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Current approaches of managing microbial diseases: focus on nanosciences technique

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ABSTRACT

Nanoscience is a fast growing research area that focuses on producing and utilizing nano-sized particles, which are measured in nanometers. Recently, nanoparticles are used in various fields. Therefore, studies on the effect of nanoparticles on microorganisms are worthy of analysis. However, using many antimicrobial agents has been avoided because of their methodical harmful effect. Hence, this review paper focuses on the use of some nanomaterials to manage microbial diseases. The discussed nanomaterials as antimicrobial agents include silver nanoparticles, gold nanoparticles and copper nanoparticles. This review also explains the mechanisms of action of some nanotechnological products to inhibit microorganisms. There are many problems in the development of an evaluation for the effect of nanomaterials on environment. Nevertheless, the defect of the approaches used to analyze nanomaterials toxicity gives no ground for hampering the development of nanotechnologies for safety using. In order to overcome this problem, ecotoxicological studies should be extended to include the analysis of the biological safety of nanomaterials in environment and accumulate experimental data.

1. Introduction

Microorganisms are serious pests that cause losses of a wide range of different crops. Control of harmful effects of microorganisms growth is a necessity. Pests in Africa continue to limit food crop harvests. Predominantly, studies indicate that losses due to pests are estimated at 30% [1,2], but localized losses due to outbreaks of major migratory pests such as locusts and armyworms can be even greater, sometimes resulting in complete crop failure [3]. Additionally, plant-parasitic nematodes cause significant economic losses in a wide variety of crops [4]. Parasitic nematodes may reduce crop yield through their feeding and movement throughout roots [5]. Overall losses caused by plant-parasitic nematodes were estimated to exceed 100 billion US dollar per year worldwide including 10%-20% yield reduction in several cash crops [4]. Yield reductions caused by plant-parasitic nematode might become much higher due to restrictions imposed by the use of chemical nematicides and the voluntary removal of some nematicides from the market [6]. For example, the most widely used chemical nematicides, Nemacur

(fenamiphos), was cancelled in 2008 because of environmental concerns. Since then, effective alternatives have been limited. Also, biological control agents have disadvantage as they possess a narrow range of treatment effect and a lack of reliability under varying environmental conditions [7]. On the other hand, natural compounds produce several materials including essential oils that are biologically active in suppressing nematodes [8]. Finally, using nanoparticles is a prominent example of nano-sized materials being applied as a means of controlling pathogen microbes. For example, Silver nanoparticles have shown evidence of being potentially effective nematicide [9], and its toxicity is associated with induction of oxidative stress in cells of nematode [10].

2. Silver nanoparticles (AgNPs)

Among various antimicrobial agents, silver has been most extensively studied and used to fight against infections and prevent spoilage since ancient times [11]. Consequently, AgNPs are produced at the highest production volume. According to the Woodrow Wilson Database [12], there were more than 1300 nanotechnological consumer products on the market in March 2011. This popularity is explained by the fact that silver is the best conductor among the materials [13]. Moreover, AgNPs have favorable chemical and physical properties such as biocompatibility. Taking advantage of this, AgNP-based electrochemical biosensing systems were

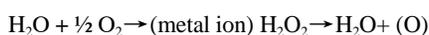
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developed that enable enhancing electron transfer between biomolecules, *i.e.*, proteins and electrode surface[14].

So, AgNPs are the most widely commercialized nanoparticles that are used as antimicrobials in various consumer products ranging from cosmetics, clothing, shoes, detergents, dietary supplements to surface coating in respirators. Water filters, phones, laptops, toys and commercial home water purification systems are examples of other products that benefited from AgNPs[15-17]. Indeed the antibacterial, antiviral, antifungal and antineoplastic properties of AgNPs are recognized[9,10,18].

AgNPs anti-microbial mechanism can be briefly explained as follows. Generally, metal ions destroy or pass through the cell membrane and bind to the SH group of cellular enzymes[19]. The consequent critical decrease of enzymatic activity causes micro-organism metabolisms change and inhibits their growth, resulting in the cell's death. The metal ions also catalyze the production of oxygen radicals that oxidize molecular structure of bacteria. The formation of active oxygen occurs according to this chemical reaction:



Such a mechanism does not need any direct contact between the anti-microbial agent and bacteria because the produced active oxygen diffuses from fiber to the surrounding environment. Therefore, metal ions inhibit the multiplication of micro-organisms. Bacteria are not permanently exposed to oxygen radicals and, thus, the ionic additive does not seem to facilitate the selection of resistant strains[20]. For example, attachment of Ag ions or nanoparticles to the bacteria because of electrostatic interaction with negative charge of bacterial cell wall are known as one of the mechanisms of cell death by Ag via rupturing cell membrane[21,22]. Moreover, nanomolar concentration of AgNPs can be efficient while Ag ions are needed at the micromolar level[22]. Also, Kim *et al.* reported that, the antimicrobial mechanism of AgNPs is related to the formation of free radicals and subsequent free radical-induced membrane damage. They confirmed that the antimicrobial activity of AgNPs was influenced by *N*-acetylcysteine. They have also suggested that free radicals that might have been derived from the surface of AgNPs were responsible for the antimicrobial activity through electron spin resonance[23].

3. Gold nanoparticles (AuNPs)

AuNPs are gaining recognition as a novel biomedical application. Yonezawa and Kunitake, have produced AuNPs stabilized with sodium (3-mercaptopropionate) via reduction of HAuCl₄[24]. AuNPs are used as carrier core coated antibiotics like streptomycin, gentamycin and neomycin. This result proved that gold nano-composites have an intense antibacterial efficiency against various Gram negative and Gram positive bacteria, *viz.* *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Micrococcus luteus*[25]. Also, Grace and Pandian concluded that metal nanoparticles may change the metabolite pathway and the release mechanism of bacterial cells. Thus, a better antibacterial efficiency can be obtained as a result of the strong efficiency of the Au/drug nano-composites[25].

AuNPs are formed by a variety of microorganisms. Though the common underlying mechanism involved in synthesis is reduction of Au⁺³ ions to form AuNPs, it has been postulated that the enzyme secreted by microorganisms play an important role in the reduction of metal ions, leading to nanoparticle nucleation and growth[26,27].

In spite of a large number of reports in microbial mediated AuNP synthesis, the mechanistic aspects have not been established and need to be investigated[28]. Such studies have been performed previously to explain the mechanism underlying AgNP synthesis, where the hydrogenase, proteins mediate and nitrate reductase mediate synthesis has been explained for this mechanism[29].

For example, in actinomycete *Thermomonospora*, enzymes were shown to play an important role in the reduction of metal ions as well as stability of nanoparticles, resulting in the efficient production of monodispersed AuNPs[30]. It has been hypothesized that proteins, polysaccharides and organic acids released by the fungi are able to differentiate crystal shapes and direct their growth into extended spherical crystals[31].

4. Copper nanoparticles (CuNPs)

CuNPs, due to their impressive properties, low cost preparation and many potential applications in catalysis, cooling fluid or conductive inks, have attracted a lot of interest in recent years[32]. Therefore, CuNPs were embedded into submicron particles of sepiolite [Mg₈Si₁₂O₃₀(OH)₄(H₂O)₄•8H₂O] and their anti-bacterial properties were compared with triclosan[33]. Also, Cubillo *et al.* reported strong bactericidal properties for both composite and triclosan[33]. However, the observation of Pape *et al.* confirmed that anti-bacterial activity of CuNPs is clearly less than that of AgNPs[34].

The most important and unique application area of CuNPs is electronics and technology (semiconductors, electronic chips, heat transfer nanofluids), as Cu ion has excellent thermophysical characteristics[35]. In addition, Sau *et al.* have been suggested other uses of CuNPs such as gas sensors[36], solar cells and lithium batteries[37]. CuNPs have been shown to inhibit the germination of microorganisms and to exhibit antiviral properties[38]. Also, CuNPs have been used in face masks, wound dressings and socks to capitalize on these biocidal qualities[39].

Cu ions were more toxic than CuNPs to all organisms except for yeast and mammalian cells *in vitro* as found by Kasemets *et al.*[40]. Consequently, this is an important finding showing that in mammalian cells *in vitro*, CuNPs may have an additional particle-specific intrinsic toxicity that is hard to predict using non-mammalian cell models. One may hypothesize that the particles are endocytosed and when already inside the cell their solubilization cannot be controlled by the mechanisms used to regulate the concentration of Cu ions in the cell. On the other hand, the toxicity assays with mammalian cells *in vitro* use serum that may disperse and coat nanoparticles[41], increasing their bioavailability to the cells. For yeast *Saccharomyces cerevisiae*, it was revealed that while the toxicity tests were conducted in protein-rich medium, CuNPs enhanced the Cu ion-associated stress. This is, assumingly, attributed to the stronger sorption of protein-coated nanoparticles onto the cell surface that was suggested to facilitate the dissolution of Cu in the close vicinity of the yeast cell wall. Noteworthyly, this effect was outstanding in complex organic medium, but not in distilled water[40].

5. Probable mechanisms of the effect of nanoparticles to inhibit microorganisms

Mechanism of action of nanoparticles toxicity is unclear. However, relatively well defined concepts are reported in the literature for some of them. For example, studies on the quantitative

uptake and accumulation of nanomaterials by whole organisms showed that nanoparticles mainly arrive into multicellular animals by ingestion and absorption through intestinal walls[42,43]. Some nanomaterials are capable of penetrating tissue barriers into cells and then interact with intracellular components[44,45]. Some types of nanomaterials (dendrimers of different degrees of generation) can disturb membrane structures and make them permeable[46]. It has been shown that nanoparticles can penetrate into cells in different ways. Some researchers observed simple diffusion through the cell membrane[47]. In addition, Shrivastava *et al.* found that the nanoparticles can modulate the signal transduction in bacteria[48]. It is a well established fact that phosphorylation of protein substrates in bacteria influences bacterial signal transduction. Dephosphorylation is noted only in the tyrosine residues of Gram negative bacteria. The phosphotyrosine profile of bacterial peptides is altered by the nanoparticles. It was found that the nanoparticles dephosphorylate the peptide substrates on tyrosine residues, leading to signal transduction inhibition and thus the halt of growth. It is nevertheless, necessary to understand that further research is required on the topic to thoroughly establish the claims[48].

As for higher plants, it is believed that the sensitivity of plants to nanomaterials is based on the capacity to filter and accumulate nanoparticles[49]. Some researchers relate the toxicity of these particles to changes in the penetrability of cell covers, whereas the adhesion of nanoparticles to the surface of cells affects the properties of membranes. It is not excluded that AgNPs penetrate the cell and damage their DNA and can release toxic Ag^+ ions during the interaction with the cell[50].

6. Effect of nanoparticles on the environments

There are conflicting opinions about the safety of nanoparticles for living objects. Some authors declare the complete harmlessness of nanomaterials, while others, on the contrary, express extreme concern over the distribution of products of new technologies and caution against this. This again emphasizes the poor knowledge and complexity of the identification of nanomaterials and their effects, not only in soil but also in aerial and aqueous environments and organisms[51]. At the present time products of nanoparticles derived from emerging technologies are viewed by the public in a more demanding perspective from the standpoint of safety and environment impact. In case of nanotechnology, the potential for exposure to nanoparticles will increase as the quantity and types of nanoparticles used in society grow[52]. The hazard of concentrated precipitates of nanoparticles for soil inhabiting and benthic organisms cannot be excluded. At this level, there are clear ideal of the hazard of nanoparticles and any general concepts of the possible mechanisms or theory explaining the effect of nanoparticles on living cells. Nevertheless, although researchers hold significant different views on the hazard of nanoparticles, most of them recognize the existence of this hazard[51].

7. Toxic effects of some currently used nanoparticles

Nanoparticles are already having an impact on environmental care, and it can be used in diverse domains. They play a major role in the field of nanotechnology. Their unique size-dependent characteristics make these materials superior and indispensable as they show unusual physical, chemical and biological properties.

Particularly, AgNPs possess potential antimicrobial activity against many pathogen microbes[53].

However, some studies claim that, nanosilver can cause adverse effects on the environment. There have been reports on how nanosilver cannot discriminate different strains of bacteria; hence, they can destroy microbes beneficial to the ecology[54]. There is evidence showing that silver ions cause changes in the permeability of the cell membrane to potassium and sodium ions at concentrations that do not even limit sodium, potassium, adenosine triphosphate, or mitochondrial activity[55]. The literature also proves that nanosilver can induce toxic effects on the proliferation and cytokine expression by peripheral blood mononuclear cells[56].

There are several accounts on the toxic effects of nanoparticles. Living cells in *in vitro* studies, were influenced by AgNPs by cytotoxicity and chromosome instability, oxidative stress, apoptosis, intracellular calcium transients, cell cycle arrest, and interference with DNA replication fidelity[57,58]. Additionally, free radical-induced oxidative stress and alteration of gene expression were reported in *in vivo* studies[59-61].

Among other adverse results, cytotoxicity and genotoxicity were observed in fish cells as caused by nanoparticles. Nanoparticles accumulate in gill tissue and bring about unfavorable effects including embryonic development of oyster, lysosomal destabilization of adult oysters, oxidative stress, double-strand break marker gamma-H2AX and the expression of p53 protein, embryonic morphological malformations in zebrafish[62,63].

The work of Burd *et al.* demonstrated that commercially available silver-based dressings (ActicoatTM, Aquacel[®], PolyMem[®], Urgotul[®]SSD) also show potential cytotoxic effect[64]. They assessed their cytotoxicity in various cultures and models such as monolayer cell culture, tissue explants culture model and mouse expurgated wound model. The results displayed that ActicoatTM and Aquacel[®] Ag, when pretreated with specific solutes, were likely to produce the most significant cytotoxic effect on both cultured keratinocytes and fibroblasts, while PolyMem[®] and Urgotul[®]SSD Ag demonstrated the least cytotoxicity. Cytotoxicity correlated with the silver released from the dressings as measured by the silver concentration in the culture medium[64]. The ecotoxicology literature shows that concentrations of AgNPs as low as just a few nanograms per liter can affect prokaryotes, invertebrates and fish resulting in a significant impact in spite of AgNPs poor characteristics[65].

8. Conclusion

Nanoparticles of Cu, Au and particularly Ag are deliberately used to suppress the growth of microorganisms. An analysis of literature shows that the evaluation of the implications of the nanoparticles distribution in the environment remains an open problem. This can be attributed to the lack of any guidelines and the absence of a consensus among researchers on experimental protocols or study designs in this field. This is aggravated by the unique properties of nanoscale materials, which cause problems during the toxicological assessment of novel nanomaterials. All of these factors give rise to conflicting and irreproducible results and slow down the progress of this field.

For these reasons, all mechanisms of the effect of any nanosized structures are not universally accepted theory with consideration for the structural characteristics of their surface and reactivity. Therefore, there is no reasoning for hampering the development

of nanotechnologies and the propagation of nanomaterials in environment taking into consideration the drawbacks of the methodological approaches used in toxicity analysis.

Conflict of interest statement

We declare that we have no conflict of interest.

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