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PII: S0001-8686(17)30006-4
DOI: doi: 10.1016/j.cis.2017.05.012
Reference: CIS 1763

To appear in: *Advances in Colloid and Interface Science*

Received date: 15 January 2017
Revised date: 10 May 2017
Accepted date: 10 May 2017

Please cite this article as: Ahmed F. Halbus, Tommy S. Horozov, Vesselin N. Paunov , Colloid particle formulations for antimicrobial applications, *Advances in Colloid and Interface Science* (2017), doi: 10.1016/j.cis.2017.05.012

Colloid Particle Formulations for Antimicrobial Applications

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Abstract

Colloidal particles are being extensively studied in various antimicrobial applications due to their small size to volume ratio and ability to exhibit a wide spectrum of antibacterial, antifungal, antialgal and antiviral action. The present review focuses on various nanoparticles (NPs) of inorganic, organic and hybrid materials, and discusses some of the methods for their preparation as well as mechanisms of their antimicrobial action. We consider the antimicrobial applications of metal oxide nanoparticles (ZnO, MgO, CuO, Cu_2O, Al_2O_3, TiO_2, CeO_2 and Y_2O_3), metal nanoparticles (NPs), such as copper, silver and gold, metal hydroxide NPs such as $Mg(OH)_2$ as well as hybrid NPs made from biodegradable materials, such as chitosan, lignin and dextran, loaded with other antimicrobial agents. Recent developments for targeted delivery of antimicrobials by using colloid antibodies for microbial cell shape and surface recognition are also discussed. We also consider recent advances in the functionalization of nanoparticles and their potential antimicrobial applications as a viable alternative of conventional antibiotics and antiseptic agents which can help to tackle antimicrobial resistance. The review also covers the recently developed environmentally benign NPs (EbNPs) as a "safer-by-design" green chemistry solution of the post use fate of antimicrobial nanomaterials.

Keywords: antimicrobials; nanoparticles; antimicrobial resistance; metal oxide nanoparticles; environmentally benign nanoparticles; colloid antibodies;

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Introduction

Conventional antimicrobial agents are usually low molecular weight species that attack and selectively kill microbial cells or suppress their growth. Due to their excessive use, many microbial strains develop resistance and their effective treatment often requires a continuous pipeline of novel antiseptic and antibiotic agents to be developed [1]. This calls for new alternative approaches to antimicrobials or unconventional protection strategies that can potentially bypass antimicrobial resistance [1]. Nanotechnology provides us with alternative approaches for development of novel antimicrobials that do not rely on the existing pathways of antibiotic action. Over the last few years there is an increasing interest in developing colloid particles of antimicrobial functionality which exhibit strong and universal antibacterial, antifungal or antiviral action towards which pathogens have not yet been able to develop resistance. Synthetic colloids with engineered antimicrobial action designed to target specific microorganisms could be deployed to address this challenge as they can potentially have high antimicrobial activity at very low particle concentrations [2]. Nanoparticles have a widely used for biological and medical applications as contrast agents for medical imaging, labelling of cells, targeting of tumours and in therapeutic drug delivery [3]. Nanoparticles have attracted significant interest for applications as antimicrobials due to their unique photoactive, electronic, optical, catalytic and thermal properties, suitable particle size and morphologies [4-6] that can be prepared with high degree of control [7-16]. Recently, inorganic nanoparticles have been broadly researched for their nanotoxicity and potential antimicrobial action [17-19] which is enhanced by their highly developed surface area. There are several metal oxides and hydroxides in the form of nanoparticles that act as antimicrobial agents which have very different mechanisms of action against microbial cells [17-19]. In this review, we will summarise the antimicrobial properties of various metal oxides and their NPs, and discuss the possible mechanisms by which they can eliminate and inhibit the growth of potentially harmful microorganisms [17]. We will also consider several application of complex colloids and hybrid organic/inorganic nanoparticles with selective antimicrobial action.

Colloid Particles as Antimicrobials

The present understanding of the possible mechanisms by which specific colloid particles kill microbial cells is still patchy and incomplete. Although a range of mechanisms of their antimicrobial activity have been explored, most of the research in this area is still ongoing.

Recent studies have been concentrated on antimicrobial inorganic nanoparticles, for example, metal oxide nanoparticles, like ZnO, MgO, CuO, Cu_2O, Al_2O_3, TiO_2,CeO_2 and Y_2O_3; metals, e.g. copper, silver, gold etc., metal hydroxides such as $Mg(OH)_2$ as well as colloids made from biodegradable materials, such as chitosan, lignin and dextran, loaded with antimicrobial agents. The metal oxides nanoparticles are divided into two different groups based on the mechanisms involved in the growth inhibition of microorganisms (Fig. 1). Metal oxide nanoparticles are among the most utilised NPs having applications in the different fields, for example, cosmetics, textile and medicine. Zinc oxide nanoparticles (ZnONPs) have already been utilised in antimicrobial agents, sunscreens, and electronics [17, 20, 21].

(Place Fig. 1 here).

Antimicrobial activity of zinc oxide nanoparticles (ZnONPs) and titania nanoparticles (TiO_2NPs)

Although bulk ZnO is not considered a biologically hazardous material, recent studies focus on highlighting potential biological toxicities of ZnO in a nanoparticulate form (ZnONPs) [22]. ZnO is found to have a high photocatalytic effectiveness and is reported as more biocompatible than TiO_2 [23,24]. ZnONPs and TiO_2NPs can both strongly absorb UV light [25] which activates them to interact with the cells in their vicinity. Their photocatalytic effect continues long after illumination with UV light, and it has been ascribed to surface electron depletion region strongly related to adsorbed negative oxygen species ($O_2^{\cdot-}$, O_2^{2-}) on the particle surface [26].

Aqueous suspensions of ZnONPs and TiO_2NPs under illumination with UV light and oxygen have the phototoxic impact due to generating reactive oxygen species (ROS), for example, superoxide ions ($O_2^{\cdot-}$) and hydrogen peroxide (H_2O_2) which is fundamental for their applications as antimicrobial agents [27]. The produced reactive species can enter into the microbial cells by diffusion and consequently, kill them or damage their cell membranes and interior which inhibits microbial growth. This mechanism utilises the photocatalytic activity of ZnONPs for their antibacterial applications in bionanomedicine and bionanotechnology. Accordingly, improvement of ZnONPs bioactivity was considered as a consequence of the created free radicals, as ZnONPs is activated by UV illumination [28]. Seven *et al*. [29] and Padmavathy and Vijayaraghavan [30] have proposed a detailed reaction mechanism of this phenomenon. Both ZnO and TiO_2 as semiconductor materials contain a valence band (VB)

and a conduction band (CB). Incident illumination with photons of energy more than 3.3 eV is directly absorbed and consequently causes an electron transfer from the VB to the CB. The transfer of electron starts a series of conceivable photoreactions with positive holes (h+) created in the VB while at the same time free electrons (e^-) are produced within the CB [29,31,32]. The positive holes (h^+), an immediate oxidant fundamental for the production reactive hydroxyl radicals ($OH^\bullet$), serve as important oxidants in the photocatalytic process [31, 33]. While the free electrons in the CB reduce oxygen molecules, which are adsorbed on the surface of the photocatalyst [33]. Padmavathy and Vijayaraghavan proposed a relationship between photon reaction of the photocatalytic particles and their antibacterial activity in a progression of interactions resulting in the generation of hydrogen peroxide (H_2O_2) molecules which can easily penetrate the membrane of cells, creating deadly harm [30]. Sawai *et al*. have ascribed the damage of the cell membrane to peroxidation of the unsaturated phospholipids as a consequence of photo-catalytically produced free radicals and H_2O_2 [34] The researchers expressed the created ROS by chemical equations which are as follows:

$$ZnO \text{ or } TiO_2 + h\nu \longrightarrow e^- + h^+$$

$$h^+ + H_2O \longrightarrow {}^{\cdot}OH + H^+$$

$$e^- + O_2 \longrightarrow {}^{\cdot}O_2^-$$

$${}^{\cdot}O_2 + H^+ \longrightarrow HO_2^{\cdot}$$

$$HO_2^{\cdot} + H^+ + e^- \longrightarrow H_2O_2$$

(Place Fig. 2 here)

Al-Awady *et al*. studied the antimicrobial effect of titania nanoparticles (TiO_2NPs) of various hydrodynamic diameters and crystallite sizes towards *C. reinhardtii* and *S. cerevisiae* upon illumination with UV and visible light for a range of nanoparticle concentrations and incubation times [35]. They also confirmed that bare TiO_2NPs affect the *C. reinhardtii* cells viability at much lower particle concentrations than for *S. cerevisiae*. The TiO_2NPs antimicrobial action increased upon illumination with UV light compared with that in dark conditions due to the oxidative stress of the produced ROS. However, they found that TiO_2NPs have also affected *C. reinhardtii* upon illumination with visible light which

indicates that they may also interfere with the microalgae's photosynthetic system leading to decreased chlorophyll content upon exposure to TiO_2NPs. Their results indicate that the larger the hydrodynamic diameter of the TiO_2NPs the lower is their antimicrobial effect, with anatase TiO_2NPs generally being more effective than rutile TiO_2NPs [35]. Some of the mechanisms of particle attachment to the microbial cells and pathways of cell damage are illustrated in Fig. 2. Due to their negative charge the generated $\dot{O}_2^-$ and $\dot{O}H^-$ species cannot easily penetrate through the negatively charged cell membrane [36]. Consequently, these species have been found to accumulate on the external surface of the microorganisms cell wall, while H_2O_2 molecules can also enter much easier through the cell membrane, leading to oxidation and damage of the cell interior [35,37,38] (see Fig. 2).Thus, photo-oxidations may illustrate the photocatalytic action of ZnO on cells and its possible impact on their DNA [39]. Dunford *et al*. have examined the impact of ZnO samples as well commercial TiO_2 samples with various proportions of anatase/rutile on DNA upon UV irradiation *in vivo*. The work uncovers that DNA in human cells is also damaged by UV irradiation in the presence of ZnO [40]. Reddy *et al*. have used flow cytometry and viability tests to study ZnONPs toxicity toward *S. aureus* and *E. coli* [41]. Other researchers have studied the antibacterial action of ZnONPs to determine the bacterial growth through the viable cells percentage and the culture turbidity by the colony counts assay [42].

(Place Fig. 3 here)

Yamamoto improved the antibacterial activity of ZnONPs by modifying the viability assessment method [44]. They believed that the antibacterial action rate was greatly enhanced by diminishing the start number of bacterial cells from 10^2 to 10^6 colony forming units. Nair *et al*. believed that the determination of the initial number of bacterial cells is essential in the assessment of the particles antibacterial action [45]. Aruoja *et al*. have studied toxicities of three oxide nanoparticles (ZnONPs, CuONPs and TiO_2NPs) and their efficiency for inhibiting the growth of microalgae *Pseudokirchneriella subcapitata* [46]. Heinlaan *et al*. have used the same three oxide nanoparticles and found that ZnONPs and CuONPs have a toxic impact on *Thamnocephalus platyurus*, the bacteria *Vibrio fischeri* and crustaceans *D. magna*, while TiO_2NPs were not toxic [47]. Therefore, the toxicity of NPs depends on the size, particle morphology, synthesis method, and test organism species, and other factors as described in Fig. 3 [26,47].

(Place Fig. 4 here)

Hu *et al*. exposed earthworms *Eisenia fetida* in soil samples to different concentrations of ZnONPs and TiO_2NPs for up to seven days to assess their toxicity. They found that these NPs can significantly harm to the great extent and destroy the earthworms at particle concentrations higher than than 1.0 g kg^{-1}, influencing the cellulase enzyme activity, mitochondria and the cell DNA [48]. Kasemet *et al*. examined the toxicity of ZnONPs, TiO_2NPs and CuONPs on *S. cerevisiae* (baker's yeast) – a unicellular eukaryotic organism for a 24 h incubation time. It was found that for *S. cerevisiae* both ZnONPs and bulk ZnO were of equivalent toxicity, while, CuONPs showed nearly 60-fold increase in toxicity compared to the bulk CuO material. However, it was discovered that both TiO_2NPs and bulk TiO_2 were non-toxic even at 20000 mg L^{-1} [49].

(Place Fig. 5 here)

Al-Awady *et al.* produced polyelectrolyte-coated TiO_2NPs with up to 4 layers of polyelectrolytes of alternating charge (PSS and PAH) using the layer-by-layer technique. They showed that the antimicrobial properties of polyelectrolyte-coated titania nanoparticles alternate with the surface charge for the particles with cationic outer layer (or bare titania) being much more effective antimicrobials than the ones with an outer layer of anionic polyelectrolyte. The anionic nanoparticles (TiO_2NPs/PSS and TiO_2NPs/PSS/PAH/PSS) showed much lower activity towards than the cationic ones, TiO_2NPs/PSS/PAH and the bare TiO_2NPs, respectively (see Fig. 4) [35]. These authors suggest that the decrease of antimicrobial action can be explained by the poor adhesion of the anionic nanoparticles (TiO_2NPs/PSS and TiO_2NPs/PSS/PAH/PSS) to the cell walls due to their electrostatic repulsion and the enhancement of the antimicrobial effect for cationic nanoparticles (TiO_2NPs and TiO_2NPs/PSS/PAH) is due to the amplification of the particle-cell electrostatically driven adhesion (Fig. 5). They illustrate that the cationic nature of the titania nanoparticles at the conditions of the experiment (pH 5) has much higher disrupting effect on the microorganisms cell wall than the photocatalytic effect and the production of ROS.

Adams *et al*. have researched the eco-toxicity impacts of ZnONPs, SiO_2NPs and TiO_2NPs on Gram-negative bacteria (*E.coli*) and Gram-positive bacteria (*Bacillus subtilis*). These authors

demonstrated that the all three nanomaterials were destructive to both bacteria to variable degrees, with their antibacterial action increasing with the nanoparticle concentration. Also, the antibacterial impact of those nanoparticles normally increased from SiO_2NPs to TiO_2NPs to ZnONPs [50]. Jong *et al*. examined the antialgal action of four oxide NPs namely ZnO, Al_2O_3, TiO_2, and SiO_2 to microalgae *Chlorella sp*. From this study, it was found that ZnONPs (20 mg L^{-1}) and TiO_2NPs (HR3, anatase, 30 mg L^{-1}) mainly inhibited the growth of the algae at an exposure time for six days EC30, while TiO_2NPs (DJ3, rutile), Al_2O_3NPs and SiO_2NPs had practically no measurable toxicity to algae. In general, nanoparticles showed higher toxicity than that of bulk materials of the same chemical composition and polymorphic form [51].

(Place Fig. 6 here)

Magnesium hydroxide ($Mg(OH)_2$NPs) and magnesium oxide nanoparticles (MgONPs)

$Mg(OH)_2$NPs have attracted much attention over years due to their wide applications in different fields like environmental processes [53-55] and pharmaceutical formulations [56-59]. However, a limited number of studies have investigated the antimicrobial effect of $Mg(OH)_2$NPs and reported that *in vivo* toxicity values are low, thus demonstrating that $Mg(OH)_2$NPs have actually a non-toxic effect to humans in sensible amounts [60]. Recently, it has been reported that $Mg(OH)_2$NPs were effective antibacterial agents towards several bacteria, like *E. coli*, *S. aureus*, *P. aeruginosa* and *B. phytofirmans* [61-66] and a number of studies have been focused on this new and effective antimicrobial agent [52]. Dong *et al*. have investigated the antibacterial action of $Mg(OH)_2$NPs on *Burkholderia phytofirmans* and *Escherichia coli* [62]. Their results indicated that $Mg(OH)_2$NPs suspensions are an effective antibacterial agent towards *B. phytofirmans* and *E. coli*, and the study examined the role of the OH^- and Mg^{2+} ions which are naturally present in $Mg(OH)_2$NPs suspension on their antimicrobial action. They showed that an alkaline medium of pH 10.4 as well as an equivalent amount of Mg^{2+} ions in the aqueous solution cannot kill the bacteria [62]. Dong *et al*. have also examined the antibacterial activity of $Mg(OH)_2$NPs against *E. coli*. They indicated that $Mg(OH)_2$NPs can kill *E. coli* even in the dark conditions, indicating that no photocatalytic properties are involved in their antibacterial action [61]. Hence, it is exciting to

notice that the antibacterial mechanism of $Mg(OH)_2$NPs seems to be very different to those of metal and metal-based compounds [66-69].

(Place Fig. 7 here)

In another study, Pan *et al*. synthesised $Mg(OH)_2$NPs from three different precursors (e.g. $MgCl_2$, $MgSO_4$ and MgO) and tested their antibacterial efficiency towards *E. coli* as a model Gram-negative bacteria [52]. Bactericidal examinations indicated that the antibacterial activity of $Mg(OH)_2$ NPs is conversely related to the particle size. Their results also revealed that the ability of $Mg(OH)_2$NPs to adhere on the bacterial surface decreased in the order $Mg(OH)_{2\_MgCl_2} > Mg(OH)_{2\_MgSO_4} > Mg(OH)_{2\_MgO}$, showing that the toxicity of the produced $Mg(OH)_2$NPs may be caused by the electrostatic interaction induced by adsorption of counter-ions (Fig. 6). This means that the type of magnesium salt used to produce the $Mg(OH)_2$NPs by hydrolysis can greatly influence their antimicrobial properties by secondary absorption of counter-ions on the particles surface. These authors propose that the antibacterial mechanism of $Mg(OH)_2$NPs on *E. coli* is likely to be as follows: Firstly, the cationic $Mg(OH)_2$NPs adsorb on the negatively charged bacterial cell wall by electrostatic attraction. Secondly, the adsorbed $Mg(OH)_2$NPs disrupts the integrity of the cell wall which then increases the permeability of bacterial cell membrane and finally causes the bacteria's death as illustrated in Figure 7 [52].

Magnesium oxide nanoparticles (MgONPs) are also very stable and biocompatible material and are strong antibacterial agents due to their alkalinity and generation of active oxygen species. It has been confirmed that the antibacterial mechanism of MgONPs is achieved by the production of superoxide on the surface of the MgONPs as well as a local increase in the pH by the hydration of the MgONPs surface with water [70,71]. According to published reports, MgONPs disrupt the cell membrane and then cause the leakage of intracellular contents, which results in the bacterial cell death [72]. Hewitt *et al*. have evaluated the effects of three ceramic powders MgO, ZnO and CaO on *E. coli*. They indicated that MgONPs initiated the sensitivity changes in *E. coli* produced by active oxygen [73]. However, Leung *et al*. have described that very efficient antibacterial action of the MgONPs could be observed in the absence of any ROS generation. They showed that the mechanism of antimicrobial action might be because of the damage of cell membrane. They reported that the toxicity of MgONPs, similar to other metal oxide NPs, is commonly due to the generation of ROS [74].

Copper nanoparticles (CuNPs) and Copper oxide nanoparticles (CuONPs)

CuNPs have exceptional biological, physical and chemical properties, and due to the low cost of their preparation have become very popular to researchers developing novel antimicrobial agents [75-77]. Usman *et al*. have studied the antimicrobial action of copper-chitosan nanoparticles with sizes in the range of 2–350 nm. They assessed the antibacterial and antifungal activities of these nanoparticles on different microorganisms, including methicillin-resistant *Staphylococcus aureus, Salmonella choleraesuis, Candida albicans, Pseudomonas aeruginosa,* and *Bacillus subtilis* [76]. Their results showed the high capability of these nanoparticles as antimicrobial agents in anaerobic conditions. However, rapid oxidation of the copper nanoparticles upon exposure to air limits their application as antimicrobials in aerobic conditions [76,78]. Katwal *et al*. developed a new electrochemical method for preparation of CuONPs with different morphologies [79] which gave enhanced antibacterial and antifungal activity against several pathogenic strains (Fig. 8).

(Place Fig. 8 here)

Mahapatra *et al*. have tested the antibacterial action of copper oxide nanoparticles (CuONPs) towards *Klebsiella pneumoniae, Salmonella paratyphi*, *Shigella strains* and *Pseudomonas aeruginosa*. According to their results, these nanoparticles showed measurable antibacterial action towards the mentioned microorganisms. They proposed that such nanoparticles cross through the bacterial cell membrane and affect vital enzymes of the bacteria which were the critical factors leading to their death. Also, they showed that CuONPs were not cytotoxic on some human cells (HeLa cell line) [78]. Azam *et al*. have reported a study on the effect of particle size on the antibacterial action of CuONPs. They examined the antibacterial activities towards two Gram-negative bacteria (*E. coli* and *P. aeruginosa*) and two Gram-positive bacteria (*B. subtilis* and *S. aureus*). It was found that CuONPs exhibited inhibitory effects towards both groups of bacteria. The authors have shown that the antibacterial action of CuONPs depends on their stability, particle size and concentration added to the bacterial growth media. They concluded that the metal nanoparticles limit bacterial growth by interacting with nanometric pores that exist on the cell membranes of most microorganisms [80]. Ahamed *et al*. have discovered that CuONPs of particle size around 23 nm had significant antimicrobial action towards different bacterial strains (*Klebsiella pneumoniae,*

Pseudomonas aeruginosa, *Escherichia coli*, *Enterococcus faecalis*, *Shigella flexneri*, *Salmonella typhimurium*, *Staphylococcus aureus*, and *Proteus vulgaris*). Among these microorganisms, *Escherichia coli* and *Enterococcus faecalis* showed the highest sensitivity to copper oxide nanoparticles while *Klebsiella pneumoniae* was almost resistant to these nanoparticles [77].

Silver nanoparticles (AgNPs) and silver oxide nanoparticles (Ag_2ONPs)

AgNPs are one of the most studied inorganic nanoparticles utilized as antimicrobial agents [81-84]. AgNPs find antimicrobial applications in the production of injection mould plastics, textiles and coating-based usages [85] and they are also widely used in biomedical applications [86,87]. Jo *et al*. have discovered that AgNPs show a good antimicrobial activity comparable to silver in its ionic form [88]. Allahverdiyev *et al*. have demonstrated that AgNPs have significant antimicrobial activity towards drug-resistant bacteria [89]. Lok *et al*. have reported that the antibacterial activity of AgNPs results from destroying the bacterial outer membrane [90]. A number of studies have suggested that AgNPs can cause pits and gaps in the bacterial membrane and after that can fragment the cell [91,92]. Egger *et al*. have also shown that Ag^+ ions emitted by AgNPs interact with disulfide or sulfhydryl groups of enzymes that lead to damage of metabolic processes which causes the bacterial cell death [85].

According to Sintubin *et al.* [93], AgNPs release silver ions (Ag+) which can damage the target cells through several different pathways: (i) Ag^+ ions binding to DNA and RNA which result in their loss of biological function; (ii) AgNPs can also react with sulphur containing peptides inside the cells and on the cell membrane which in affects their viability. (iii) AgNPs can potentially destabilise cell membrane proteins and inhibit various intracellular enzymes. (iv) at high AgNPs concentration, the released Ag^+ ions affect the cytoplasm components and nucleic acids whereas at lower concentrations they tend to inhibit respiratory chain enzymes and impair membrane permeability to proton and phosphates [93].

Mie *et al*. have examined the antibacterial action of their custom-synthesized AgNPs of particle size 19 nm towards eight different microorganisms utilizing the disk diffusion method. Their results showed that such AgNPs synthesized using *Parmotrema praesorediosum* have potential antibacterial action towards Gram-negative bacteria. Therefore, the authors recommended that such synthesized AgNPs could be used in the pharmaceutical and biomedical industries [94]. Hernández-Sierra *et al*. have studied the

bactericidal action of AgNPs, ZnONPs, and AuNPs against *Streptococcus mutans*. The authors demonstrated that that AgNPs displayed the most effective antibacterial action for controlling *S. mutans*, suggesting that AgNPs could be utilized in fighting dental caries since it usually is caused by *S. mutans* [95]. Besinis *et al*. have also examined the toxicity effect of AgNPs towards *S. mutans* and showed that the antibacterial activity of AgNPs towards *Streptococcus mutans* was higher than that of chlorhexidine [96]. Zarei *et al*. have studied toxicities of AgNPs against four foodborne pathogens namely *Escherichia coli*, *Vibrio parahaemolyticus*, *Listeria monocytogenes* and *Salmonella typhimurium*. As indicated by their results, AgNPs had the strongest antibacterial impact against the mentioned pathogens. Thus, the authors concluded that AgNPs could be a good option for cleaning and disinfection of equipment and surfaces in the food-related environments [97]. Additionally, AgNPs have been reported to be less toxic than numerous different disinfectants. Marambio-Jones and Hoek had reviewed the antibacterial effects of the AgNPs and their implications for the environment and human health [98]. Kim *et al.* reported strong antifungal effect of AgNPs against pathogenic yeast [99].

Ag_2ONPs have been found to have very strong antimicrobial properties and may be considered as an alternative of most modern antiseptic agents [89, 100]. Sondi and Salopek-Sondi have tested the antimicrobial activity of Ag_2ONPs towards *E. coli*. These authors believed that when *E. coli* were exposed to Ag_2ONPs nanoparticles, they can end the cell cycle at the G_2/M phase because of the DNA damage through oxidative stress [101]. Such nanoparticles would be promising substitutes for various broad spectrum antibiotics.

Gold nanoparticles (AuNPs)

AuNPs are thought to be so important in the development of antibacterial action because of their photothermal activity, nontoxicity, polyvalent impacts, high ability to functionalization and ease of detection [102-105]. Cui *et al*. have reported that the antimicrobial action of AuNPs do not include any ROS-related mechanisms [106] rather than the adhesion of the AuNPs to the bacterial membrane followed by membrane potential modification and ATP level decline. In addition, AuNP have been found to inhibit the tRNA by binding to the ribosomes [106]. Tiwari *et al*. have tested the antibacterial and antifungal effects of the AuNPs functionalized with 5-fluorouracil towards *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Aspergillus fumigatus*, *Aspergillus niger* and *Micrococcus luteus*. Their results revealed that the AuNPs had higher antibacterial activity towards Gram-

negative bacteria than Gram-positive bacteria because of the easier nanoparticle transfer into the Gram-negative bacteria. Likewise, they indicated antifungal activity against *Aspergillus fumigatus* and *Aspergillus niger* [103].

Zhou *et al*. have investigated antibacterial effects of Au and AgNPs on bacillus Calmette-Guérin (BCG) and *E. coli*. According to their results, AgNPs showed excellent antibacterial activity on both the Gram-positive bacteria BCG and the Gram-negative bacteria *E. coli*. They also investigated AuNPs with a weakly bound capping agent (citrate) and a strongly bound capping agent (poly-allylamine hydrochloride, PAH). The researchers showed that the PAH could strongly interact with the bacterial cell membrane because of its positively charged nature. The authors commented on the mechanisms of interaction between AuNP and AgNPs and *E. coli*.[104] These bacterial cells were found to take up single citrate-coated AuNPs or aggregates of AuNPs complexes. The PAH-coating facilitated the AuNPs uptake into the bacterial cells followed by lysis. However, most of the AgNPs were trapped on the cell walls [104].

Aluminium oxide nanoparticles (Al_2O_3NPs)

Aluminium oxide nanoparticles have a wide range of applications in different fields such as personal care products as well as industrial sorbents and fillers. Alumina forms very stable nanoparticles which are impervious to temperature changes and have a hexagonal close packing structure, including the O_2^- and the Al^{3+} ions that fill 65% of all the octahedral sites existing in the structural network [107-110]. Sadiq *et al*. have studied the action of Al_2O_3NPs as anti-oxidants that block the generation of reactive oxygen species (ROS), indirectly blocking apoptosis, which starts the ROS defence system, before finishing the cell death program [110]. Furthermore, they have reported the growth inhibition of the pathogen *E. coli* by alumina nanoparticles with a particle size of approximately 179 nm in the concentration range of 10-1000 µg mL^{-1}. The majority of the metal oxides act as antimicrobials by using the processes of production of ROS, which leads to damage of the bacterial cell wall. However, Al_2O_3NPs can likewise act as a radical scavenging agent which have non-toxic effect to the human cell [110]. The method of action of Al_2O_3NPs towards *E. coli* can be explained by an initial adhesion of positively charged alumina nanoparticles to the negatively charged bacterial cell surface. When a bacterial cell influences a human cell, it leads to the generation of ROS, which can be very damaging to human health, as it can cause DNA damage that could be a probable cause of cancer. Since, Al_2O_3NPs have a radical scavenging property,

they block the production of ROS, which leads to bacterial cell death, before the human cells are damaged [110,111].

Cerium oxide nanoparticles (CeO_2NPs)

CeO_2 is a technologically significant material because of its properties and applications in different fields ranging from engineering to biological sciences [112]. Santos *et al*. have found that at lower temperatures the CeO_2NPs have antimicrobial action towards different bacteria, including *Shewanellaoneidensis*, *Pseudokirchneriella subcapitata*, *E. coli* and *B. subtilis*, due to damaging of the microorganisms cell walls [112]. Many studies state that the concentration of Ce^{3+} increases compared to Ce^{4+} as the size of the nanoparticles decreases, with the concentration of Ce^{3+} is under 1% in suspension of 10 nm CeO_2NPs, while it increases to 6% for CeO_2NPs. There are O_2 gaps present in the oxidation states of these two CeO_2NPs. The production of an O_2 vacancy is accompanied by the reduction of the Ce^{4+} formula to the Ce^{3+}, resulting in the loss of O_2 molecule. This distinctive radical scavenging property of CeO_2 (IV) nanoparticles makes them an attractive option for applications in wound healing dressings. Moreover, CeO_2NPs have an important antimicrobial action, as they can act as radical scavengers and block the ROS generation which can also eliminate microorganisms [112,113].

Yttrium oxide nanoparticles (Y_2O_3NPs)

Y_2O_3NPs have multiple applications in mechanical polishing, chemical synthesis and as additives to drugs, varnishes, food and cosmetics [114]. Y_2O_3NPs have one of the highest free energy of formation of their oxide structure [115] and do not deviate from their stoichiometry under the normal temperature and pressure conditions or by the impact of atmospheric CO_2 and H_2O vapours. Y_2O_3NPs have two polymorphs, which are A and B form of hexagonal close-packing structure (hcp). Atou *et al*. have indicated that the antioxidant properties of the Y_2O_3NPs prevent the cell death because of excessive oxidative stress [116]. Furthermore, Schubert *et al*. have shown that the properties of Y_2O_3NPs are dependent on their structure but independent of the particle size in the range of 6-1000 nm. The researchers also showed that the Y_2O_3NPs act as direct antioxidants to limit the amount of reactive oxygen species required to kill the cells [117]. The Y_2O_3NPs are relatively non-toxic to neutrophils and macrophages which is a very beneficial wound healing property [113,117].

(Place Fig. 9 here)

Colloid antibodies for microbial cells shape and surface recognition

Conventional antimicrobial nanoparticles have one major drawback as they cannot specifically differentiate between microbial and human cells, which is why they could potentially have a toxic effect on human health. This is the reason why direct replacement of common antibiotics with antimicrobial nanoparticles formulations can be challenging. This can be partially overcome by functionalising antimicrobial nanoparticles with antibodies. An interesting alternative was recently proposed by Borovicka *et al.* where a combination of antimicrobial nanoparticles with inorganic shells imprinting the shape of target microbes [119] was used in their cell shape-selective recognition and killing in a mixture with microbial cells of different cell shape and size. These "colloidal cell imprints" were prepared by depositing silica on microbial cells pre-coated with AuNPs. These composite shells were then partially fragmented by ultrasound and the fragments were recovered after removing the templated cells with a bleaching solution [118] (see Fig. 9).

(Place Fig. 10 here)

The incubation of these AuNPs-functionalised colloidal cell imprints in a mixture of microbial cells of various shapes (Fig. 9) showed that they attach only to cells matching the imprinted cell shape and deliver antimicrobial agent (gold nanoparticles) directly to their membranes. Since the AuNPs have photothermal properties, irradiation with laser led to cell shape selective killing of microbial cells due to overheating of their surface in contact with the imprint (see Fig. 9b and Fig. 10). The same approach can be applied with many other antimicrobial nanoparticles. This cell shape recognition of the microbial cell imprints minimises the direct exposure of other cells to antimicrobial nanoparticles [118]. Generally, the size recognition of the target cell and its colloid imprint amplifies the magnitude of the interaction energy between their surfaces. When the free interaction energy (sum of electrostatic, van der Waals and biospecific interactions) between the surfaces of the target microbial cell and its colloid imprint is attractive, the cell size and shape matching amplifies the attraction. For micrometre-sized target cells and moderate ionic strength this can result in more than three orders of magnitude difference in the interaction energy [120]. Rahma *et al.*

developed similar approach by using hemispherical silica shell particles produced by templating yeast cells with silica followed by their fragmentation, bleaching and surface functionalisation with N-chloramines. Antimicrobial testing was carried out on Gram-negative (*E. coli*) and Gram-positive (*B. cereus*) bacteria and confirmed their superior antimicrobial efficacy compared with small molecule antiseptic agents [121]. This approach opens a number of new avenues for building powerful selective biocides based on combinations of colloid antibodies and cell killing strategies based on nanoparticles which can be applied in new antibacterial therapies.

(Place Fig. 11 here)

Environmentally benign antimicrobial nanoparticles

Biodegradable antimicrobial nanoparticles with cores prepared from renewable materials could be used as sustainable delivery system for active payloads in molecular or ionic form, such as metal ions and other useful bioactive components [123]. Lignin is the most abundant aromatic biopolymer in nature [124]. It has an amorphous 3D structure [125,126], and it is naturally degradable and biocompatible [127,128]. Biodecomposition of lignin in the environment [129,130] transforms it in soil humus [131]. Frangville *et al.* [132] and Richter *et al.* [122,133] proposed two alternative methods for preparation of environmentally biodegradable lignin nanoparticles from Kraft and Organosolv lignin which can be loaded with hydrophilic [132] and hydrophobic [132,133] antimicrobial payloads. Their work was extended by Richter *et al*. by synthesizing environmentally-benign antimicrobial nanoparticles from lignin cores infused with silver-ion [122] (see Fig. 12). These lignin nanoparticles were turned cationic by adsorption of a cationic polyelectrolyte, polydiallyldimethylammonium chloride (PDAC) to give Ag^{+}-loaded environmentally benign nanoparticles (EbNPs-Ag^{+}-PDAC). The cationic nature of these particles facilitated the targeted adhesion of the nanoparticles to negatively-charged cell membranes of a range of bacteria. These particles exhibit broad-spectrum antimicrobial activity during application, while offering an environmentally friendly alternative to metallic silver nanoparticles (Fig. 13). The EbNPs-Ag^{+}-PDAC exhibit broad spectrum biocide action and are capable of killing common Gram-negative and Gram-positive human pathogens as well as quaternary amine-resistant bacteria, while using 10× less silver when compared with conventional branched

poly ethylene imine–coated AgNPs (BPEI-AgNPs) and $AgNO_3$ aqueous solution. The array of high-throughput screening tests on mammalian cells and zebrafish embryos indicate that the EbNPs have decreased impact on the majority of biological endpoints, when compared with equivalent mass of AgNPs and Ag^+. However, the EbNPs-Ag^+-PDAC were showed to have time-limited antimicrobial action after they can release their residual silver ions [122].

(Place Fig. 12 here)

Different methods for characterisation of the nanoparticle antimicrobial action have been employed, e.g. growth inhibition method [134], the estimation of the minimum inhibitory particle concentration [93], and the minimum bactericidal concentration [135]. Nanoparticles have also been used to encapsulate and deliver antibacterial. Martins *et al.* has encapsulated violacein poly-(D,L-lactide-co-glycolide) (PLGA) nanoparticles to deliver it as bactericidal agent. This minimum inhibitory concentration of PGLA NPs-loaded violacein has been found to be five times lower than free violacein in solution [136]. Biodegradable nanoparticles made of dextran loaded with silver carbene complex have also been shown by Ornelas-Megiatto *et al.* to have higher antibacterial activity compared to the free silver complex [137]. Hybrid nanoparticles (e.g. magnetite), whose surfaces are coated by polymers (chitosan/PGA) of high affinity for the microbial cells have shown a boost in their antimicrobial efficiency.
Qi *et al.* demonstrated that the vancomycin-modified mesoporous silica nanoparticles (MSNs⊂Van) can efficiently target and kill Gram-positive bacteria over macrophage-like cells (Fig. 13). Owing to the specific hydrogen bonding interactions of vancomycin toward the terminal D-alanyl-D-alanine moieties of gram-positive bacteria, the MSNs⊂Van exhibited enhanced recognition for Gram-positive bacteria due to the multivalent hydrogen binding effect [138].

(Place Fig. 13 here)

(Place Table 1 here)

Biomedical and industrial applications of antimicrobial nanoparticles

Recently, nanoparticles have offered great possibilities for applications as antimicrobial agents. Metal and metal oxide based nanoparticles with antimicrobial action could find many

applications in health related and industrial products, like food preservation, cosmetics, home and personal care, water treatment and crop protection as shown in Fig. 14 [21].

(Place Fig. 14 here)

ZnONPs and colloidal size ZnO powders have numerous applications in pharmaceutical and cosmetic formulations, textile industry, electronics and electro technology industries and photocatalysis due to their distinct properties such as large binding energy, wide bandgap and chemical stability [152]. Moreover, ZnONPs are used as antimicrobial agents for surface coatings on walls and wallpapers. $Mg(OH)_2$NPs are approved as additives in a number of foods and drugs [153]. Furthermore, the MgONPs can be utilized in medical treatments as well as in environmental preservation and food processing [154]. TiO_2NPs have already been utilized in cosmetics, waste water treatment and foods. AgNPs have also been used in textiles and other consumer goods for surface sterilization [21]. The antifungal and antiviral activity of nanoparticles has not yet been studied extensively but it is a very promising area with a huge potential. Silver nanoparticles ware recently used by Lara *et al.* as antiviral agents against HIV-1 strain at non-cytotoxic levels. It showed good efficiency at the early stage of viral replication [155].

(Place Table 2 here)

Table 1 summarizes the modes of action of various antimicrobial particles and Table 2 points to their advantages and drawbacks.

Conclusions

Nanotechnology offers unconventional approaches for fighting microbes that do not rely on the existing pathways of antibiotic action. This makes possible to address the challenge of antimicrobial resistance by using nanoparticles with engineered antimicrobial action designed to target specific pathogens. There is a lot of ongoing work on several classes of inorganic and organic colloid particles of added functionality which exhibit strong and universal antibacterial, antifungal and antiviral action towards which microbes have not been able to develop resistance. We have discussed the mechanisms by which such nanoparticles attack microbial cells or inhibit their growth, which involve generation of reactive oxygen species (ROS) upon irradiation with UV light, cell membrane disruption due to the NPs cationic

surface, ROS scavenging, emission of heavy ions, as Ag^{+} and Cu^{2+} on the cell surface, etc. Various strategies have recently been pursued in search of antimicrobial agents based on natural as well as synthetic nanoparticles. The latter include nanoparticles synthesised from various metals, as copper, gold and silver and metal oxides, e.g. copper, zinc, titanium, aluminium and magnesium, as well as low soluble metal hydroxides, as $Mg(OH)_2$. These inorganic nanoparticles have very different mechanisms of antimicrobial activity and can retain their antimicrobial action in a range of adverse conditions. Smaller nanoparticles usually show greater antimicrobial activity due to larger surface-to-volume ratio in suspension and greater area of contact with targeted microbial cells. However, significant research effort is needed to carefully test their side effects, environmental impact and potential nanotoxicity before nanoparticles can be safely and broadly used as efficient substitutes of conventional antimicrobials.

Acknowledgements

A.F.H. thanks the Iraqi Government, the Higher Committee for Education Development of Iraq and the University of Babylon, Iraq for the financial support for his PhD study during the work on this project. The authors are also grateful to Dr Anupam Das for technical assistance.

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Table 1. Commonly used nanoparticles as antimicrobial agent, their surface properties and the cell-nanoparticle interactions.

Type of nanoparticles	**Surface properties at pH 7**	**Cell-particle interactions**	**Refs.**
ZnO NPs	Cationic, IEP 9.7	Bacterial attachment by electrostatic interactions, ROS generation on the surface of the particles; zinc ion release, membrane dysfunction; and nanoparticles internalization into cell.	[139-144]
MgO NPs	Cationic IEP 9.8-12.7	Electrostatic interactions, Damaging the cell membrane and then causing the leakage of intracellular contents and death of the bacterial cells.	[70,72-74]
Cu NPs and CuO NPs	Cationic IEP 9.5-10	Release of Cu^{2+}, electrostatic interactions, Crossing of nanoparticles from the bacteria cell membrane and then damaging the vital enzymes of bacteria.	[77,78,142,145]
Al_2O_3 NPs	Cationic	bacterial attachment (electrostatic	[146]

	IEP 8-9	interaction) damage to the bacterial cell wall and increase the permeability.	
TiO_2 NPs	Cationic IEP 6.8	Electrostatic interactions, oxidative stress via the generation of ROS; lipid peroxidation that cause to enhance membrane fluidity, disrupt the cell integrity.	[35,89,143,147-149]
CeO_2 NPs	Cationic IEP6.7-8.6	There are oxygen gaps present in the oxidation states of these two CeO_2 NPs. The creation of an oxygen vacancy is accompanied by the reduction of the Ce^{4+} form to the Ce^{3+}, resulting in the loss of an oxygen molecule. This unique radical scavenging property of ceria makes them an attractive option in wound healing. CeO_2 nanoparticles have a good antimicrobial activity, as they can act as radical scavengers and block the ROS production to eliminate bacteria.	[112,113,117]
Y_2O_3 NPs	Cationic IEP7.2-8.9	The Y_2O_3 nanoparticles act as direct antioxidants to limit the amount of reactive oxygen species required to kill the cells.	[117]
Ag NPs and Ag_2O NPs	Cationic IEP 9.4	Release of Ag^+, electrostatic interactions, Ion release; induction of pits and gaps in the bacterial membrane; interact with disulfide or sulfhydryl groups of intracellular enzymes that lead to disruption of metabolic processes. DNA loses its replication ability and the cell cycle halts at the G_2/M phase owing to the DNA damage (in the case of Ag_2O).	[85,91,92,145,150, 151]
Au NPs	Cationic IEP 5.5-6.8	Electrostatic interactions, attachment of these nanoparticles to membrane which change the membrane potential and then cause the decrease the ATP level; and inhibition of tRNA binding to the ribosomes.	[102,103,105,106]
$Mg(OH)_2$ NPs	Cationic IEP 10-12.7	Electrostatic interactions, Firstly, the cationic $Mg(OH)_2$NPs adsorb on the negatively charged bacterial cell wall by electrostatic attraction. Secondly, the adsorbed $Mg(OH)_2$NPs disrupts the integrity of the cell wall which then increases the permeability of bacterial cell membrane and finally	[52]

		causes the bacteria's death.	

Table 2. A brief list of advantages and drawbacks of antimicrobial nanoparticles.

Type of antimicrobial nanoparticles	Advantages and applications	Drawbacks
ZnO NPs	Antimicrobial, photocatalytic activity; high stability; cheap and easy to prepare; bactericidal effects on both Gram-positive and Gram-negative bacteria; antibacterial activity against spores which are resistant to high temperature treatment [139-144].	Conventional antimicrobial nanoparticles have one major drawback as they cannot specifically differentiate between microbial and human cells
MgO NPs	Effective against both Gram-positive and Gram-negative bacteria; high stability; low cost; availability [70,72-74].	Non-specific antimicrobial action;
Cu NPs and CuO NPs	Effective against Gram-positive and Gram-negative bacteria; high stability; easy to fabricate, antifungal activity 77,78,142,145]. The [antibacterial and antifungal activities of these nanoparticles on different microorganisms, including methicillin-resistant *Staphylococcus aureus*, *Salmonella choleraesuis*, *Candida albicans*, *Pseudomonas aeruginosa*, and *Bacillus subtilis* [76].	Could potentially have a toxic effect on human health. This is the reason why direct replacement of common antibiotics with antimicrobial nanoparticles formulations can be challenging.
Al_2O_3 NPs	Antimicrobial properties, inert, cheap and easy to fabricate, Al_2O_3NPs can act as a radical scavenging agent which have non-toxic effect to the human cell [110].	Could potentially have a toxic effect on human health upon dissolution in acidic environment.
TiO_2 NPs	Antimicrobial properties, suitable photocatalytic properties; cheap and easy to make, high stability; effective antifungal for fluconazole resistant strains, no toxicity in dark condition.TiO_2NPs affect the *C. reinhardtii* cells viability at much lower particle concentrations [35,89,143,147-149].	Non-specific antimicrobial action;
CeO_2 NPs	Antimicrobial, catalyst support, radical scavenger [113] at lower temperatures the CeO_2NPs have antimicrobial action towards different bacteria, including *Shewanellaoneidensis*, *Pseudokirchneriella subcapitata*, *E. coli* and *B. subtilis*, due to damaging of the microorganisms cell walls [112].	Non-specific antimicrobial action; Expensive to make in large quantities.

Y_2O_3 NPs	Antimicrobial, UV protection, radical scavenger [113,117].	Non-specific antimicrobial action; Expensive to make in large quantities.
Ag NPs and Ag_2O NPs	High antimicrobial activity against both bacteria and drug-resistant bacteria, antifungal activity on spore-producing fungal plant pathogens, high stability, nontoxicity, disinfectant, electrical conductive, UV protection [85,91,92,145,150,151].	Non-specific antimicrobial action; This can be partially overcome by functionalising antimicrobial nanoparticles with antibodies (see Fig. 9) [118,119]
Au NPs	Nontoxicity, not inducing any ROS-related process; high ability to functionalization, polyvalent effects; ease of detection; photothermal activity [102,103,105,106]. The antibacterial and antifungal effects of the AuNPs functionalized with 5-fluorouracil towards *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Aspergillus fumigatus*, *Aspergillus niger* and *Micrococcus luteus*. Their results revealed that the AuNPs had higher antibacterial activity towards Gram-negative bacteria than Gram-positive [103].	Expensive to make in large quantities.
$Mg(OH)_2$ NPs	Antibacterial, environmental processes, pharmaceutical formulations. Due to its non-toxicity and low cost, $Mg(OH)_2$ is an approved drug and food additive [52-59,61]. $Mg(OH)_2$NPs were effective antibacterial agents towards several bacteria, like *E. coli*, *S. aureus*, *P. aeruginosa* and *B. phytofirmans* [61-66]	Only moderately efficient as antimicrobial agents; require relatively high particle concentrations to act as antimicrobials; sensitive to pH of the environment.
EBNPs	Biodegradable environmental friendly; can outperform inorganic antimicrobials, more cost effective than AgNPs; Tested against *E. coli*, *P. aeruginosa* and *Ralstonia sp.* [122,133,136-138]	Complexity of fabrication; Non-specific antimicrobial action;
Colloid antibodies	Cell shape specific better selectivity- see e.g. [118-120]	Cost of production; Complexity of fabrication

FIGURE CAPTIONS

Fig. 1. Classification of colloid particles as antimicrobial agents.

Fig. 2. Schematics of the photocatalytic reactions of TiO_2NPs and their antimicrobial action due to the formation of reactive oxygen species. Reproduced with permission from Ref. [35].

Fig. 3**.** Schematic overview of the nanotoxic impact of metal oxide NPs. The essential factors that result in toxicity towards microbial cells include nanoparticle size, dissolution, structure and morphology, exposure routes, etc. The cell destroying mechanisms include oxidative stress, genotoxicity, coordination effects and non-homeostasis [26,43].

Fig. 4. The effect of anatase TiO_2NPs coated with different number of layers of anionic (PSS) and cationic (PAH) polyelectrolytes on the viability of *C. reinhardtii* at different particle concentrations (0, 100 and 500 mg mL^{-1}). The cells were incubated with the bare and the coated TiO_2NPs in dark conditions (A–D) and under UV light (E–H), respectively. The antimicrobial was assessed for: (A and E) bare TiO_2NPs; (B and F) TiO_2NPs/PSS; (C and G) TiO_2NPs/PSS/PAH and (D and H) TiO_2NPs/PSS/PAH/PSS at different nanoparticle concentrations and exposure times. Reproduced with permission from Ref. [35].

Fig. 5. (A) Mechanism of cytotoxic action of TiO_2NPs due to the generation of reactive oxygen species (ROS) in the presence of sunlight and oxygen which can lead to cell damage. (B) The adhesion of the uncoated TiO_2NPs to the cell wall surfaces is favoured due to their opposite surface charges. (C) The interaction between the anionic surface of the cell membrane and TiO_2NPs coated with anionic polyelectrolyte is repulsive. The cationic TiO_2NPs and TiO_2NPs/PSS/PAH nanoparticles are expected to be more toxic to the cells than the anionic TiO_2NPs/PSS particles. Reproduced with permission from Ref. [35].

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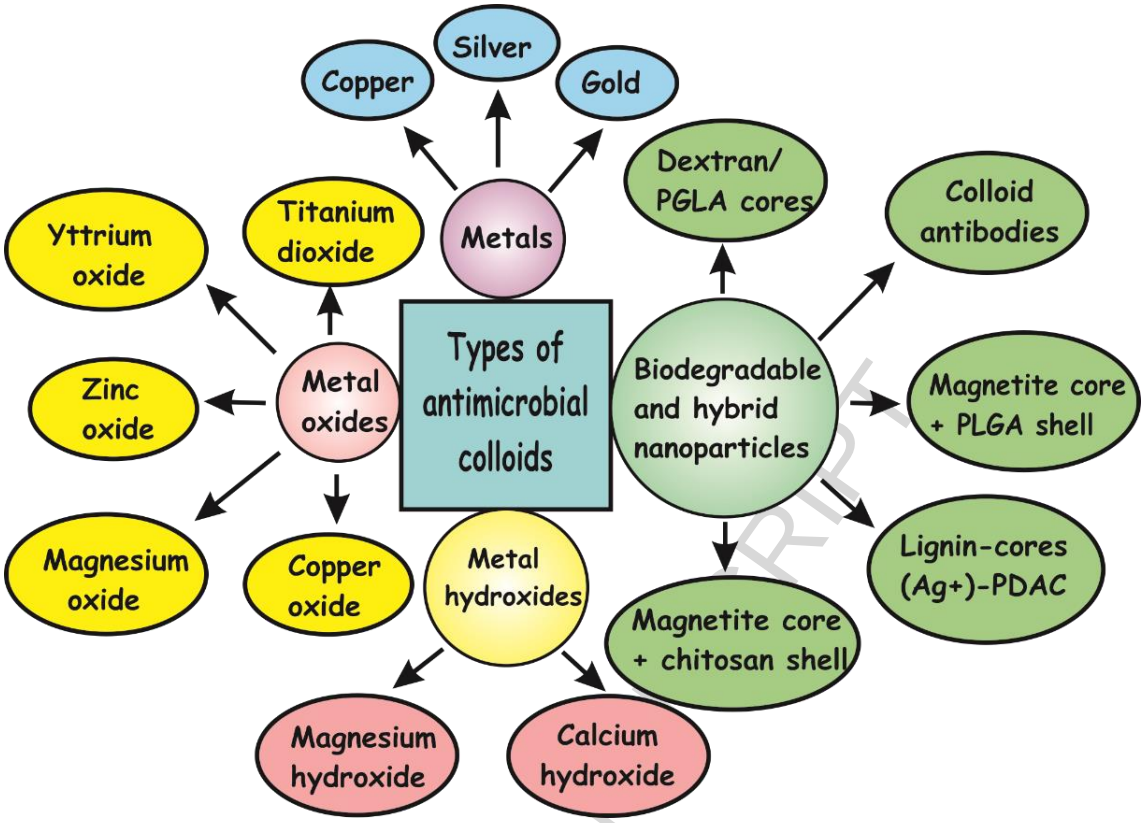

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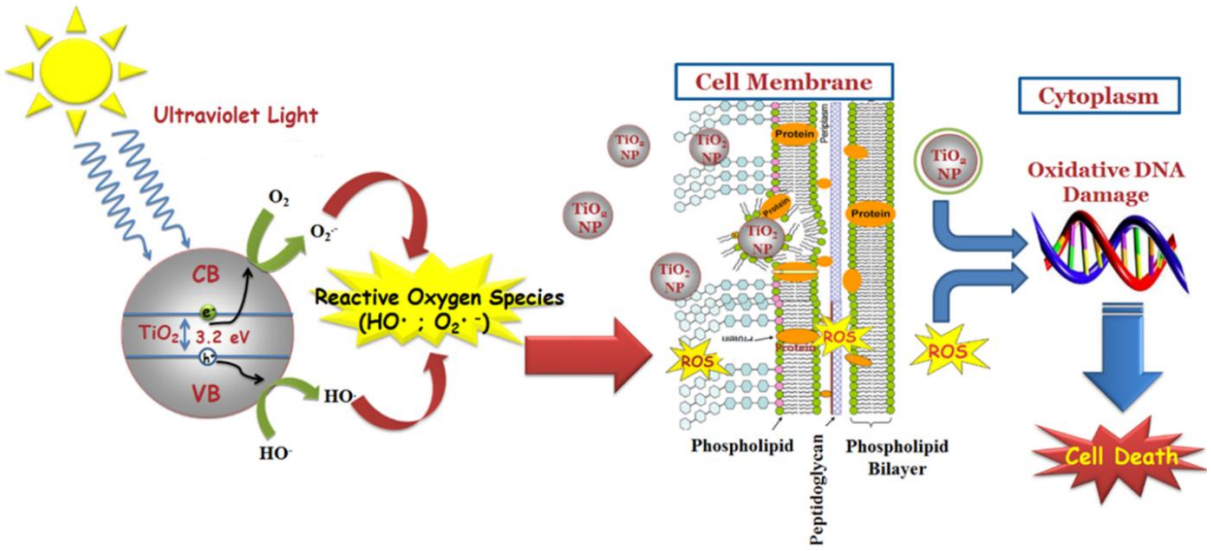

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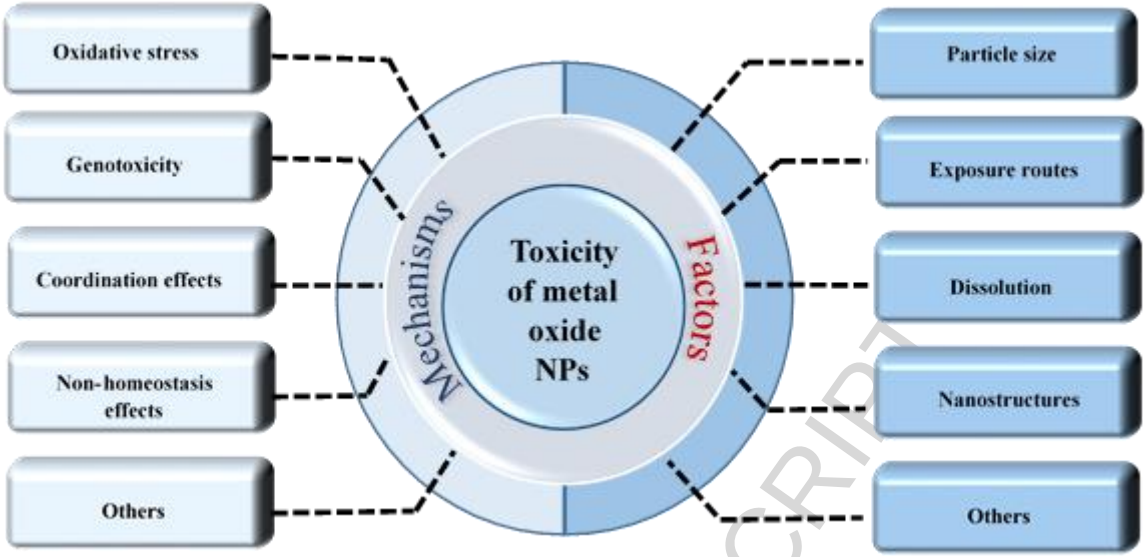

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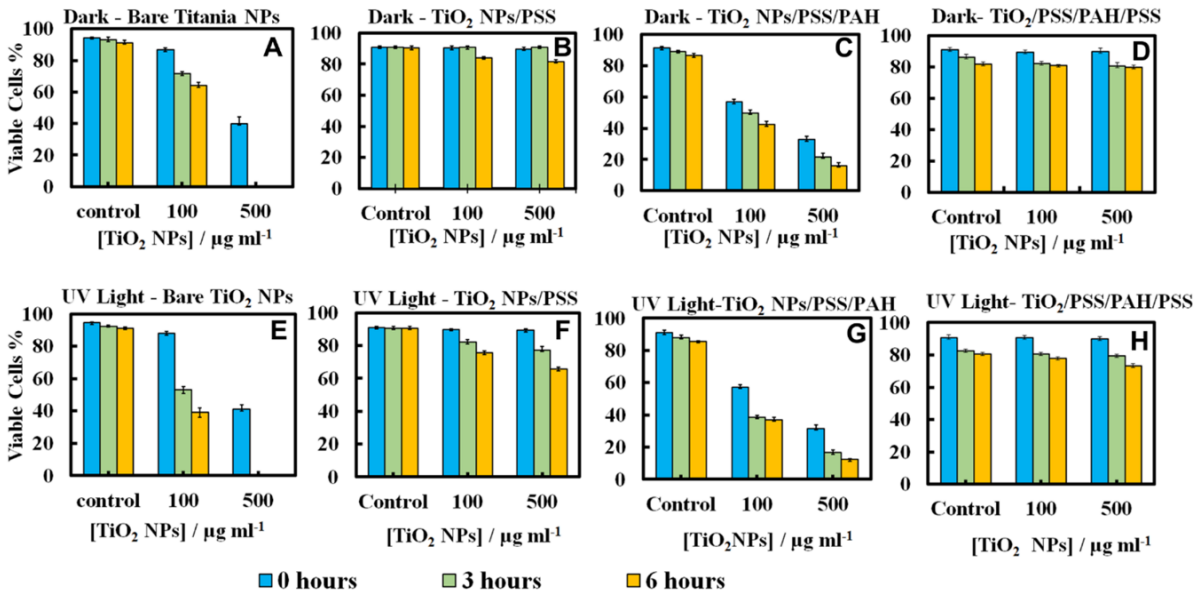

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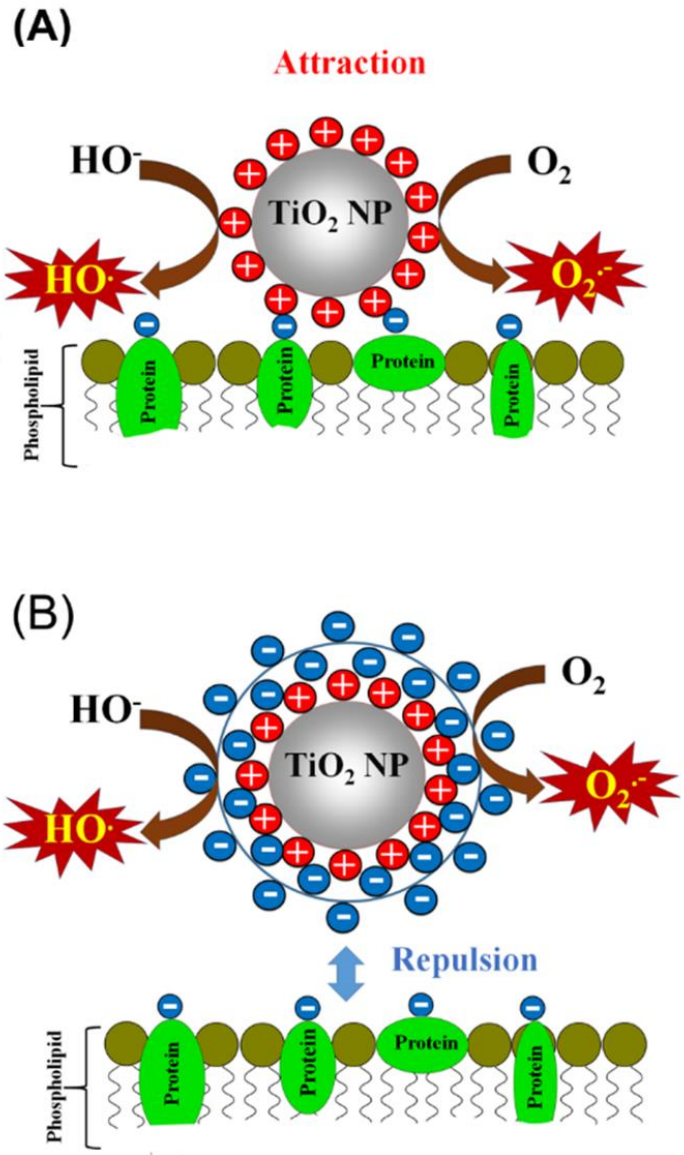

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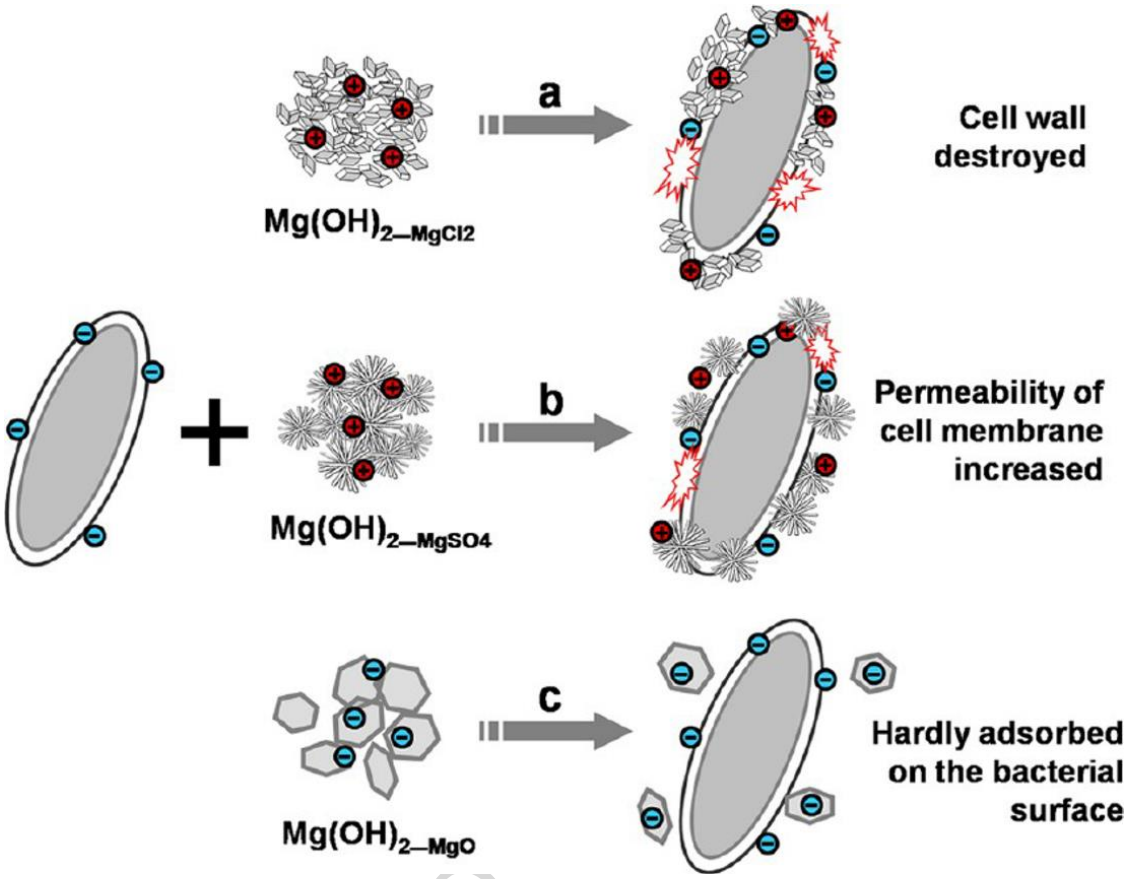

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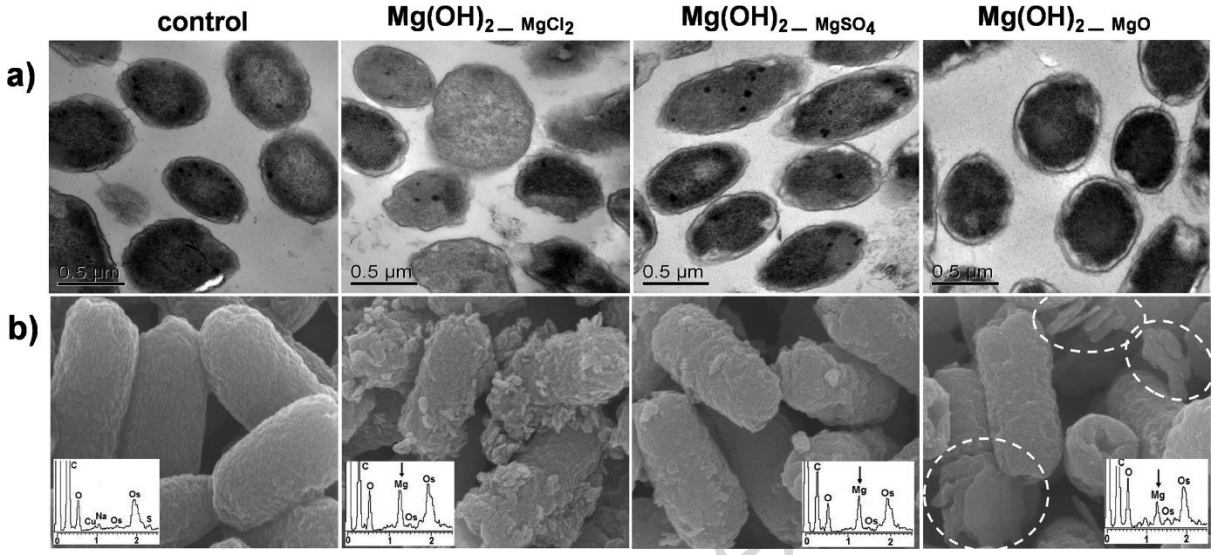

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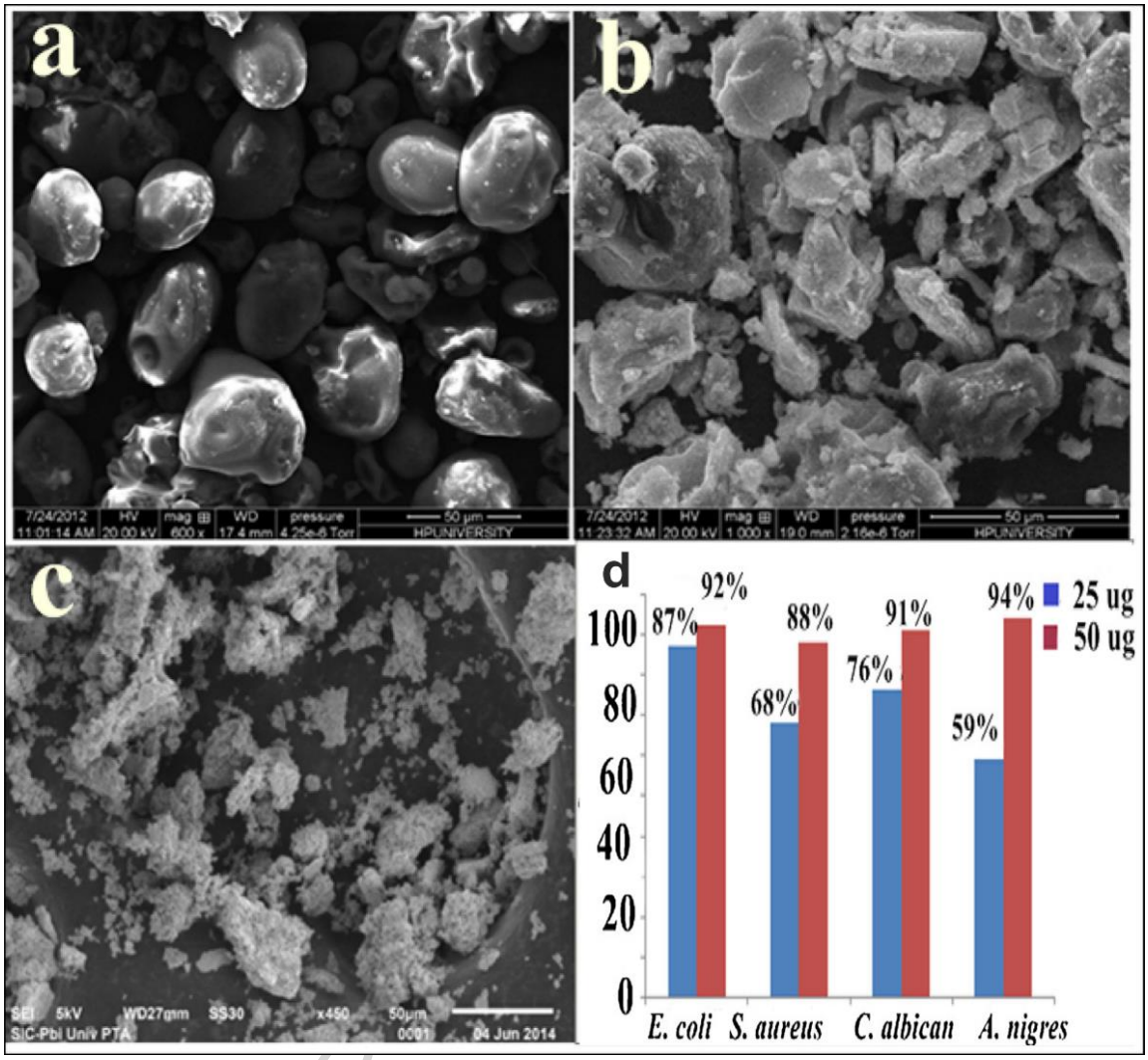

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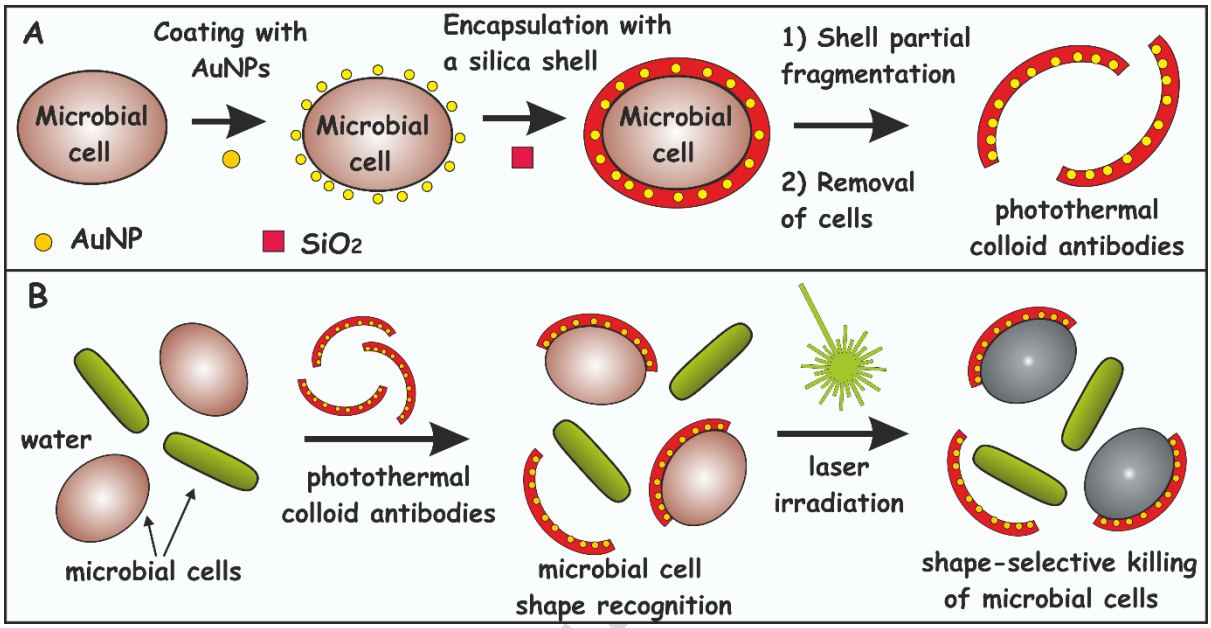

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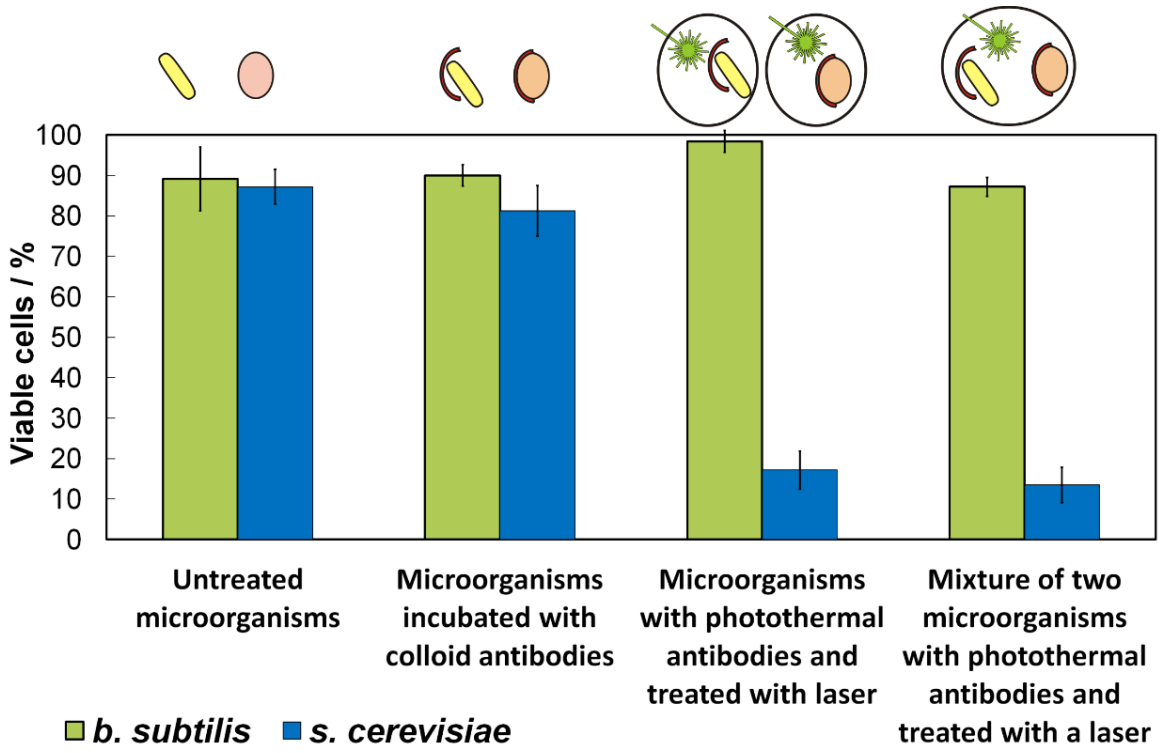

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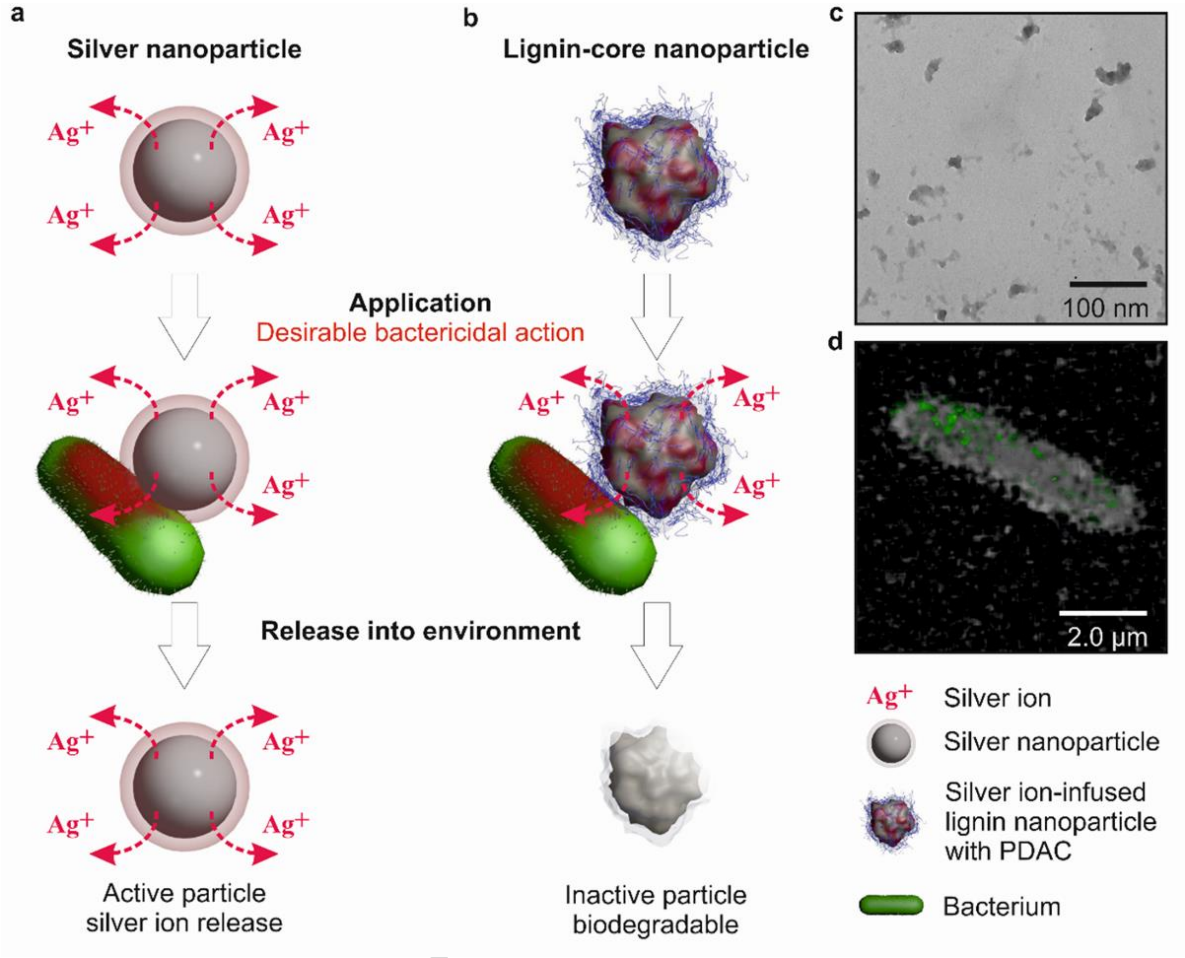

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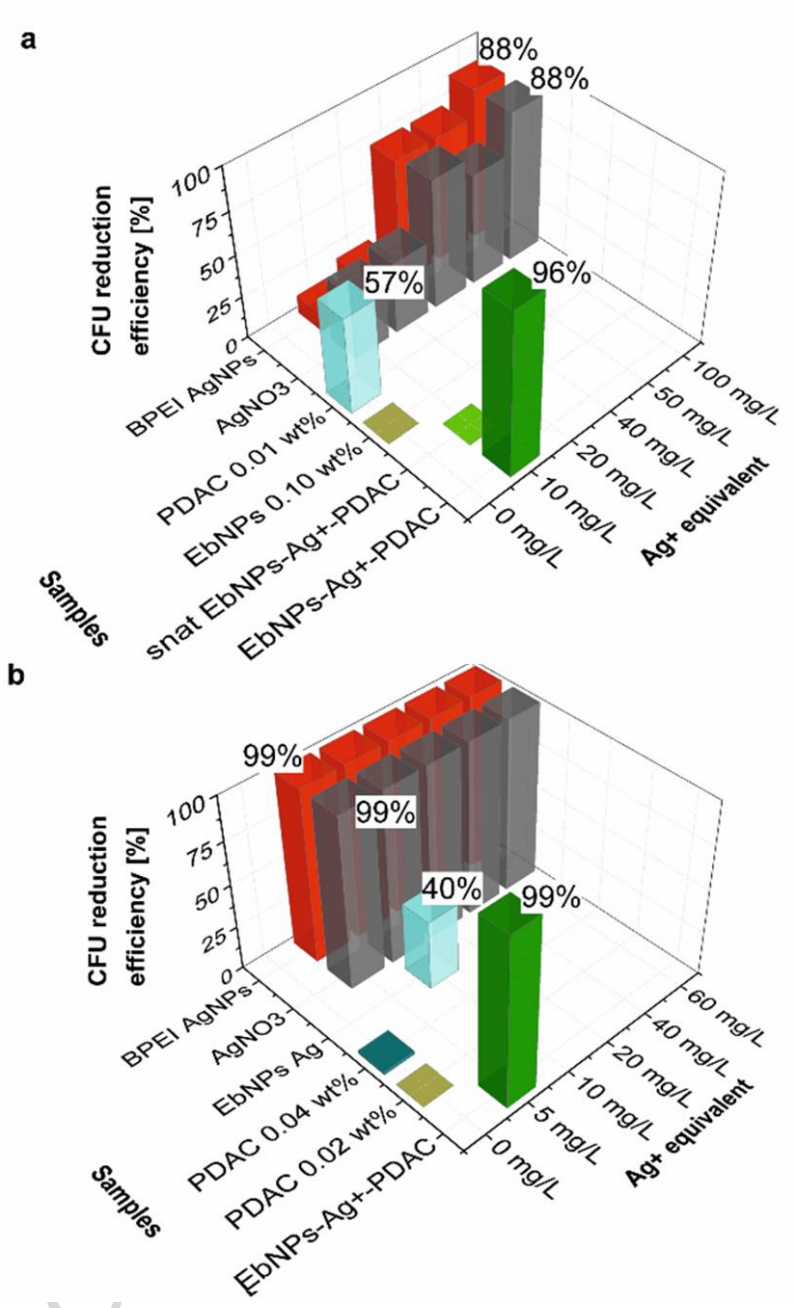

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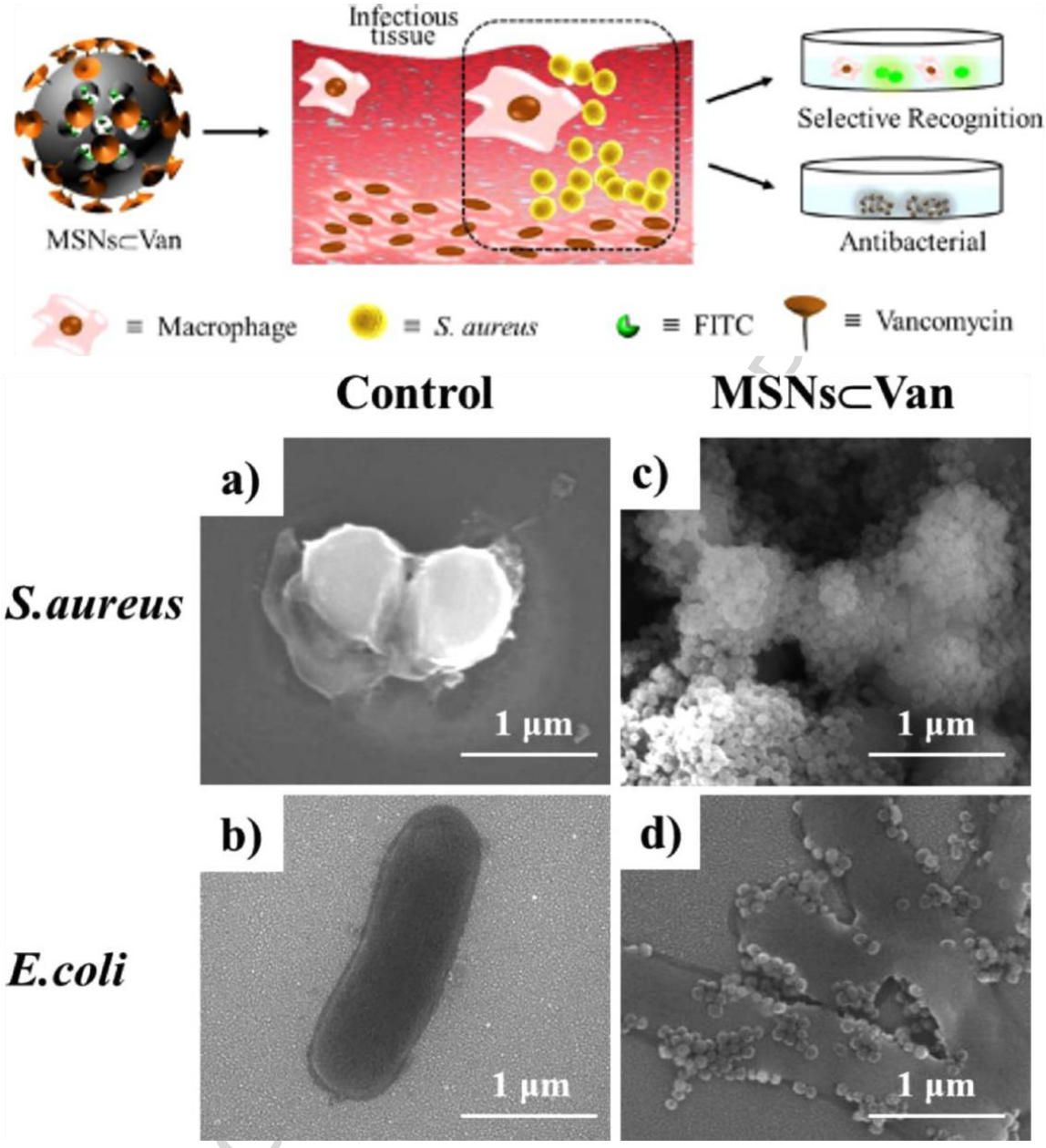

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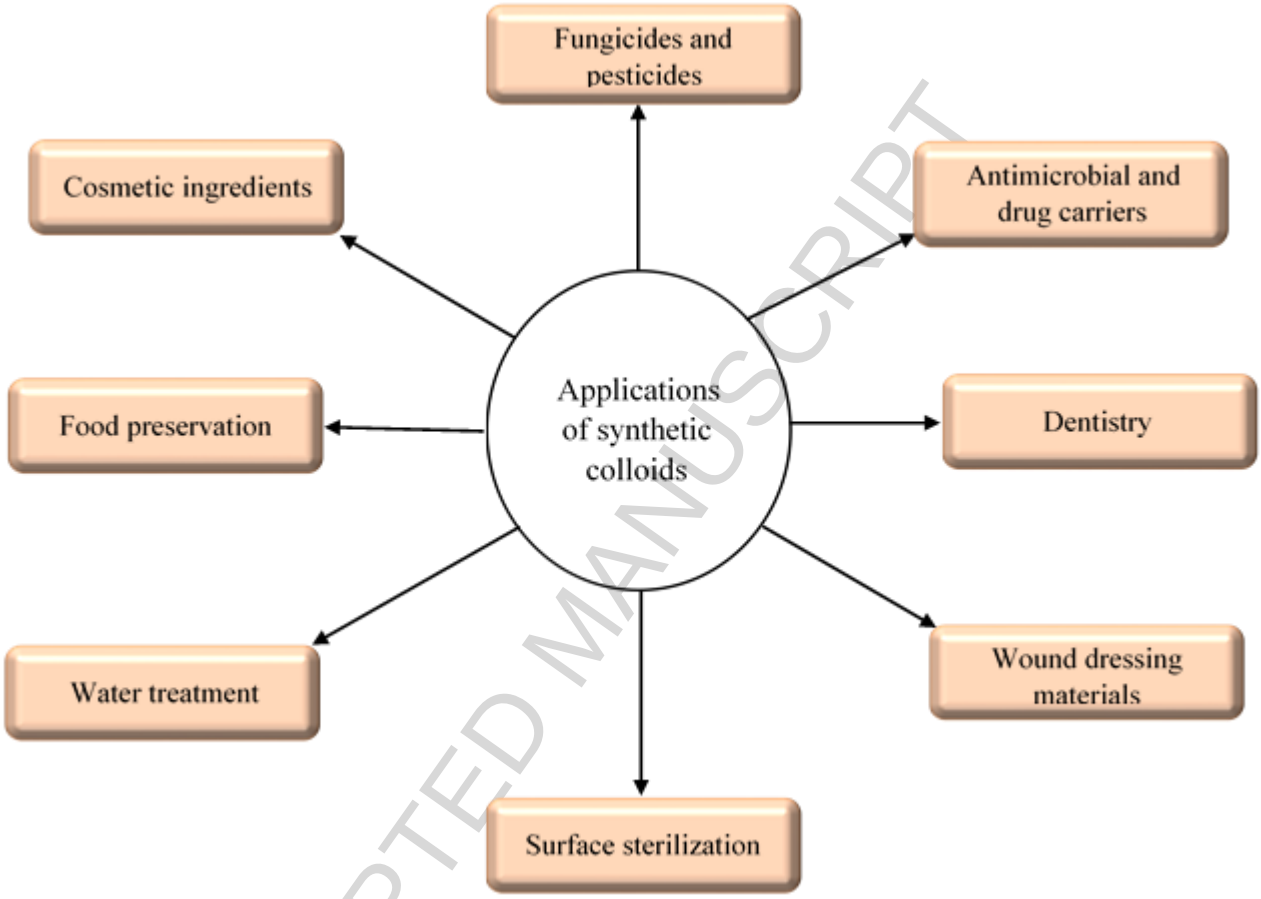

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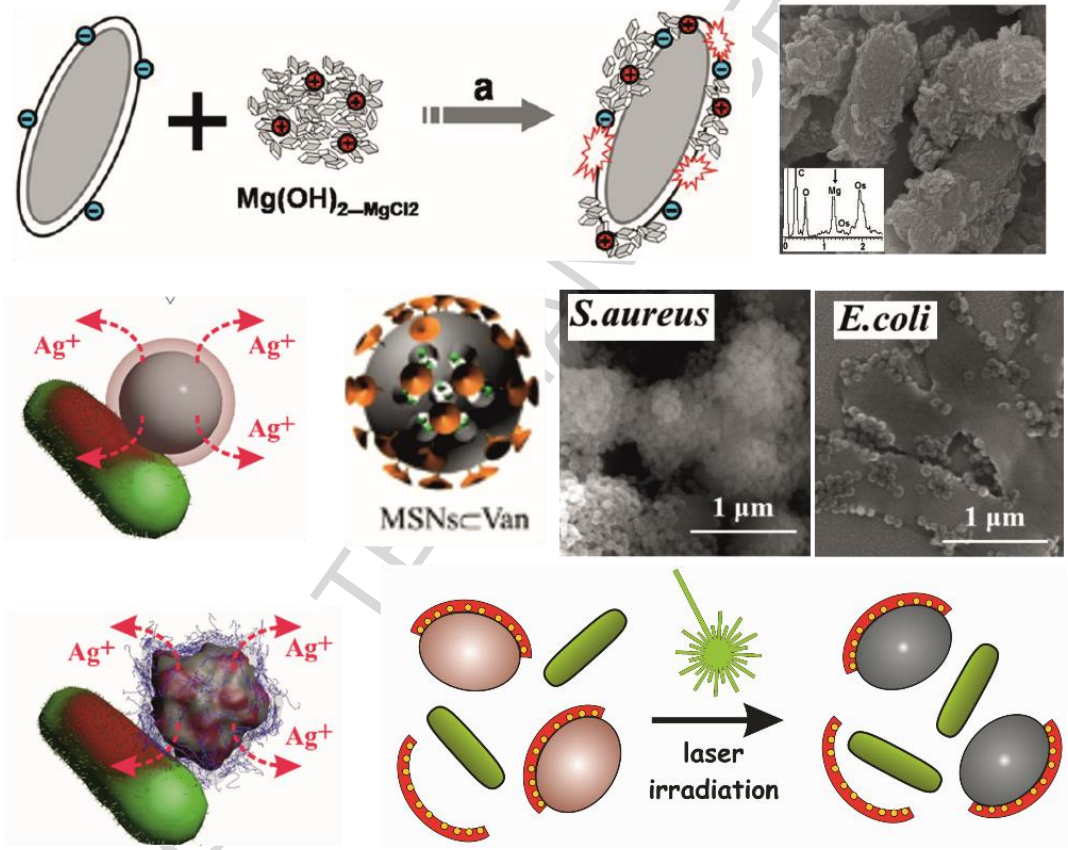
GRAPHICAL ABSTRACT

Colloid Particle Formulations for Antimicrobial Applications

Ahmed F. Halbus,[1] Tommy S. Horozov,[1] Vesselin N. Paunov*[1]

[1] *School of Mathematics and Physical Sciences (Chemistry), University of Hull, Hull, HU6 7RX, UK.*



This review focuses on various inorganic, organic and hybrid nanoparticles, and discussed their methods of preparation, mechanisms of antimicrobial action and applications.

Highlights

- Nanotechnoloy approaches that can potentially bypass antimicrobial resistance.
- Review of nanoparticles of universal antibacterial, antifungal and antiviral action.
- Mechanisms by which nanoparticles attack microbial cells or inhibit their growth
- Recent developments for targeted delivery of nanoparticle antimicrobials
- Using colloid antibodies for microbial cell shape and surface recognition
- Environmentally benign nanoparticles as a safer-by-design green antimicrobial nanomaterials