajan (2015) showed the
345 antibiofilm property of Epoxy/Ag-TiO₂ polymer nanocomposite coatings against
346 *Staphylococcus aureus* and *Escherichia coli* under static conditions, and suggested
347 that this property may be due to combined release of biocide, and photocatalytic
348 activity. Lungu et al. (2014) synthesized two Ag-TiO₂ nanocomposites (31.3 ± 0.5
349 nm and 23.4 ± 0.4 nm) and screened their antimicrobial activity. Results showed a
350 good antibiofilm activity against several strains including *Bacillus subtilis* IC 12488,
351 *Staphylococcus aureus* IC 13204, *Escherichia coli* IC 13147 and IC13529, *Klebsiella*
352 *pneumoniae* 1204 and IC 13420, except MRSA 1307. TiO₂ nanoparticles had effective
353 antifungal properties at the concentration of 5.14, 5.35 µg/mL for fluconazole
354 susceptible and resistant strain of *Candida albicans* biofilms compared to fluconazole
355 drug, respectively (Haghighi et al. 2013). Shirakawa et al. (2016) evaluated TiO₂
356 coatings on biofilm formation on glass, which were exposed to the open atmosphere
357 for 5 months in São Paulo city, and found that TiO₂ coating inhibited the formation of
358 fungal filaments, hence reduced overall biofilm cover.

359 2.3 Zinc nanoparticles (ZnO NPs)

360 Zinc nanoparticles (ZnO NPs) are extensively used in a wide variety of
361 commercial products like food (Shi et al. 2014), textiles (Dastjerdi and Montazer 2010;
362 Petkova et al. 2014) and medicine (Rasmussen et al. 2010; Eshed et al. 2012). ZnO in
363 nanoscale has shown strong antimicrobial activities on a broad spectrum of microbes,
364 and great potential for microbial control and restriction of biofilm formation (Sawai et
365 al. 2003; Applerot et al. 2012). The exact antimicrobial mechanism of ZnO NPs is still
366 unknown. However, several studies have indicated that the formation of ROS is the
367 main antimicrobial mechanism of ZnO NPs and clearly indicated that ZnO NPs or
368 powders in aqueous solution can produce various ROS including H_2O_2 (Sawai et al.
369 1998; Yamamoto 2001; Zhang et al. 2008; Jalal et al. 2010; Gordon et al. 2011;
370 Espitia et al. 2012; Shi et al. 2014; Padmavathy and Vijayaraghavan 2016). The
371 generation of ROS and the disruption of cell membranes caused by ZnO NPs seemed
372 to have bactericidal activity. In addition, other mechanisms for the antimicrobial
373 activity of ZnO NPs have also been reported, such as the interaction of ZnO with the
374 microbial cell membranes and the generation of damage on microbial surface (Zhang
375 et al. 2007; Zhang et al. 2008; Xie et al. 2011), and release of Zn^{2+} as antimicrobial
376 ions (Reddy et al. 2007a; Applerot et al. 2012; Padmavathy and Vijayaraghavan 2016).
377 Several factors can affect the antimicrobial activity of ZnO NPs, including size
378 (Zhang et al. 2007; Ohira et al. 2008; Palanikumar et al. 2014), surface area
379 (Padmavathy and Vijayaraghavan 2016), concentration (Reddy et al. 2007a; Hossain
380 et al. 2014; Padmavathy and Vijayaraghavan 2016), pH (Zhang et al. 2008; Hossain et
381 al. 2014) and the presence of other antimicrobial agents (Dutta et al. 2010; Bhadra et

al. 2011; Gordon et al. 2011). ZnO NPs are of relatively low cost and effective in size dependency against a wide range of microorganisms (Palanikumar et al. 2014). These include pathogens such as bacteria *Klebsiella pneumoniae* (Reddy et al. 2014), *Listeria monocytogenes*, *Salmonella enteritidis* (Jin et al. 2009), *Streptococcus mutans*, *Lactobacillus* (Kasraei et al. 2014), and *Escherichia coli* (Jin et al. 2009; Liu et al. 2009b), and fungi *Botrytis cinerea* and *Penicillium expansum* (He et al. 2011) with low toxicity to human cells (Reddy et al. 2007a). Furthermore, ZnO is currently listed as a “generally recognized as safe (GRAS)” material by the U.S. Food and Drug Administration and is used as food additive (Espitia et al. 2012; Shi et al. 2014). Many reports have indicated that ZnO NPs have better activity towards gram-positive bacteria than towards gram-negative bacteria (Jones et al. 2008; Xie et al. 2011). Tawale et al. (2010) justified the low inhibition rate of gram-positive bacteria *Staphylococcus aureus* compared with gram-negative *Escherichia coli*. The reason may probably be due to the difference of cell membrane structure. ZnO nanoparticles containing formulations have been utilized for external uses as antibacterial agents in lotions and ointments.

Several studies have investigated the antibiofilm activity of ZnO nanoparticles. It is a known fact that ZnO NPs are not stable when dispersed in water, therefore manufacturers use several surface modifying agents to increase the stability of ZnO NPs. A white appearance, UV-blocking properties, and ability to prevent biofilm formation make ZnO NPs suitable for fabric (Dastjerdi and Montazer 2010) and glass (Applerot et al. 2012) industries as coating materials designated for medical and other

404 devices. ZnO NPs can effectively suppress biofilm formation of *Pseudomonas*
405 *aeruginosa* (Dwivedi et al. 2014; Lee et al. 2014; Garcia-Lara et al. 2015; Hassani
406 Sangani et al. 2015). ZnO NPs were found to markedly inhibit biofilm formation and
407 the production of pyocyanin, pseudomona squinolone signal (PQS), pyochelin, and
408 hemolytic activity of *Pseudomonas aeruginosa* without affecting the growth of
409 planktonic cells, and the effect require the *czc* regulator CzcR (Lee et al. 2014).
410 Applerot et al. (2012) showed that coating glass with ZnO NPs could inhibit biofilm
411 formation for both *Escherichia coli* 1313 and *Staphylococcus aureus* 195, and that the
412 pre-exposure to ZnO-coated surfaces increased bacterial susceptibility to antibiotics,
413 providing a versatile platform for a wide range of applications both in medical and
414 industrial settings. Vaseeharan et al. (2015) have shown that the antibiofilm activity of
415 chitosan-ZnO composite against the *Vibrio parahaemolyticus* and *Bacillus*
416 *lechiformis* bacteria isolated from aquatic environment at a concentration of 40 ~
417 60 µg/mL. Gold-based zinc oxide nanostructures (Au@ZnO) were shown to have
418 inhibition of microbial growth and biofilm by disruption of cellular functions and
419 biofilms via ROS-dependent generation of superoxide anion radical (Gholap et al.
420 2016). ZnO/polyacrylamide nanocomposite (ZnO/PAM.NC10) exhibited antibiofilm
421 activity against *Bacillus subtilis* and *Escherichia coli* (Morsi et al. 2016).

422 2.4 Other metal NPs

423 Several other metal NPs were also used for studying the biofilm dynamics.
424 Ferromagnetic NPs has been reported cleaved macromolecules presented in biofilms
425 in the presence of hydrogen peroxide and acted like biofilm-degrading enzymes (Gao

et al. 2014; Thukkaram et al. 2014). Surface of wound dressing fibers coated with the obtained nanofluid, which was composed of functionalized magnetite nanoparticles and Satureja hortensis essential oil, strongly inhibited *Candida albicans* adherence and subsequent biofilm development comparing with regular uncoated materials (Anghel et al. 2013). Tripathy et al. (2016) coated glass surfaces with quanta-CuO, and found the surface showed a very high contact bacteria-killing capacity towards *Staphylococcus aureus* and *Escherichia coli* as a result of contact killing and/or copper ion release killing mechanisms. Cu₂O-NPs exerted their action by disruption of the bacterial cell membrane and can be used as effective antistaphylococcal and antibiofilm agents in diverse medical devices (Singh et al. 2015a). Eshed et al. (2013) coated teeth with MgF₂ NPs layer, and the coating successfully inhibited *Streptococcus mutans* biofilm formation by over 60 %. The MgF₂ NPs could attach and penetrate into the cells, cause disruption in the membrane and induce membrane lipid peroxidation, and once internalized could interact with chromosomal DNA. Surfaces coated with MgF₂ NPs effectively restricted biofilm formation of *Escherichia coli* C600 and *Staphylococcus aureus* FRF1169 (Lellouche et al. 2009). The Se NPs (10-50 nm) biosynthesized by Khiralla and El-Deeb (2015) has showed sharp effect as an antibiofilm agent against *Enterococcus faecalis*, *Staphylococcus aureus*, *Escherichia coli* O157:H7, *Salmonella typhimurium* and *Salmonella enteritidis* where they lost their ability to form biofilm (100 %). The antibiofilm activities of gold NPs (Sathyanarayanan et al. 2013; Castillo-Martínez et al. 2015; Nithya and Jayachitra 2016), calcium fluoride NPs (Kulshrestha et al. 2016) and other

448 mental NMs have also been reported.

449 Ag, TiO₂ and ZnO NPs have some similarities such as their inorganic nature,
450 similarities in the variety of synthesis methods used and the similarities in their
451 toxicity to the environment. However, there are some differences in bioavailability,
452 applications and regulations shown in Table 4. Despite the controversies and ongoing
453 debates, Ag NMs are perhaps the most promising antibacterial metal NMs. The strong
454 antibiofilm effect of Ag NPs is indisputable.

455 **2.5 Chitosan and chitosan based nanocomposites**

456 Chitosan, a copolymer of N-acetylglucosamine and glucosamine derived by
457 deacetylation of chitin compound (Tikhonov et al. 2006), has been studied extensively
458 throughout the world in due of its broad-spectrum antimicrobial activity (Tikhonov et
459 al. 2006; Friedman et al. 2013; Ibrahim et al. 2014). The antimicrobial activity of
460 chitosan can be increased by packaging chitosan into NPs (Qi et al. 2004; Blecher et
461 al. 2011; Friedman et al. 2013). They are promising as low-cost and low-tech
462 disinfectants, particularly in developing countries (Li et al. 2008b).

463 The exact mechanism of the antimicrobial action of chitin, chitosan, and their
464 derivatives is still unknown, however, different mechanisms have been proposed. One
465 mechanism is the positively charged chitosan molecules interacting with the
466 negatively charged bacterial surface to cause agglutination, thus increasing membrane
467 permeability, which eventually induces a rupture and leakage of intracellular
468 components (Qi et al. 2004). According to another proposed mechanism, chitosan
469 could chelate with trace metals or essential nutrients so as to inhibit enzyme activities

470 and the microbial growth (Qi et al. 2004; Huh and Kwon 2011). It has also been
471 proposed that when chitosan is liberated from the cell wall of fungal pathogens by the
472 host's hydrolytic enzymes, it penetrates to the nucleus of fungi and inhibits mRNA
473 and protein syntheses by binding to microbial DNA (Rabea et al. 2003).

474 The antimicrobial activity of chitosan is influenced by a number of factors that
475 include the type of chitosan, the degree of chitosan polymerization, molecular weight,
476 solvent, pH, its charges and solubility (Chung 2003; Rabea et al. 2003; Qi et al. 2004;
477 Don et al. 2005; Fernandes et al. 2010; Tavaría et al. 2013). Chitosan, however,
478 exhibits its antimicrobial activity only under acidic condition because of its poor
479 solubility above pH 6.5. Thus, water-soluble chitosan derivatives (soluble in both
480 acidic and basic physiological circumstances) may be good candidates as a biocide
481 (Rabea et al. 2003; Je and Kim 2006).

482 Chitosan and chitosan based nanocomposites exhibit high antimicrobial activity
483 as their unique character. NPs synthesized with chitosan and alginate demonstrated a
484 direct antimicrobial activity in vitro against *Propionibacterium acnes*, the bacterium
485 linked to the pathogenesis of acne, probably through inducing the disruption of the
486 cell membrane (Friedman et al. 2013). Chitosan NPs and copper-loaded NPs could
487 inhibit the growth of *Escherichia coli*, *Salmonella choleraesuis*, *Salmonella*
488 *typhimurium*, and *Staphylococcus aureus*, and the exposure of *Salmonella*
489 *choleraesuis* to the chitosan NPs led to the disruption of cell membranes and the
490 leakage of cytoplasm (Qi et al. 2004). Nanocomplexes prepared from chitosans with
491 high MW showed a low antimicrobial effect (20 ~ 25 % of cells damaged), whereas

those prepared from low-MW chitosans showed high antimicrobial effect (> 95 % of cells damaged) on *Streptococcus mutans* (de Paz et al. 2011). The ability of chitosan as both a complexing and stabilizing agent is usually utilized to form uniformly deposited NMs with other NPs. Nanostructured chitosan (CS) and a chitosan–Zn (Zn–CS) coated textiles showed antimicrobial activity towards *Enterococcus faecalis* and *Escherichia coli*. A more than two-fold increase of the antibacterial activity of Zn–CS NPs coated textiles was detected as compared to the fabrics treated with the sonochemically synthesized CS NPs alone (Perelshtein et al. 2013).

Chitosan and chitosan based nanocomposites are also potential antibiofilm agents. Surfaces coated with the naturally-occurring polysaccharide chitosan significantly resisted biofilm formation by *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Candida albicans* with reductions in biofilm viable cell numbers ranging from 95 % to 99.9997 % (Carlson et al. 2008). Chitosan–Ag NPs exhibited excellent antibiofilm activity against *Pseudomonas aeruginosa*, whereas treatment of *Staphylococcus aureus* with the same concentration of chitosan showed no significant inhibition in biofilm formation (Prajna Jena 2012). Wei et al. (2009) found that films with chitosan-based silver nanoparticles exhibited both fast and long-lasting antibacterial effectiveness against *Escherichia coli*. Chitosan-based zinc oxide nanoparticles showed significant inhibition of growth and biofilm formation against *Micrococcus luteus* and *Staphylococcus aureus* (Dhillon et al. 2014). Tan et al. (2015) noted that the β -N-acetyl-glucosaminidase (DspB) immobilized on carboxymethyl chitosan

514 nanoparticles (CMCS) showed increased antibiofilm activity against *Staphylococcus*
515 *aureus*, *Staphylococcus epidermidis*, and *Actinobacillus actinomycetemcomitans* due
516 to the improvement of the enzyme stability and the antibiofilm activity of CMCS
517 nanoparticles. Synthesized cefotaxime loaded chitosan based nano-antibiotics
518 demonstrated broad-spectrum antibiofilm and anti-pathogenic activity against clinical
519 isolates of multi drug resistant *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*,
520 *Escherichia coli*, and methicillin resistant *Staphylococcus aureus* (Jamil et al. 2016).
521 Ferulic acid encapsulated chitosan nanoparticles (FA-CSNPs) reduced *Candida*
522 *albicans* biofilm cell viability up to 22.5 %, and induced disruption of biofilm
523 architecture, suggesting that it could be used as an effective alternative to the
524 conventional antifungal therapeutics (Panwar et al. 2016). Biodegradable chitosan
525 nanoparticles (CSNPs) enhanced the efficacy of methylene blue (MB)-antimicrobial
526 photodynamic inactivation (APDI), it may be due to the disruption of biofilm
527 structure by polycationic CSNPs and subsequently deeper and higher penetration of
528 MB into the biofilms (Darabpour et al. 2016). Bioactive polymeric chitosan
529 nanoparticles functionalized with rose-bengal (CSRBnp) showed significant
530 antibacterial activity, reduced viability of *Enterococcus faecalis* biofilms and
531 disruption of biofilm structure by adhering to bacterial cell surface, increasing the
532 permeability of the membrane and lysing the cells subsequent to photodynamic
533 treatment (Shrestha et al. 2014).

534 Chitosan has been shown to be useful in many different areas, and specifically in
535 agriculture, wastewater treatment, food, and biomedicine fields (Rabea et al. 2003; Qi

et al. 2004; Fernandes et al. 2008; Li et al. 2008b; Tin et al. 2009). It has several advantages over other antimicrobials, as indicated by high antimicrobial activity, by broad spectrum of activity against bacteria, viruses and fungi, and by a low toxicity on mammalian cells. However, chitosan is an effective antimicrobial only at acidic pH and depends on the availability of charged amino groups (No et al. 2002; Rabea et al. 2003). The preparation of water-soluble derivatives of chitosan may eventually overcome this limitation.

2.6 Carbon nanotubes (CNTs)

Carbon nanotubes (CNTs) are cylindrical nanostructures made of pure carbon atoms covalently bonded in hexagonal arrays (Hyung et al. 2007). They are increasingly being assessed for use in water purification owing to their high surface area, antimicrobial activity, electronic properties, and ease of functionalization (Li et al. 2008b; Brady-Estévez et al. 2008, 2010). Single-walled nanotubes (SWCNTs) are a single pipe with a diameter in the range of 1~5 nm, while multi-walled tubes (MWCNTs) have several nested tubes with lengths varying from 100 nm to several tens of micrometers. Early studies indicated profound cytotoxicity of CNTs in alveolar macrophage. Presented here in the order of its toxicity are: SWCNTs>MWCNTs>quartz>C₆₀. Surprisingly, the effect of CNTs has not received much attention, probably because of the poor aqueous dispersion of pure CNTs (Li et al. 2008b). Recently, it was demonstrated that surfactants or polymers could be used to facilitate the aqueous disparity of CNTs (Hyung et al. 2007).

The CNTs' antimicrobial mechanism is not fully understood. Previous studies on

558 CNTs' cytotoxicity have concluded that membrane stress (i.e., direct CNTs bacteria
559 contact resulting in membrane perturbation and the release of intracellular contents)
560 was the primary cause of cell death (Kang et al. 2007; Arias and Yang 2009; Liu et al.
561 2009a; Obraztsova et al. 2009). Others suggest that oxidative stress (Kang et al. 2008;
562 Aslan et al. 2010; Rodrigues and Elimelech 2010) and CNTs electronic structure
563 (Vecitis et al. 2010) also play key roles. A three-step SWCNT antimicrobial
564 mechanism has been proposed, which involves (i) initial SWNT-bacteria contact, (ii)
565 membrane perturbation, and (iii) electronic structure-dependent bacterial oxidation
566 (Vecitis et al. 2010). The antimicrobial activity of CNTs is dependent on a number of
567 factors, including size (Kang et al. 2008), electronic structure (Vecitis et al. 2010),
568 surface (Arias and Yang 2009), length (Yang et al. 2010), and surfactant solutions
569 (Dong et al. 2012).

570 Antimicrobial activity of CNTs requires direct contact between CNTs and target
571 microorganisms (Kang et al. 2007; Li et al. 2008b). Recent work, however, has shown
572 scalable applications that use low-cost and widely available CNTs for inactivation of
573 microbes. Inclusion of oxidized single-wall (O-SWCNTs) or multi-wall CNTs
574 (O-MWCNTs) were reported to cause polymer nanocomposites (PNCs) surfaces to
575 exhibit antimicrobial properties towards *Pseudomonas aeruginosa* (Goodwin Jr et al.
576 2015). The MWCNTs-nisin composite showed up to 7-fold higher antimicrobial
577 property than pristine MWCNTs against *Escherichia coli*, *Pseudomonas aeruginosa*,
578 *Staphylococcus aureus* and *Bacillus subtilis* (Qi et al. 2011). While the
579 MWCNT-cefalexin composite showed 2-fold higher antimicrobial property than

580 pristine MWCNTs against *Staphylococcus aureus* and *Bacillus subtilis* (Qi et al.
581 2012). *Escherichia coli* and *Staphylococcus epidermidis* viability and metabolic
582 activity were significantly diminished in the presence of SWCNTs-polymer poly
583 (lactic-co-glycolic acid) (PLGA), and up to 98 % of bacteria died within one hour on
584 SWCNTs-PLGA versus 15-20 % on pure PLGA (Aslan et al. 2010).

585 CNTs coatings can significantly prevent biofilm formation. The thin layer of
586 CNTs can effectively remove bacteria by size exclusion, and the retained bacteria are
587 largely inactivated by CNTs within hours (Brady-Estévez et al. 2010). The effects of
588 SWCNTs and MWCNTs on biofilm formation from *Bacillus anthracis* spores were
589 investigated by Dong and colleagues (Dong et al. 2014). Their results showed that
590 nisin coating on MWCNTs sheets decreased surface hydrophobicity, reduced spore
591 attachment, and reduced the germination of attached *Bacillus anthracis* spores by 3.5
592 folds, and further inhibited the subsequent biofilm formation by 94.6 % compared to
593 that on uncoated MWCNTs sheet (Dong et al. 2014). In another study, 200 µg/mL
594 SWCNTs decreased the germination of attached spores by 93.14 %, completely
595 inhibiting subsequent biofilm formation (Dong and Yang 2014). MWCNTs-nisin
596 composite had a dramatically improved capability to prevent biofilm formation both
597 on a deposited film and in suspension, and the MWCNTs-nisin deposit film exhibited
598 a 100-fold higher antibiofilm property than the MWCNTs deposit film (Qi et al. 2011).
599 Analogously, MWCNTs-cefalexin composite film effectively inhibited cell adhesion
600 (Qi et al. 2012). Covalent binding of SWCNTs to polyamide membranes were
601 observed to achieve up to 60 % inactivation of bacteria attached to the membrane

602 within 1 h of contact time, suggesting the potential of covalently bonded SWNTs to
603 delay the onset of membrane biofouling during operation (Tiraferri et al. 2011).
604 SWCNTs-coated substratum had 10 times less biofilm colonization and biomass
605 production of *Escherichia coli* K12 than a control substratum without SWCNTs
606 (Rodrigues and Elimelech 2010).

607 In addition, CNTs-based filtration technology catches some attention. Kang et al.
608 (2007) prepared a SWCNTs-coated filter and observed 87 % reduction of the
609 *Escherichia coli* cells on the SWCNTs-coated filter after the 60 min incubation. A
610 poly vinylidene fluoride (PVDF) membrane coated with a thin layer of SWCNTs for
611 water purification showed effective inactivation of *Escherichia coli* (Brady-Estévez et
612 al. 2008, 2010). Unlike conventional filters, CNTs filters can be cleaned repeatedly to
613 regain their full filtering efficiency (Srivastava et al. 2004; Kang et al. 2007;
614 Brady-Estévez et al. 2008). Additional advantages of the CNTs filters include ease of
615 production, gravity-driven or low-pressure operation, cytotoxicity towards microbes,
616 high portability (Srivastava et al. 2004; Kang et al. 2007; Brady-Estévez et al. 2008).
617 With a small intermittent voltage (2 ~ 3 V), MWCNTs can directly oxidize attached
618 bacteria and lead to inactivation in seconds. The applied electric potential also
619 enhances viral transport to the anodic CNTs. Such CNTs filters can be used as high
620 performance point-of-use (POU) devices for water disinfection with minimal to no
621 power requirement (Vecitis et al. 2011; Rahaman et al. 2012). These benefits provide
622 incentive for continued development of CNTs-based filtration technology for water
623 treatment and other separation processes. However, it is important to recognize that

624 other complex solution chemistry and the presence of foulants in source water may
625 impact CNTs filters performance.

626 As we explore opportunities for leveraging the unique properties of CNTs for
627 water purification applications, it is critical to consider simultaneously the potential
628 risks of incorporating these advanced materials in drinking water production. The
629 risks of nanomaterial exposure to humans are a function of both exposure and toxicity.
630 Application of the CNTs filters to drinking water treatment will require appropriate
631 designs that minimize human and environment exposure by immobilizing the CNTs in
632 the filter. As we develop functional applications of NMs in water treatment, we will
633 need to monitor the lifespan release of NMs to ensure human health and filter
634 durability. Although CNTs have some adverse effects on human health and the
635 environment, further research can increase its benefit and decrease its unfavorable
636 effects.

637 **2.7 Fullerenes**

638 Fullerenes are soccer ball-shaped molecules composed of carbon atoms (C_{60} , C_{70} ,
639 etc.), and, when derivatized with functional groups, they become soluble and show
640 antibacterial effects (Tsao et al. 2002; Tegos et al. 2005; Brant et al. 2006). In
641 particular, numerous techniques have been developed for creating stable aqueous
642 suspensions for fullerene with a large range of sizes (Fortner et al. 2005; Duncan et al.
643 2007; Lyon et al. 2006). The nC_{60} NPs are noted for their potent and broad
644 antibacterial activity (Lyon et al. 2006; Li et al. 2008b).

645 The antimicrobial mechanism for fullerenes is still under debate. The debatable

antibacterial mechanism for nC_{60} includes photocatalytic ROS production that is responsible for the membrane damage in eukaryotic cells (Sayes et al. 2005; Markovic et al. 2007; Lyon et al. 2008c). However, studies on nC_{60} assert that antibacterial activity is ROS-independent oxidative stress (Fang et al. 2007; Lyon et al. 2008c). Other possible mechanisms have also been reported, including effect on respiratory chain, disruption of the cell membrane structure (Tsao et al. 2002; Cataldo and Da Ros 2008), interaction with membrane lipids and intercalation into them (Tegos et al. 2005; Cataldo and Da Ros 2008; Deryabin et al. 2014; Dizaj et al. 2015). The antimicrobial activity of fullerene is also affected by the size and surface area of it (Dizaj et al. 2015), the type of functional group used (Li et al. 2008b; Deryabin et al. 2014). Several previous reports demonstrated that cationic derivatives showed the best antibacterial effect on *Escherichia coli* and *Shewanella oneidensis*, while the anionic derivatives were almost ineffective (Cataldo and Da Ros 2008; Nakamura and Mashino 2009; Deryabin et al. 2014). This could be owing to the strong interactions of negatively charged bacteria with the cationic fullerenes (Nakamura and Mashino 2009).

Fullerenes have antimicrobial and antibiofilm activity against various microorganisms. Although pristine fullerene C_{60} demonstrated no antimicrobial activity, fullerenols ($\text{C}_{60}(\text{OH})_{12}$, $\text{C}_{60}(\text{OH})_{36} \cdot 8\text{H}_2\text{O}$, and $\text{C}_{60}(\text{OH})_{44} \cdot 8\text{H}_2\text{O}$) exhibited good antimicrobial activity against *Propionibacterium acnes*, *Staphylococcus epidermidis*, *Candida albicans*, and *Malassezia furfur*. In particular, $\text{C}_{60}(\text{OH})_{44}$ exhibited a strong and wide-ranging antimicrobial activity comparable to that of

catechin via inhibition of microbial cell growth and not via bactericidal activity (Aoshima et al. 2009). Studies reported that the employed derivative was able to inhibit environmental bacteria after photo irradiation (Cataldo and Da Ros 2008; Deryabin et al. 2014). Tegos et al. (2005) demonstrated that cationic fullerenes with hydrophilic groups, after photo irradiation, showed a broad-spectrum antimicrobial activity and more than 99.99 % of bacterial and fungal cells were rapidly killed. Mizuno et al. (2011) reported that cationic-substituted fullerene derivatives that possessed either basic or quaternary amino groups were highly effective as antimicrobial photo sensitizers (PS) against *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans*. Zhang et al. (2015) have reported that cationic fullerene and potassium iodide potentiated the antimicrobial photodynamic inactivation against *Acinetobacter baumannii*, methicillin-resistant *Staphylococcus aureus* and *Candida albicans*. Encapsulated C₆₀ can still exert antimicrobial properties in water, which might be more applicable due to the flexibility of the encapsulation. Both fullerols and encapsulated fullerenes can be considered for potential disinfection applications (Lyon et al. 2006; Li et al. 2008b). Alekseeva et al. (2014) found that the polystyrene/fullerene composite films manifest bacteriostatic and fungistatic effect. Ballatore and coworkers evaluated the photodynamic inactivation of bacteria of novel electrogenerated porphyrin-fullerene C₆₀ polymeric films, and results showed the film was an interesting and versatile photodynamic active surface to eradicate bacteria (Ballatore et al. 2015). Fullerene C₆₀ nanoparticles, introduced as an aqueous suspension, had size-dependent effects on soil bacterial community composition in

690 the low organic matter system (Tong et al. 2016).

691 **3. Barriers of antimicrobial NMs for microbial control and biofilm formation**

692 While NMs hold significant promise for microbial control and biofilm formation,
693 significant barriers stand between some of these promises and their delivery. Issues
694 such as technical hurdles, cost effectiveness and potential environmental and human
695 risk must be addressed.

696 **3.1 Technical hurdles**

697 Although nanotechnology enabled microbial control have shown great promise
698 in laboratory studies, their readiness for commercialization vary widely. Some are
699 already on the market, while others require further research before they can be
700 considered for full-scale applications. Because most studies on antimicrobial activities
701 of NMs have been conducted in relatively simple and clean environment, the
702 sustainability of their antimicrobial activities in natural or complicated solutions is
703 unclear. Adsorption onto geosorbents, and coating by natural organic matter have
704 been shown to reduce toxicity of nC₆₀ on bacteria (Li et al. 2008a). When coated on
705 surfaces to prevent microbial attachment and biofilm formation, antimicrobial
706 nanoparticle coatings may rapidly lose their effectiveness due to adsorption of
707 extracellular polymeric material and occlusion by precipitating debris (Lyon et al.
708 2008b).

709 Another challenge in efficient application of antimicrobial NMs in preventing
710 microbial attachment and biofilm formation is dependent upon the dispersion and
711 retention of NMs and the sustainability of antimicrobial activity. While NPs provide

712 very high specific surface area, which is a primary reason for their high reactivity, the
713 aggregation in water negates this benefit. NPs such as TiO_2 aggregate severely when
714 added to water. Although very stable in pure water, coagulation of nC_{60} can be
715 induced by salt (Lyon et al. 2008a). The application of NPs as an effective
716 antimicrobial agent should not cause microbial resistance even after long-term usage.
717 However, there have been reports on bacterial resistance to antimicrobial compounds
718 (Cloete 2003; Davies and Davies 2010), such as, silver (Silver et al. 2006), chromium
719 compounds (Ramírez-Díaz et al. 2008), quaternary ammonium compounds
720 (Sundheim et al. 1998) and antibiotics (Fisher et al. 2005). Another concern is that a
721 widespread usage of silver NPs (e.g. as a component of disinfectants) might lead to
722 silver-resistant bacterial strains (Markowska et al. 2013).

723 In addition, to date, little is known about the occurrence, fate and toxicity of NPs.
724 The limitations in our knowledge are partly due to the lack of methodology for the
725 detection and characterization of engineered NPs in complex matrices, i.e. water, soil
726 or food. Some reviews have provided an overview on this topic (Tiede et al. 2008; da
727 Silva et al. 2011), but few techniques can detect NMs in complex aqueous matrices
728 and they are expensive and with many limitations. Future work should focus on
729 addressing these challenges. NMs also can be immobilized on various platforms such
730 as resins and membranes to avoid further separation. However, current
731 immobilization techniques usually result in significant loss of treatment efficiency.
732 Further research is needed to develop simple, low-cost methods to immobilize NMs
733 without significantly impacting its performance. For magnetic NPs/nanocomposites,

low-field magnetic separation is a possible energy-efficient option.

3.2 Cost effectiveness

Broad acceptance of novel water and wastewater treatment nanotechnologies depends on both their performance and affordability. Most nanotechnology based treatment options are high-performance enabling more efficient treatment, but their costs are currently high. This represents a significant but not insurmountable barrier. The need to treat increasingly complex contaminant mixtures and produce higher quality water at lower cost is pushing the boundaries of current treatment paradigms. A considerable fraction of the nanomaterial production cost is related to separation and purification. Prices of research-grade NMs have remained relatively constant over the past decade and they did not drop significantly without increased demand and production scale-up. Note that, the feasibility of using NMs for water treatment can be enhanced by producing NMs of lower purity. For example, amino-fullerene photocatalysts made with fullerene soot rather than ultrapure C₆₀ (a cost savings of ~ 90 %) exhibited a minimal (< 10 %) loss of effectiveness (Lee et al. 2010). Furthermore, long-term reusability of NMs enhances their cost-effectiveness. Encouraging examples include photocatalysts that retain activity through multiple reuse cycles (Lee et al. 2010) and regeneration of nanoadsorbents (Roberts et al. 2007) and magnetically separable multifunctional NMs (Yavuz et al. 2006).

3.3 Potential toxicity

Retention of NMs is critical not only because of the cost associated with the loss of NMs, but also, and more importantly, because of the potential impacts of NMs on

human health and ecosystems. Our understanding of the potential human health and environmental implication of NMs is improving with the increasing number of nanotoxicity studies in the past few years. For example, the non-toxicity of nanostructured silver on membrane surface has been proven by growing human fibroblasts at various concentrations of silver NPs (Wen et al. 2007). Skin-innoxiousness of nanostructured silver colloidal solution especially in the case of smaller NPs has been demonstrated via the skin irritation test performed on rabbits (Lee and Jeong 2005). Silver is mentioned as an almost non-toxic to mammalian systems (Dastjerdi and Montazer 2010). Incubation of astrocyte primary cultures with magnetic iron oxide NPs has also demonstrated that the particles do not induce any acute damage to these brain cells (Geppert et al. 2009). However, another report implied that Ag NPs at high doses could have genotoxic and cytotoxic effects on human cells (Jena et al. 2012). In vitro experiments, Park and coworkers showed that the potency of silver NPs to induce cell damage, compared to silver ions, is cell type and size-dependent (Park et al. 2011a). As we know, prolonged exposure to soluble silver-containing compounds may produce an irreversible pigmentation in the skin (argyria) and the eyes (argyrosis), in addition to other toxic effects, including organ damages (e.g., liver and kidney), irritation (e.g., eyes, skin, respiratory, and intestinal tract), and changes in blood cell counts (Drake and Hazelwood 2005).

About 30 organizations from different countries are investigating the potential risks of nano-structured materials with the aim of developing appropriate test methods to assess their possible side-effects on the human health and the environment. Several

articles have summarized the potential toxicity and environmental management of NMs (Dreher 2004; Auffan et al. 2009; Bystrzejewska-Piotrowska et al. 2009; Levard et al. 2012). The toxic effect of inhalation of CNTs has been shown in vivo testing (Dawson 2008). Potential CNTs health hazards, because of its similarity to asbestos fibers, have also been warned (Service 1998). Generally, ZnO powders or NPs are bio-safe within a certain range, but may become hazardous at higher concentrations. ZnO NPs have also been shown to reduce the viability of human T cells at a high concentration of 5 mM (Reddy et al. 2007a; Qu et al. 2012). Bulk TiO₂ particles (> 100 nm) are known to be harmless to humans and animals. High dosage of inhalation nano-TiO₂ can act as a pulmonary inflammation agent and be harmful for body tissues (Geppert et al. 2009). Until we fully understand the short- and long- term toxicity, which need more time and more investigation, people should be cautious about the potential toxicities of nano-structured materials.

4. Critical research needs

As discussed above, significant limitations exist on the use of NMs for microbial control and biofilm formation. This calls for more researches to further assess their applicability and to address their limitations.

First, the performance of various nanotechnologies under natural environmental conditions needs to be tested. Future studies need to be done under more realistic conditions to assess the applicability and efficiency of different nanotechnologies as well as to validate nanomaterial enabled sensing technologies. Secondly, the long-term efficacy of these nanotechnologies is largely unknown as most laboratory

800 studies have been conducted over relatively short periods of time. Research
801 addressing the long-term performance of nanotechnologies in microbial control is of
802 great need.

803 There are currently two approaches to address the cost issue. One proposed
804 approach is to use low purity NMs without significantly compromising efficiency as
805 much of the production cost is related to separation and purification (Qu et al. 2012).
806 Low-cost NMs should be explored for potential applications in microbial control.
807 Alternatively, the cost-effectiveness can be improved by retaining and reusing NMs.
808 Effective and reliable methods are needed to anchor the NPs to reactor surfaces or the
809 selective layer of filtration membranes, or to separate and retain suspended NPs in
810 order to reduce costs associated with premature material loss and to prevent potential
811 human health and environmental impacts. This includes developing better surface
812 coating techniques perhaps through nanoparticle surface functionalization,
813 minimizing membrane fouling by the nanomaterial suspension, and impregnating NPs
814 into filter packing materials, e.g. granular activated carbon, or ion exchange resins.
815 Advances in these areas may allow incorporation of antimicrobial NMs into microbial
816 control.

817 Risk assessment for many NMs can benefit from the extensive toxicological
818 database available for their bulk counterparts and shared constituents. However,
819 allotropic NMs such as fullerenes and CNTs do not have bulk counterparts precluding
820 such comparisons and suggesting the need for more careful toxicity studies. In a broad
821 prospective, risk assessment should consider every stage in the life cycle of NMs

(Eckelman et al. 2012). Minimizing risks to public and environmental health could be achieved by curtailing potential exposure through nanoparticle immobilization onto reactor surfaces or support media. This may have the ancillary benefit of reduced nanoparticle aggregation and improved activity (Lee et al. 2010). For NPs that release toxic metals (e.g., nanostructured Ag and metallic quantum dots), it is important to control their dissolution, e.g., by using stabilizing coatings or optimizing nanoparticle shape and size. Depending on the application scenario, barrier technologies (e.g., membranes and magnetic separation) may be used to recover nanoparticle and prevent their release (Qu et al. 2012). Risk minimization should also consider the design of safer NMs using constituents that are inherently nonhazardous. A significant challenge facing this strategy is to reduce toxicity without stifling nanomaterial performance.

It is important to note that most of the disinfection processes of nanomaterial are based upon the results of planktonic tests. However, such tests do not mimic the behavior of biofilm cells and can be highly ineffective when applied to control biofilms. Due to the limited efficacy of nanomaterial in preventing or treating biofilms, a number of alternative strategies need to be devised. Another strategy for biofilm control that is currently receiving serious consideration is based on interference with bacterial cell-to-cell communication (quorum sensing). Because quorum sensing plays a vital role in infections caused by human, animal and plant pathogens, the identification of mechanisms that disrupt this system is a hot topic in microbiology. Quorum sensing inhibitors are likely to be effective in controlling bacterial infections,

844 while having no effect on human cells (Defoirdt et al. 2013; Markowska et al. 2013).
845 It is conceivable that quorum sensing inhibition may represent a natural, widespread,
846 antimicrobial strategy with significant impact on biofilm formation (Dong et al. 2002;
847 Simões et al. 2010). Some NMs have been reported to have anti-quorum sensing
848 (anti-QS) activity, such as AgCl-TiO₂ nanoparticles (Naik and Kowshik 2014), silver
849 nanowires (Wagh et al. 2013), mycofabricated biosilver nanoparticles (Singh et al.
850 2015c), spice oil nanoemulsions (Venkadesaperumal et al. 2016), Swarna-based
851 herbo-metallic colloidal nano-formulation (Singh et al. 2015b). A good understanding
852 of the cell-cell signaling phenomenon of bacteria such as *Listeria monocytogenes* can
853 be used to control the biofilm formation process by the identification of products that
854 can act as quorum sensing antagonists (Simões et al. 2009, 2010). This property can
855 lead to the development of new and efficient natural products for biofilm control in
856 our future study.

857 5. Summary

858 Microbial control in food, biomedical, natural environment (especially aquatic
859 environment) and industrial processing aims to reduce/eradicate microbes and their
860 activity, and to prevent/control the formation of biological deposits on the process
861 equipment. Metal, natural compound-based and carbon-based nanoparticle types have
862 shown tremendous potential as bactericidal and fungicidal elements, demonstrating
863 their potential as efficient antimicrobials in medical and environmental issues. Despite
864 numerous studies conducted over the last decade there are still considerable gaps in
865 our knowledge about the antimicrobial properties of NPs. Furthermore, the precise

866 basis of their antimicrobial activity has yet to be defined. Nonetheless, the strong
867 anti-bacterial effect of NPs is indisputable. Much more needs to be learned about the
868 impact of antimicrobial NMs on microbial biofilms and their recovery responses to
869 damage, as microorganisms can develop resistance and subsequently survive
870 previously effective control procedures. To overcome these barriers, interdisciplinary
871 research collaboration among academic and research institutions, industry,
872 government, and other stakeholders would be essential. Future research addressing
873 cost, economics, and safety is likely to overcome many of the current limitations and
874 create more opportunities for biofilm control.

875

876 **Conflict of Interests**

877 The authors declare that there is no conflict of interests regarding the publication of
878 this paper.

879

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1736 **Figure legends:**

1737 **Figure 1.** A schematic representation of the steps a new bacterial species takes in
1738 forming a biofilm on a substrate. First, the grey bacteria represent an aquatic species
1739 that swim towards the substrate and bind reversibly to the surface. And then the
1740 bacteria secrete binding molecules such as adhesion proteins that cause irreversible
1741 attachment. Once settled, the bacteria proliferate and form microcolonies, which lead
1742 to the development of a mature biofilm. Once the environmental conditions become
1743 unfavorable, equilibrium exists between the accumulation and detachment.

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1745 **Figure 2.** Various antimicrobial mechanisms exerted by NMs. Multiple mechanisms
1746 of antimicrobial action of chitosan-containing NPs (chitosan), silver-containing NPs
1747 (Ag NPs), zinc oxide-containing NPs (ZnO NPs), titanium dioxide-containing NPs
1748 (TiO₂ NPs), and carbon based NPs (CNTs and Fullerenes). ROS refers to reactive
1749 oxygen species.

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Figure 1.

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Figure 2.

Table 1. Antimicrobial activity of NMs.

Type of NMs	Target organism	Ref.
Metals NPs		
Ag NPs	methicillin resistance <i>Staphylococcus aureus</i> (MRSA), methicillin resistance <i>Staphylococcus epidermidis</i> (MRSE)	Ansari et al. 2015
Ag NPs	<i>Escherichia coli</i> , <i>Staphylococcus aureus</i> , <i>Candida albicans</i>	Ghosh et al. 2010
Ag NPs	multidrug-resistant <i>Pseudomonas aeruginosa</i> , ampicillin-resistant <i>Escherichia coli</i> O157:H7, erythromycin-resistant <i>Streptococcus pyogenes</i>	Lara et al. 2010
Ag NPs	<i>Escherichia coli</i>	Pal et al. 2007
Ag NPs	<i>Staphylococcus aureus</i> , <i>Escherichia coli</i>	Shahverdi et al. 2007
Ag NPs	<i>Escherichia coli</i>	Xiu et al. 2012
Ag NPs (Bio-Ag ⁰⁻⁶)	<i>Pseudomonas aeruginosa</i> ATCC 27853	Zhang et al. 2014
ELE-Ag NPs synthesized by using aqueous leaf extract of <i>Eucalyptus globulus</i> (ELE)	<i>Pseudomonas aeruginosa</i> , <i>Escherichia coli</i> , methicillin-resistant <i>Staphylococcus aureus</i> (MRSA), methicillin-sensitive <i>Staphylococcus aureus</i> (MSSA)	Ali et al. 2015
Ag NPs synthesized by using tea extract	<i>Staphylococcus aureus</i> , <i>Escherichia coli</i>	Goswami et al. 2015
Kocuran-capped Ag NPs	<i>Staphylococcus aureus</i> , <i>Escherichia coli</i>	Kumar et al. 2014
Starch-stabilized Ag NPs	<i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i> PAO1, <i>Shigella flexneri</i> , <i>Salmonella typhi</i> , <i>Mycobacterium smegmatis</i>	Mohanty et al. 2012
Silver-carbene complex (SCC10)-loaded into l-tyrosine polyphosphate NPs	<i>Pseudomonas aeruginosa</i>	Hindi et al. 2009
Silver carbene complexes (SCC) NPs	methicillin-resistant <i>Staphylococcus aureus</i> (MRSA), multidrug resistant <i>Acinetobacter baumannii</i> (MRAB),	Leid et al. 2012

Ag-TiO ₂ nanocomposites	<i>Bacillus anthracis</i> , <i>Yersinia pestis</i> <i>Bacillus subtilis</i> IC12488, <i>Staphylococcus aureus</i> IC13204, <i>Escherichia coli</i> IC13147 and IC13529, <i>Klebsiella pneumoniae</i> 1204 and IC13420	Lungu et al. 2014
Ag NPs, ZnO NPs	<i>Streptococcus mutans</i> , <i>Lactobacillus</i>	Kasraei et al. 2014
Ag NPs, CuO NPs	<i>Escherichia coli</i> , <i>Bacillus subtilis</i>	Yoon et al. 2007
TiO ₂ photocatalysis	<i>Escherichia coli</i>	Benabbou et al. 2007
TiO ₂ photocatalysis	<i>Escherichia coli</i> , <i>Lactobacillus acidophilus</i>	Choi et al. 2007a, 2007b
TiO ₂ photocatalysis	<i>Escherichia coli</i>	Gogniat and Dukan 2007
TiO ₂ photocatalysis	<i>Kocuria rhizophila</i>	Muranyi et al. 2010
Nanosized TiO ₂	<i>Escherichia coli</i> , <i>Pseudomonas aeruginosa</i> , <i>Klebsiella pneumoniae</i> , <i>Staphylococcus aureus</i>	Desai and Kowshik 2009
TiO ₂ , SiO ₂ , ZnO NPs	<i>Escherichia coli</i> DH5 α , <i>Bacillus subtilis</i> CB310	Adams et al. 2006
Nitrogen-doped TiO ₂	<i>Escherichia coli</i> , <i>Shigella flexneri</i> , <i>Listeria monocytogenes</i> , <i>Vibrio parahaemolyticus</i> , <i>Staphylococcus aureus</i> , <i>Streptococcus pyogenes</i> , <i>Acinetobacter baumannii</i>	Wong et al. 2006
TiO ₂ NPs codoped with nitrogen and silver (Ag ₂ O/TiON)	<i>Escherichia coli</i> AN 387	Wu et al. 2010
ZnO NPs	<i>Escherichia coli</i>	Dutta et al. 2010
ZnO NPs	<i>Pseudomonas aeruginosa</i>	Dwivedi et al. 2014
ZnO NPs	<i>Botrytis cinerea</i> , <i>Penicillium expansum</i>	He et al. 2011
ZnO NPs	<i>Staphylococcus aureus</i>	Jones et al. 2008
ZnO NPs	<i>Pseudomonas aeruginosa</i>	Lee et al. 2014
ZnO NPs	<i>Escherichia coli</i> O157:H7	Liu et al. 2009b
ZnO NPs	<i>Escherichia coli</i> DH 5 α	Padmavathy and Vijayaraghavan 2016

ZnO NPs	<i>Salmonella paratyphi</i> B, <i>Klebsiella pneumoniae</i> MTCC109, <i>Bacillus subtilis</i> MTCC441, <i>Enterobacter aerogenes</i> MTCC111, <i>Staphylococcus epidermidis</i> MTCC3615, Methicillin resistant-MRSA, <i>Candida albicans</i> MTCC227, <i>Malassezia pachydermatis</i>	Palanikumar et al. 2014
ZnO NPs	<i>Campylobacter jejuni</i>	Xie et al. 2011
ZnO nanofluids	<i>Escherichia coli</i>	Zhang et al. 2007, 2008
ZnO powders	<i>Staphylococcus aureus</i> , <i>Escherichia coli</i>	Yamamoto 2001
ZnO powder with crystallographic	<i>Escherichia coli</i> , <i>Staphylococcus aureus</i>	Ohira et al. 2008
Zinc oxide quantum dots NPs	<i>Listeria monocytogenes</i> , <i>Salmonella Enteritidis</i> , <i>Escherichia coli</i> O157:H7	Jin et al. 2009
ZnO tetrapods	<i>Escherichia coli</i> , <i>Staphylococcus aureus</i> , <i>Candida albicans</i>	Tegos et al. 2005
Gold-based zinc oxide nanostructures (Au@ZnO)	<i>Pseudomonas aeruginosa</i>	Gholap et al. 2016
Zn/Fe oxide composite NPs	<i>Staphylococcus aureus</i> , <i>Escherichia coli</i>	Gordon et al. 2011
Plant Mediated Gold NPs using <i>Garcinia cambogia</i>	<i>Bacillus subtilis</i> , <i>Escherichia coli</i> , <i>Listeria monocytogenes</i> , <i>Proteus vulgaris</i> , <i>Vibrio parahaemolyticus</i>	Nithya and Jayachitra 2016
Naturally occurring antimicrobial substances based NMs		
Natural compound chitosan	<i>Escherichia coli</i> , <i>Staphylococcus aureus</i>	Chung et al. 2003
Natural compound chitosan	<i>Staphylococcus aureus</i> , <i>Escherichia coli</i>	Fernandes et al. 2008
Natural compound chitosan	<i>Burkholderia cenocepacia</i>	Ibrahim et al. 2014
Natural compound chitosan	<i>Staphylococcus aureus</i> , <i>Staphylococcus epidermidis</i> , <i>Escherichia coli</i>	Tavaria et al. 2013
Natural compound chitosan	<i>Escherichia coli</i> , <i>Pseudomonas aureofaciens</i> , <i>Enterobacter agglomerans</i> , <i>Bacillus subtilis</i> , <i>Candida kruisei</i> , <i>Fusarium oxysporum f. sp. radicans</i> , <i>lycopersici</i>	Tikhonov et al. 2006

Natural compound chitosans and chitooligosaccharide mixtures	<i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Pseudomonas aeruginosa</i> , <i>Candida albicans</i>	Fernandes et al. 2010
Natural compound chitosans and chitosan oligomers	four gram-negative (<i>Escherichia coli</i> , <i>Pseudomonas fluorescens</i> , <i>Salmonella typhimurium</i> , and <i>Vibrio parahaemolyticus</i>) and seven gram-positive bacteria (<i>Listeria monocytogenes</i> , <i>Bacillus megaterium</i> , <i>B. cereus</i> , <i>Staphylococcus aureus</i> , <i>Lactobacillus plantarum</i> , <i>L. brevis</i> , and <i>L. bulgaricus</i>).	No et al. 2002
Chitosan NPs	<i>Candida albicans</i> , <i>Fusarium solani</i>	Yien et al. 2012
Chitosans and chitosan oligosaccharide	<i>Pseudomonas aeruginosa</i>	Tin et al. 2009
Chitosan NPs	<i>Streptococcus mutans</i>	de Paz et al. 2011
Nanostructured chitosan	<i>Enterococcus faecalis</i> , <i>Escherichia coli</i>	Perelshtein et al. 2013
Chitosan NPs and copper-loaded NPs	<i>Escherichia coli</i> , <i>Salmonella choleraesuis</i> , <i>Salmonella typhimurium</i> , <i>Staphylococcus aureus</i>	Qi et al. 2004
Chitosan-alginate NPs	<i>Propionibacterium acnes</i>	Friedman et al. 2013
Chitosan-stabilized silver nanoparticles (CS-Ag NPs)	<i>Pseudomonas aeruginosa</i> , <i>Salmonella typhi</i> , <i>Staphylococcus aureus</i>	Prajna Jena 2012
Chitosan-based Ag NPs	<i>Escherichia coli</i> ATCC 51813, <i>Staphylococcus aureus</i> ATCC 27661, <i>Bacillus subtilis</i> ATCC 6051	Wei et al. 2009
Chitosan capped ZnO nanorods	<i>Escherichia coli</i>	Bhadra et al. 2011
Chitosan based zinc oxide nanoparticles (ZnO-CTS NPs)	<i>Micrococcus luteus</i> , <i>Staphylococcus aureus</i>	Dhillon et al. 2014
Chitosan/poly(acrylic acid)/poly(ethylene glycol) diacrylate (PEGDA) composite	<i>Escherichia coli</i> , <i>Staphylococcus aureus</i>	Don et al. 2005
Synthesized cefotaxime loaded	<i>Klebsiella pneumoniae</i> , <i>Pseudomonas aeruginosa</i> , <i>Escherichia coli</i>	Jamil et al. 2016

chitosan based nano-antibiotics	methicillin resistant <i>Staphylococcus aureus</i>	
Carbon-based NMs		
O-carbon nanotubes (CNTs) / poly (vinyl alcohol) (PVOH) nanocomposites	<i>Pseudomonas aeruginosa</i>	Goodwin Jr et al., 2015
Single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs)	<i>Escherichia coli</i>	Kang et al. 2008
SWCNTs	<i>Salmonella typhimurium, Bacillus subtilis, Staphylococcus aureus</i>	Arias et al. 2009
SWCNTs	<i>Escherichia coli</i> K12, Bacteriophage MS2	Brady-Estévez et al. 2008
SWCNTs	Bacteriophage MS2	Brady-Estévez et al. 2010
SWCNTs	<i>Salmonella enterica, Escherichia coli</i>	Dong et al. 2012
SWCNTs	<i>Escherichia coli</i> K12	Kang et al. 2007
SWCNTs	<i>Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus subtilis</i>	Liu et al. 2009a
SWCNTs	<i>Escherichia coli</i> K12 TG1, <i>Photobacterium leiognathi</i>	Obraztsova et al. 2009
SWCNTs	<i>Escherichia coli</i>	Tiraferri et al. 2011
SWCNTs	<i>Escherichia coli</i>	Vecitis et al. 2010
SWCNTs	<i>Salmonella typhimurium</i>	Yang et al. 2010
SWCNTs incorporated within the biomedical polymer poly (lactic-co-glycolic acid) (PLGA)	<i>Escherichia coli, Staphylococcus epidermidis</i>	Aslan et al. 2010
MWCNTs	viruses MS2, <i>Escherichia coli</i>	Vecitis et al. 2011
Nisin-coated MWCNTs sheet	<i>Bacillus anthracis</i>	Dong et al. 2014
MWCNTs -cefalexin composite	<i>Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus subtilis</i>	Qi et al. 2012

MWCNTs-nisin composite	<i>Escherichia coli</i> , <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> , <i>Bacillus subtilis</i>	Qi et al. 2011
Fullerenes (C60)	<i>Escherichia coli</i> , <i>Staphylococcus aureus</i>	Alekseeva et al. 2014
Fullerenes (C60)	<i>Propionibacterium acnes</i> , <i>Staphylococcus epidermidis</i> , <i>Candida albicans</i> , <i>Malassezia furfur</i>	Aoshima et al. 2009
Fullerene-based particles (nC60)	<i>Pseudomonas mendocina</i>	Lyon et al. 2008b
Fullerene (nC60)	<i>Escherichia coli</i>	Lyon et al. 2008c
Fullerene water suspensions	<i>Bacillus subtilis</i>	Lyon et al. 2006
C60-water suspension (nano-C60)	<i>Escherichia coli</i> , <i>Bacillus subtilis</i>	Lyon et al. 2005
Buckminsterfullerene (C60)	<i>Pseudomonas putida</i> , <i>Bacillus subtilis</i>	Fang et al. 2007
Porphyrin-fullerene C60 dyad (TCP-C60)	<i>Staphylococcus aureus</i> , <i>Escherichia coli</i>	Ballatore et al. 2015
Fullerene derivatives bearing amine (AF)	<i>Escherichia coli</i>	Deryabin et al. 2014
Cationic-substituted fullerene	<i>Staphylococcus aureus</i> , <i>Escherichia coli</i> , <i>Candida albicans</i>	Mizuno et al. 2011
C60-dimalonic acid	<i>Escherichia coli</i>	Nakamura and Mashino 2009
Cationic fullerene (LC16)	<i>Acinetobacter baumannii</i> , methicillin-resistant <i>Staphylococcus aureus</i> , <i>Candida albicans</i>	Zhang et al. 2015

Table 2. Antibiofilm activity of NMs.

Type of NMs	Target organism	Ref.
Ag NPs	marine biofilms were grown in situ in a coastal site (Singapore Harbour)	Fabrega et al. 2011
Ag NPs	sixteen different marine biofilm forming bacterial strains	Inbakandan et al. 2013
Ag NPs	<i>Pseudomonas aeruginosa</i> , <i>Staphylococcus epidermidis</i> , <i>Escherichia coli</i>	Kalishwaralal et al. 2010
Ag NPs	<i>Candida albicans</i>	Lara et al. 2015
Ag NPs	<i>Pseudomonas aeruginosa</i>	Martinez-Gutierrez et al. 2013
Ag NPs	<i>Candida albicans</i> , <i>Candida glabrata</i>	Monteiro et al. 2011, 2012
Ag NPs	<i>Pseudomonas aeruginosa</i>	Palanisamy et al. 2014
Ag NPs	<i>Streptococcus mutans</i>	Pérez-Díaz et al. 2015
Ag NPs	a marine microalga <i>Dunaliella tertiolecta</i> and a freshwater green alga community.	Ren et al. 2014
Ag NPs	<i>Escherichia coli</i> , <i>Enterococcus</i> , <i>Staphylococcus aureus</i> , coagulase-negative staphylococci, <i>Pseudomonas aeruginosa</i> , <i>Candida albicans</i>	Roe et al. 2008
Ag NPs	<i>Thiotrichales</i> and other wastewater biofilms bacteria	Sheng and Liu 2011
Ag NPs	<i>Candida glabrata</i> , <i>Candida albicans</i>	Silva et al. 2013
Ag NPs	<i>Staphylococcus epidermidis</i> RP62A	Taglietti et al. 2014
Silver nanowires	<i>Pseudomonas aeruginosa</i> NCIM 2948	Wagh et al. 2013
ELE-Ag NPs synthesized by using aqueous leaf extract of <i>Eucalyptus globulus</i> (ELE)	<i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i>	Ali et al 2015
Gum arabic capped-silver nanoparticles (GA-Ag NPs)	multi-drug resistant (MDR) <i>Pseudomonas aeruginosa</i>	Ansari et al. 2014
Biogenic Ag NPs synthesized using tea extract	<i>Staphylococcus aureus</i> , <i>Escherichia coli</i>	Goswami et al. 2015

Ag NPs using a novel plant extract of <i>A. cobbe</i> combined with conventional antibiotics (ampicillin and vancomycin)	<i>Pseudomonas aeruginosa</i> , <i>Shigella flexneri</i> , <i>Staphylococcus aureus</i> , <i>Streptococcus pneumonia</i>	Gurunathan et al. 2014
Citrate-capped Ag NPs	<i>Pseudomonas aeruginosa</i> PAO1	Habash et al. 2014
Kocuran-capped Ag NPs	<i>Staphylococcus aureus</i> , <i>Escherichia coli</i>	Kumar et al. 2014
Starch-stabilized Ag NPs	<i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i> PAO1	Mohanty et al. 2012
Chitosan-stabilized Ag NPs	<i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i>	Prajna Jena 2012
Colloidal nanostructured silver	athogenic strains	Shahrokh and Emtiazi 2013
Bacillus licheniformis cell free extract (BLCFE) coated Ag NPs	<i>Vibrio parahaemolyticus</i> Dav1	Shanthi et al. 2016
Mycofabricated biosilver nanoparticles (mfAg NPs)	<i>Pseudomonas aeruginosa</i>	Singh et al. 2015c
Ag-TiO ₂ nanocomposites	<i>Bacillus subtilis</i> IC 12488, <i>Staphylococcus aureus</i> IC 13204, <i>Escherichia coli</i> IC 13147 and IC13529, <i>Klebsiella pneumoniae</i> 1204 and IC 13420	Lungu et al. 2014
AgCl-TiO ₂ NPs	<i>Chromobacterium violaceum</i>	Naik and Kowshik 2014
Epoxy/Ag-TiO ₂ nanocomposite	polymer <i>Staphylococcus aureus</i> ATCC6538, <i>Escherichia coli</i> K-12	Natarajan 2015
TiO ₂ NPs	<i>Candida albicans</i>	Haghighi et al. 2013
TiO ₂ NPs	fungal filaments	Shirakawa et al. 2016
ZnO NPs and TiO ₂ NPs	<i>Streptococcus mitis</i> ATCC 6249 and Ora-20	Khan et al. 2016
ZnO NPs	<i>Escherichia coli</i> 1313, <i>Staphylococcus aureus</i> 195	Applerot et al. 2012
ZnO NPs	<i>Pseudomonas aeruginosa</i>	Dwivedi et al. 2014
ZnO NPs	<i>Pseudomonas aeruginosa</i>	Lee et al. 2014
ZnO NPs	<i>Pseudomonas aeruginosa</i>	Garcia-Lara et al. 2015

ZnO NPs	<i>Pseudomonas aeruginosa</i>	Hassani Sangani et al. 2015
ZnO and CuO NPs	<i>Streptococcus mutans</i>	Eshed et al. 2012
Core/shell (ZnO/polyacrylamide) nanocomposite (ZnO/PAM.NC10)	<i>Bacillus subtilis, Escherichia coli</i>	Morsi et al. 2016
Magnetite Nanostructure (Fe ₃ O ₄) NPs modified with Satureja hortensis essential oil	<i>Candida albicans</i> ATCC 10231	Anghel et al. 2013
Ferromagnetic (Fe ₃ O ₄) NPs	<i>Escherichia coli, Pseudomonas aeruginosa</i>	Gao et al. 2014
Iron-oxide (Fe ₃ O ₄) NPs	<i>Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa</i>	Thukkaram et al. 2014
Gold nanorods (AuNRs)	<i>Enterococcus faecalis, Staphylococcus aureus, Streptococcus mutans, Streptococcus sobrinus, Streptococcus oralis, Streptococcus salivarius, Escherichia coli</i>	Castillo-Martínez et al. 2015
Gold and Iron-Oxide NPs	<i>Staphylococcus aureus, Pseudomonas aeruginosa</i>	(Sathyanarayanan et al. 2013)
Gold-based zinc oxide nanostructures (Au@ZnO)	<i>Pseudomonas aeruginosa</i>	Gholap et al. 2016
Plant mediated gold NPs using Garcinia cambogia	<i>Bacillus licheniformis</i>	Nithya and Jayachitra 2016
Swarna-based herbo-metallic colloidal nano-formulation (Uh-Au@Nano-CF)	<i>Streptococcus mutans</i>	Singh et al. 2015b
MgF ₂ NPs	<i>Streptococcus mutans</i>	Eshed et al. 2013
MgF ₂ NPs	<i>Escherichia coli</i> C600, <i>Staphylococcus aureus</i> FRF1169	Lellouche et al. 2009
Selenium NPs	<i>Bacillus cereus, Enterococcus faecalis, Staphylococcus aureus, Escherichia coli</i> O157:H7, <i>Salmonella Typhimurium, Salmonella Enteritidis</i>	Khiralla and El-Deeb 2015

Calcium fluoride (CaF ₂) NPs	<i>Streptococcus mutans</i>	Kulshrestha et al. 2016
Cuprous oxide (Cu ₂ O) NPs	<i>Staphylococcus aureus</i>	Singh et al. 2015a
Quanta-CuO	<i>Staphylococcus aureus</i> , <i>Escherichia coli</i>	Tripathy et al. 2016
Natural compound chitosan	<i>Staphylococcus epidermidis</i> , <i>Staphylococcus aureus</i> , <i>Klebsiella pneumoniae</i> , <i>Pseudomonas aeruginosa</i> , <i>Candida albicans</i>	Carlson et al. 2008
Chitosan NPs	<i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i>	Darabpour et al. 2016
Chitosan NPs	<i>Streptococcus mutans</i>	de Paz et al. 2011
Chitosan-stabilized silver nanoparticles (CS-AgNPs)	<i>Pseudomonas aeruginosa</i> , <i>Salmonella typhi</i> , <i>Staphylococcus aureus</i>	Prajna Jena 2012
Chitosan-based Ag NPs	<i>Escherichia coli</i> ATCC51813, <i>Staphylococcus aureus</i> ATCC27661, <i>Bacillus subtilis</i> ATCC6051	Wei et al. 2009
Chitosan based zinc oxide nanoparticles (ZnO-CTS NPs)	<i>Micrococcus luteus</i> , <i>Staphylococcus aureus</i>	Dhillon et al. 2014
β-N-acetyl-glucosaminidase immobilized on carboxymethyl chitosan NPs	<i>Staphylococcus aureus</i> , <i>Staphylococcus epidermidis</i> , <i>Actinobacillus actinomycetemcomitans</i>	Tan et al. 2015
Synthesized cefotaxime loaded chitosan based nano-antibiotics	<i>Klebsiella pneumoniae</i> , <i>Pseudomonas aeruginosa</i> , <i>Escherichia coli</i> , methicillin resistant <i>Staphylococcus aureus</i>	Jamil et al. 2016
Ferulic acid encapsulated chitosan NPs	<i>Candida albicans</i>	Panwar et al. 2016
Bioactive polymeric chitosan NPs functionalized with rose-bengal	<i>Enterococcus faecalis</i>	Shrestha et al. 2014
Chitosan-ZnO composite	<i>Vibrio parahaemolyticus</i> , <i>Bacillus lechiformis</i>	Vaseeharan et al. 2015
Nisin-coated MWCNTs sheet	<i>Bacillus anthracis</i>	Dong et al. 2014
SWCNTs	<i>Bacillus anthracis</i>	Dong and Yang 2014
MWCNTs-nisin composite	<i>Staphylococcus aureus</i>	Qi et al. 2011

MWCNTs-cefalexin composite	<i>Escherichia coli</i> , <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> , <i>Bacillus subtilis</i>	Qi et al. 2012
SWCNTs	<i>Escherichia coli</i>	Tiraferri et al. 2011
SWCNTs	<i>Escherichia coli</i> K12	Rodrigues and Elimelech 2010
Fullerene (C60)	soil bacterial community composition	Tong et al. 2016
Porphyrin-fullerene C60 dyad (TCP-C60)	<i>Staphylococcus aureus</i> , <i>Escherichia coli</i>	Ballatore et al. 2015
Spice oil nanoemulsions	<i>Chromobacterium violaceum</i> CV026	Venkadesaperumal et al. 2016

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Table 3. Mechanisms and applications of antimicrobial NMs.

Type of NMs	Proposed mechanisms of antimicrobial action	Factors that influence antimicrobial activity	Applications	Ref.
Ag	Release of Ag ⁺ ions; disruption of cell membrane and electron transport; DNA damage	Particle size and shape; surface area; type of coating; Ag ⁺ release; type of microorganism.	Dressing for surgical wound and diabetic foot; antibacterial agent; portable water filters; coatings for medical devices, refrigerators, and food containers;	(Pal et al. 2007; Li et al. 2008b; Blecher et al. 2011; Huh and Kwon 2011; Knetsch and Koole 2011)
TiO ₂	Production of ROS; cell membrane and cell wall damage.	Particle size and shape ; concentration of TiO ₂ ; type of microorganism; intensity and wavelength of light; degree of hydroxylation; pH; temperature; availability of oxygen; retention time.	Air purifiers; water treatment systems for organic contaminant degradation; antibacterial agent; food sterilizing agent	(Maness et al. 1999; Oppezzo and Pizarro 2001; Kühn et al. 2003; Choi et al. 2007b; Reddy et al. 2007b)
ZnO	Formation of ROS; Interaction of NPs with	Particle size and shape; particle concentration; solvent and pH;	Antibacterial creams; lotions and ointment; deodorant; self-cleaning	(Sawai et al. 1998; Zhang et al. 2008; Gordon et al. 2011;

	bacteria, damaging the bacterial cell; release of Zn ²⁺ ions from nanoparticles	type of microorganism.	glass and ceramics; surface coating of medical device; mouthwash; food packaging.	Espitia et al. 2012; Shi et al. 2014; Padmavathy and Vijayaraghavan 2016)
Chitosan	Increased permeability and rupture of membrane; chelation of trace metals; enzyme inactivation	The type of chitosan; the degree of chitosan polymerization; molecular weight; solvent and pH.	Drinking water disinfectants; bacteria immobilizer; microbicide in agriculture and biomedical products; flocculants in water and wastewater treatment.	(Chung 2003; Rabea et al. 2003; Qi et al. 2004; Je and Kim 2006; Li et al. 2008b)
CNTs	Cell membrane damage by ROS; oxidation of cell membrane proteins and lipids	Particle size; particle length; type of functional group; type of buffer; concentration; surface charge.	Antibacterial agent; biofouling-resistant membranes; water filter; surface-coating	(Kang et al. 2007; Kang et al. 2008; Brady-Estévez et al. 2008; Aslan et al. 2010; Brady-Estévez et al. 2010;)
Fullerenes	Destruction of cell membrane integrity; enhancing activity of infiltrating neutrophil	Particle size; type of functional group; surface charge	Potential disinfection applications; photodynamic therapy	(Sayes et al. 2005; Fang et al. 2007; Markovic et al. 2007; Maleki Dizaj et al. 2015)

Table 4. Similarities and differences among Ag, TiO₂ and ZnO NPs.

Factors		Ag	TiO ₂	ZnO
<u>Similarities</u>	Synthesis	Several synthesis routes allow for better control of shape and size.		
	Nature	Inorganic nature (better stability compared to organic agents).		
	Antimicrobial activity	Exhibit antibacterial activity against gram-positive and gram-negative bacteria as well as fungi.		
	Potential toxicity	Due to their small sizes and variable properties, they may be hazardous to the human health and environment.		
	Cost	Depending on the synthesis method, they can each be prepared in a cost-effective manner.		
<u>Differences</u>	Bioavailability	Chronic intake of silver products results in the accumulation of silver over time, producing argyria in the skin or argyrosis in the eyes.	Pure Ti and TiO ₂ are extensively used for dental and orthopedic implants owing to their high mechanical properties and biocompatibility.	ZnO has been used in foodstuffs due to its ability to decompose into Zn ions in the human body.
	Regulation	EU safety regulations limit the presence of silver ions in food matrices to 0.05 mg Ag/kg.	TiO ₂ dust, when inhaled, has recently been classified by the International Agency for Research on Cancer (IARC) as an IARC Group 2B carcinogen possibly carcinogenic to humans.	It is currently listed by the FDA as a “generally recognized as safe (GRAS)” material.
	Application	Portable water filters; clothing; medical devices; surface coatings; membranes.	Air and water pollution control systems and self-cleaning surfaces.	An active ingredient for dermatological applications in creams, lotions and ointments; self-cleaning glass and ceramics.
	Antimicrobial mechanism	It is largely attributed to the release of Ag ⁺ .	The photocatalytic antibacterial activity is attributed to ROS under UV light	Production of ROS and release of Zn ²⁺ ions.
	Toxicity	It has some risks when used as a	Bulk TiO ₂ particles (> 100 nm) are	ZnO has litter toxicity in bulk

evaluation	drug disinfectant such as causing argyrosis and argyria, especially when large amounts of silver ions are used on an open wound. However, silver is nontoxic to humans in minute concentrations.	known to be harmless to humans and animals. High dosage of inhalation nano-TiO ₂ can act as a pulmonary inflammation agent and be harmful for body tissues.	size. ZnO NPs have been shown to reduce the viability of human T cells at an elevated concentration. Its toxicity effects were dose dependent rather than size dependent.
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