International Journal of Antimicrobial Agents 49 (2017) 137–152

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Review

Metal oxide nanoparticles as antimicrobial agents: a promise for the future

Azhwar Raghunath, Ekambaram Perumal *

Molecular Toxicology Laboratory, Department of Biotechnology, Bharathiar University, Coimbatore 641 046, Tamil Nadu, India

ARTICLE INFO

Article history:
Received 29 July 2016
Accepted 11 November 2016

Keywords:
Antibiotic resistance
Antimicrobial agents
Mechanism of action
Metal oxide
Micro-organisms
Nanotoxicity

ABSTRACT

Microbial infectious diseases are a global threat to human health. Excess and improper use of antibiotics has created antimicrobial-resistant microbes that can defy clinical treatment. The hunt for safe and alternate antimicrobial agents is on in order to overcome such resistant micro-organisms, and the birth of nanotechnology offers promise to combat infectious organisms. Over the past two decades, metal oxide nanoparticles (MeO-NPs) have become an attractive alternative source to combat microbes that are highly resistant to various classes of antibiotics. Their vast array of physicochemical properties enables MeO-NPs to act as antimicrobial agents through various mechanisms. Apart from exhibiting antimicrobial properties, MeO-NPs also serve as carriers of drugs, thus barely providing a chance for micro-organisms to develop resistance. These immense multiple properties exhibited by MeO-NPs will have an impact on the treatment of deadly infectious diseases. This review discusses the mechanisms of action of MeO-NPs against micro-organisms, safety concerns, challenges and future perspectives.

1. Introduction

In the past two decades, the field of nanotechnology has grown exponentially since its birth and has made an immense impact on physical, chemical, earth and biological sciences [1–5]. There has been an immense extension of nanomaterial applications and uses as a result of basic and applied research from scientists all over the world. One such class of nanomaterials is metal oxide (MeO) nanoparticles (NPs), ranging in size from 1 to 100 nm and available in different shapes and sizes. MeO-NPs possess unique physical and chemical characteristics linked to their nanometre size, thus offering versatility. MeO-NPs are key constituents in catalysis, diagnosis, drug delivery, semiconductors, sensing and solid oxide fuel cells [6,7]. Beyond these uses, MeO-NPs are utilised as antimicrobial agents [8–10] and hence have received much attention recently.

Metal and oxygen elements combine to form MeOs where both high and low melting-point metals can be found. Based on their different electronic structures, MeOs exhibit metallic, semiconductor and insulator characteristics. Metallic and semiconductor MeOs are formed by the combination of oxides with metals from groups 3–12 of the periodic table, whereas insulator MeOs are formed from metals in groups 1, 2 and 13–18 [11]. The semiconductors are further classified into i-, n- and p-types [12]. Intrinsic semiconductors are i-type semiconductors having properties both of insulators and conductors. The n-types are electron-excess semiconductor oxides with free electrons as charge carriers and will have either excess cations or deficient anions. The p-types are electron-deficit semiconductors with a cation-deficient oxide and this cation vacancy provides the additional electrons for reactivity. These features confer unique chemical and physical properties to MeO-NPs through which they interact with biological systems [13]. The different properties of MeO-NPs are the major contributors to antimicrobial activity. The alkalinity of the calcium oxide (CaO) and magnesium oxide (MgO) NP surface is the significant component in conferring antimicrobial activity [14]. These alkali MeO-NPs are more soluble owing to their contribution to alkalinity in the medium, which cannot be found with MeO semiconductors such as neutral zinc oxide (ZnO) NPs [15]. The electrostatic nature of positively-charged cerium oxide (CeO_2) NPs determines their microbicidal property [16]. Titanium dioxide (TiO_2) NPs are semiconductor photocatalysts that can inhibit the growth of even ultraviolet (UV) radiation-resistant and desiccation-tolerant bacteria [17].

Infectious diseases are one of the main causes of mortality in the world and the hunt for antimicrobial agents without resistance is warranted. The spread of infectious diseases is a threat to the global population. The emergence of antibiotic-resistant and multidrug-resistant (MDR) strains both of Gram-positive and Gram-negative microbes is a public health concern. Such emergence of resistance is due to indiscriminate use of antibiotics, leading to the evolution of new antibiotic-resistant strains at a faster pace.

* Corresponding author. Molecular Toxicology Laboratory, Department of Biotechnology, Bharathiar University, Coimbatore 641 046, Tamil Nadu, India. Fax: +91 422 242 5706.
E-mail address: ekas2009@buc.edu.in (E. Perumal).

http://dx.doi.org/10.1016/j.ijantimicag.2016.11.011
0924-8579/

MeO-NPs offer promise as antimicrobial agents against a broad spectrum of micro-organisms, including drug-resistant strains. However, knowledge of the antimicrobial activity of MeO-NPs is crucial as antibiotic resistance to conventional anti-Gram-negative agents is on the rise and poses a great challenge to humans. This necessitates the development of new antimicrobial agents required in antimicrobial therapy, food industries, water purification and textile industries. The availability of many different MeO-NPs with diverse physicochemical and functional properties makes them good antimicrobial agents as an alternative to conventional antibiotics. MeO-NPs serve as better antimicrobial agents compared with traditional anti-infectious agents owing to their high surface area-to-volume ratio; with modifications in this parameter, MeO-NPs with novel chemical, electrical, magnetic, mechanical and optical properties can be developed [18]. The antimicrobial efficacy is defined by the size of the particle, the aqueous medium used and light intensity. A variety of MeO-NPs have been explored for their antimicrobial properties. Alterations or destruction of the cell wall as well as enzyme and nucleic acid pathway disruption are chief mechanisms [19]. These mechanisms are completely different from those employed by antibiotics. Antibiotics target bacterial cell wall synthesis, DNA-directed RNA polymerase, DNA gyrase, DNA replication, folic acid metabolism and protein synthesis. Bacteria are capable of developing resistance against these mechanisms by one or more means, but the modes of action exhibited by MeO-NPs are completely different from those manifested by antibiotics. MeO-NPs induce cellular damage in prokaryotic cells [20] through altering cellular processes both at the biochemical and molecular levels [21]. Hence, MeO-NPs offer promise as antimicrobial agents. However, knowledge on antimicrobial mechanisms is in its infancy and is growing steadily. In this review, we summarise the synthesis, microbicidal mechanisms and toxicity concerns of MeO-NPs (Table 1).

2. Synthesis of MeO-NPs

The method of synthesis determines the properties and applications of MeO-NPs. In the determination of antimicrobial activities of MeO-NPs, most researchers preferred chemical methods over commercially available MeO-NPs and here we briefly described the commonly used methods.

2.1. Chemical

The most preferred chemical method involves the reaction mixture (high-boiling solvent, precursors and surfactants) being slowly heated to a high temperature during the synthesis process. Highly monodisperse MeO-NPs are produced during this method and the major steps are monomer formation and accumulation, nucleation, and growth [97]. The size and diameter of the particles are controlled by the growth process and solvent boiling point, respectively. Cadmium oxide (CdO), CeO_2, iron III oxide (Fe_2O_3), MgO, ZnO, vanadium pentoxide (V_2O_5), TiO_2, iron (II, III) oxide (Fe_3O_4) and graphene oxide NPs have been chemically synthesised and examined for their antimicrobial potential.

2.2. Biosynthesis

Plant extracts or microbial secretions with precursor compounds are stirred constantly on a magnetic stirrer at 100–120 °C for 24 h to facilitate the formation of MeO-NPs [35]. The resultant mixture is centrifuged and the supernatant is discarded. The pelleted MeO-NPs are dried naturally in a watch glass. Copper oxide (CuO), Fe_3O_4 and ZnO NPs have been biosynthesised and assayed for their microbicidal activities.

2.3. Sol-gel

This wet route method involves the condensation and hydroxylation of precursor molecules. The crystalline nanostructures obtained are influenced by the gel properties. In addition, agitation, concentration of precursors, pH and temperature of the gel regulate the hydrolysis and condensation reactions [98]. A predetermined nanostructure with monodisperse and amorphous phases can be obtained. The homogeneity of the reaction products can be controlled [99]. NPs such as TiO_2 and ZnO have been prepared and assayed for their bactericidal activities.

2.4. Co-precipitation

In co-precipitation, a salt precursor is converted into its respective metal hydroxide in an aqueous medium with the addition of ammonium hydroxide or sodium hydroxide. The chloride salts obtained are washed, whilst hydroxides are removed by heating to obtain the desired MeOs. Co-precipitation involves brief nucleation followed by nuclei growth onto the crystal surface through solute diffusion [100,101]. The size and size distribution cannot be controlled owing to the kinetic factors, but can be adjusted by alteration of the nature of the salts used, ionic strength, pH and temperature. Fe_3O_4 and ZnO NPs have been obtained and their antimicrobial activities have been tested.

2.5. Electrochemical

This method uses electrolyte solutions with a two-electrode setup where the bulk metal will be kept in anode and transformed into metal clusters [38,102]. To stabilise the metal clusters, tetraalkylammonium salts are used as supporting electrolyte. Electrolysis is carried out in a nitrogen atmosphere to remove the dissolved oxygen, and the metal cations migrate to the cathode whereas the bulk metal is oxidised at the anode. The residual oxygen in the electrolytic bath oxidises the metal into respective MeOs. Ammonium stabilisers prevent agglomeration with metal powders. The current density controls the cluster size. Chromium(III) oxide (Cr_2O_3), CuO and CuO multi-armed NPs have been synthesised and their toxic effects on micro-organisms have been validated.

2.6. Wet chemical

The wet chemical route is a simple and cost-efficient method [103] and employs any surface irrespective of shapes and curves with wide applicability. The precursors are mixed in ultrapure water and are stirred for 30 min, combined and heated for 45 min, and collected by centrifugation. CuO nanorods, Fe_3O_4 and ZnO NPs have been produced and tested against micro-organisms.

2.7. Pyrolytic

The primary step in this technique is to atomise the solution and to mix with soluble polymers and integrate into the porous matrix before heating the precursor molecules. These steps prevent growth during sintering, aggregation and agglomeration. The MeO-NPs along with the matrix can act as catalyst as such. However, this technique is not good for composite MeO-NP synthesis. Cobalt oxide (Co_3O_4) NPs have been prepared [32] and their bactericidal activity has been tested.

2.8. Microwave

In this simple benchtop method, the precursors are dissolved in deionised water separately and are made into a mixture of 100 mL solution followed by stirring continuously for 10 min at room