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Mechanism of Action of Antibacterial Activity of Biosynthesised Zinc Oxide Nanoparticles - A Review

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Now-a-days, nanotechnology has become increasingly important in the biomedical and pharmaceutical antimicrobial strategy due to their wide spectrum of action at nano-scale level. Antibacterial agents are very important in the textile industry, water disinfection, medicine, food packaging *etc*. This review focuses on the synthesis and mechanism of antibacterial activity of zinc oxide nanoparticles (ZnO NPs). The antibacterial activity of ZnO NPs is determined by the mode of synthesis, organisms used, size of the nanoparticles *etc.* The variations in the antibacterial activity of ZnO NPs are mostly attributed to their high specific surface area-to-volume ratios and their distinctive physicochemical properties.

Keywords: Nanoparticles; biosynthesis; ZnO; antibacterial; mechanism.

1. INTRODUCTION

Nanoparticles are microscopic particles with at least one dimension less than 100 nm. Nanoparticles are of great scientific interest because they bridge the gap between bulk materials and atomic or molecular structures. Nanoparticles can be broadly grouped in two categories namely organic and inorganic nanoparticles. Organic nanoparticles include

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carbon nanoparticles (fullerenes) while the inorganic nanoparticles include magnetic nanoparticles, noble metal nanoparticles like gold and silver and semiconductor nanoparticles like titanium oxide and zinc oxide. Inorganic nanoparticles have created great interest among the researchers, as they provide superior material properties with functional versatility [1].

Nanoparticle research is an area of intense scientific research due to the wide variety of potential applications such as in biomedical, optical and electrical fields. These have mostly been formed in chemical reactions either by combustion or by condensation [2]. Nanoparticles are expected to form the basis of many of the technological and biological innovations of this century, exhibiting distinct advantageous physical, chemical and biological properties and hybrid techniques. The synthesis of nanoparticles with specific morphologies and properties has been one of the most important aspects of nanoscience which studies material whose size lies within the nanometer range (1 nm=10^{-9} m). These nanostructures have been used in catalysis, sensors, water purification, antibacterial and nano-electronics. The noble metals such as gold, silver and platinum have been widely applied in products that directly come in contact with the human body such as detergent, soaps, cosmetic products and toothpaste besides medical and pharmaceutical applications [3].

2. ZINC OXIDE NANOPARTICLES

Zinc oxide nanoparticles (ZnO NPs) are unstable, easily agglomerates and are very difficult to recycle after use. Preventing the agglomeration of these nanostructures is the key factor for preserving the high photoactivity of nanoscale photocatalysts, low level or even absence of agglomerations suggest that the Critical Coagulation Concentration of the nanoparticles will correlate positively with the specific surface area, *i.e*. particles with higher specific surface area exhibited higher stability. Furthermore, the strong dependence on the specific surface area indicates that, it is the surface chemistry rather than the bulk properties that dominated in the microstructure [4].

To reduce or overcome the problem of agglomeration, one of the most efficient methods is to use of semiconductor-based hetero structures with desirable compositions and/or morphologies. The properties of these semiconductors have been modified by adding noble metals with complementary properties to form core-shell, hetero, and/or doped structures [5]. Zinc oxide nanomaterials are non-toxic with wide band gap has been identified as a potential semiconducting material for exhibiting room temperature ferromagnetism when doped with transition metals [6]. Doping of transition metals into zinc oxide nanoparticles have been considered to be an effective method to fine-tune the energy level structure of the host which can be further improved by the different concentrations of the dopants leading refining the optical properties [7].

Highly ionic nanoparticulate metal oxides (ZnO NPs) are unique in that they can be produced with high surface areas and unusual crystal structures. Compared to organic nanomaterials, inorganic nanomaterials such as ZnO possess superior durability, greater selectivity and heat resistance. It is known that the green synthesis of ZnO nanoparticles is much safer and environmentally friendly as compared to chemical synthesis [8]. The size of the synthesised ZnO nanoparticles was in the range of 60-70 nm. The larger nanoparticles of ZnO resulted from the agglomeration of smaller nanoparticles. Generally, Biological synthesis methods of ZnO nanoparticles have shown more attractive benefits relative to the conventional chemical synthesis methods.

3. BIOLOGICAL SYNTHESIS OF ZnO NPs

Biological methods emerged as an alternative to the conventional methods for synthesis of NPs. Synthesis of inorganic nanoparticles by biological systems makes nanoparticles more biocompatible and environmentally benign. Moreover, the process is cost effective too. Many bacterial, as well as fungal species, have been used for zinc oxide nanoparticles synthesis. This synthesis always takes longer reaction times and demands subsequent extraction and recovery steps. On the contrary, in plant extract mediated synthesis such as the modified oxalate method [6] and the -mangosteen leaf extract [9], the reaction times have been reported to be very short compared to that of microbial synthesis. Most importantly, the process can be suitably scaled up for large scale synthesis of NPs [10]. Green synthesis provided advancement over chemical and physical method as it is cost effective, environment friendly, easily scaled up for large-scale synthesis furthermore, there is no need to use high pressure, energy, temperature and toxic chemicals. Using plants for nanoparticle synthesis is advantageous over other biological processes because it eliminates the elaborate process of maintaining cell cultures and can also be suitably scaled up for large-scale synthesis of nanoparticles under non- aseptic environment [9].

The ‘‘bio - synthesis’’ of metallic nanoparticles receives more attention due to their uncommon optical, photo-chemical, chemical and electrical properties [11]. The bio - methods of nanoparticle synthesis using biological entities like bacteria, yeast, fungi and plants are stated to be clean, nonhazardous, in-expensive and environmentally tolerable when compared to chemical methods. The use of microorganisms or plant-based biomimetic methods consumes very little energy, generate very little pollution and mostly operate under conditions of normal temperature and pressure [12]. Among the several biological methods of nanoparticle synthesis, microbe facilitated synthesis of nanoparticle is, however, not commercially viable as they involve maintenance of highly hygienic conditions and very complex processes of maintaining microbial cultures. Additionally, the microorganisms require a relatively longer incubation time for the reduction of metallic ions as compared to plants which attained such education in a much shorter time due to the presence of water soluble phytochemicals which act as reducing agents [13,14,15].

4. ANTIBACTERIAL ACTIVITY OF ZnONPs

The antimicrobial activity of nanoparticles has been studied largely with human pathogenic bacteria, mainly *E. coli* and *S. aureus* [16]. The ZnO NP is currently being considered as an antibacterial agent in both micro as well as nano scale formulations [17]. Results have specified that ZnO nanoparticles show antibacterial action apparently better than micro particles. However, the exact mechanisms of the antibacterial action have not yet been clearly understood though it has been advised that the rule of reactive oxygen species (ROS) produced on the surface of the particles (zinc ion) release membrane dysfunction and nanoparticles internalization are the main reason of cell swelling. Disc diffusion method was used for the assessment of antibacterial activity of ZnO nanoparticles against *Bacillus subtilis* [18]. The zone of inhibition was more for both ZnO nanoparticles and antibiotics like nitrofurantoin, tetracycline, nalidixicacid, gentamicin and methicillin.

Zinc oxide exhibited the antibacterial activity like many other metal oxide groups and like the others only few have been scaled down to the nano size. The advantage of using inorganic oxides such as zinc oxide as antimicrobial agents is that they contain mineral elements essential to humans and exhibit strong activity even when administered in small amounts. ZnO nanoparticles exhibited strong antibacterial activities on a broad spectrum of bacteria [19]. The antibacterial activity of antibiotics along with ZnO nanoparticles was investigated against pathogenic bacterium, *Proteus vulgaris* using disc diffusion technique [20]. *Proteus vulgaris* was resistant against penicillin and ampicillin but the highest increase in the inhibition zones (antibiotic with ZnO nanoparticles) were observed for erythromycin. The moderate increase in inhibition zones were against penicillin followed by Ampicillin in combination with ZnO nanoparticles.

Antibacterial properties of ZnO nanoparticle of *E. coli, P. aeruginosa* and *S. aureus* was reported [21]. Antibacterial properties of nanoparticle increased with increase in concentration of nanoparticles [22]. In both Gram positive and Gram negative bacteria, cell wall and cell membrane are crucial in maintaining the osmotic balance and integrity of cell. Damage of bacterial cell integrity could be the reason in present study [23]. Based on the results obtained from disc and well agar diffusion methods, it can be suggested that in comparison with Gram-positive bacteria, the growth of gram-negative bacteria is inhibited at higher concentrations of ZnO nanoparticles. It has been proposed that the higher susceptibility of Gram-positive bacteria could be related to differences in cell wall structure, cell physiology, metabolism or degree of contact [24]. The results of time-dependant antibacterial activity of ZnO nanoparticles showed that cfu of the tested bacteria for each concentration decreased gradually during 72 h, whereas colony formation of control solution remained uncountable [25].

Significant differences were observed between antibacterial activities of bulk ZnO. The antibacterial efficacy increased with decreasing particle size from bulk ZnO to white ZnO nanoparticles, Particle concentration seems to be more effective on the inhibition of bacterial grown than particle size under the condition of this work [26]. The enhanced bioactivity of smaller particle probably is attributed to the higher surface area to volume ratio [27]. ZnO nanoparticles are effective antibacterial agents both on Gram-positive and Gram-negative bacteria. The same results were confirmed in the study of [28] in which Gram-negative membrane and Gram positive membrane disorganisation was approved by transmission electron microscopy of bacteria ultrathin sections.

5. MECHANISM OF ANTIBACTERIAL ACTIVITY of ZnO NPs

Antibacterial activity of biological synthesised ZnO nanoparticles was seen against Gram negative (*Pseudomonas aeruginosa, Klebsiella pneumoniae, E. coli, Proteus vulgaris*) and Gram positive (*Staphylococcus aureus*) bacteria [29]. The zone of inhibition of ZnO nanoparticles against Gram negative and Gram positive bacteria was measured and the results indicated that ZnO nanoparticles synthesised from *Murraya koenigii* extract showed effective antibacterial activity both in Gram negative and Gram positive bacteria. Therefore, the mechanism of inhibition of bacterial growth by ZnO nanoparticles could be attributed to damage of the bacterial cell membrane and extrusion of the cytoplasmic contents thereby resulting in the death of the bacterium.

The antimicrobial activity of the ZnO nanoparticles was tested against gram negative bacteria S*almonella typhi* and *Klebsiella pneumonia* [30]. The results for the antimicrobial activity of ZnO (chemical) and green ZnO indicated that green ZnO showed excellent antibacterial activity against *Salmonella typhi* and *Klebsiella pneumoniae.* The remarkable antimicrobial activities of green ZnO nanoparticles are due to the generation of surface oxygen species which leads to the killing of the pathogens while the enhanced antibacterial activity is attributed to surface defects on ZnO abrasive surface texture. One functional application of the ZnO antibacterial bioactivity was discussed in food packaging industry where ZnO NPs are used as an antibacterial agent toward food borne diseases [31]. Proper incorporation of ZnO NPs into packaging materials can cause interaction with food borne pathogens, thereby releasing NPs onto food surface where they come in contact with bad bacteria and cause the bacterial death and/or inhibition. Antibiotics such as Amikacin, Gentamicin and ciprofloxacin were impregnated with Zinc oxide nanoparticles synthesied from *Ficus carica* which showed good activities against *Staphylococcus aureus*, *Proteus*, *Acinetobacter*, *Pseudomonas aeruginosa* and *Escherichia coli* [32]. Antimicrobial susceptibility showed that most of the bacterial isolates were resistant towards antibiotics that became sensitive after nanoparticles application. Nano-sized ZnO exhibited varying morphologies and showed a significant antibacterial activity over a wide spectrum of bacterial species explored by a large body of researchers. ZnO is currently being investigated as an antibacterial agent in both microscale and nanoscale formulations. ZnO exhibited significant antimicrobial activities when particle size is reduced to the nanometer range, then nano-sized ZnO interacted with bacterial surface and/or with the bacterial core where it entered inside the cell and subsequently exhibited distinct bactericidal mechanisms [33].

The properties of ZnO nanoparticle are strongly influenced by the particle size and mechanism of cell inhibition. The properties include disruption of cell membrane, altering the permeability, electrostatically binding to the cell surface and accumulation of nanoparticle in cytoplasm [34]. Nanoparticles of pure and copper - nitrogen co - doped ZnO were used for studying their antibacterial and antifungal activity. *E.coli, Pseudomonas* and *Aspergillus* were used for bacterial and fungal strains [35]. The bacterial strain as well as fungal strain was injected to form the active strain by using well diffusion method. The oxy radicles were highly accountable for the death of bacteria and also prevent from the further attack of bacteria. The released peroxides sheltered the ZnO nanoparticles.

Antimicrobial activity of zinc oxide nanoparticles was known from the very distant past and has many applications in disinfecting medical devices, water purification and wound healing, creams, lotions and antibacterial creams. Zinc oxide is one of the nanoparticles which are used in an industrial scale in many countries. The mechanism of action of zinc oxide is similar to other nanoparticles, but it acts mostly through destruction of bacterial walls. Zinc oxide nanoparticles have been widely used against Gram-positive and Gram negative bacteria [36]. Nano-sized ZnO exhibits varying morphologies and shows significant antibacterial activity over a wide spectrum of bacterial species explored by a large body of researchers [37-41]. ZnO is currently being investigated as an antibacterial agent in both microscale and nanoscale formulations. ZnO exhibits significant antimicrobial activities when particle size is reduced to the nanometer range, then nano-sized ZnO can interact with bacterial surface and/or with the bacterial core where it enters inside the cell and subsequently exhibits distinct bactericidal mechanisms [42]. The interactions between these unique materials and bacteria are mostly toxic and have been exploited for antimicrobial applications such as in food industry.

Interestingly, ZnONPs are reported by several studies as non-toxic to human cells [43], this aspect necessitated their usage as antibacterial agents, noxious to microorganisms and hold good biocompatibility to human cells. The various antibacterial mechanisms of nanomaterials are mostly attributed to their high specific surface area-to-volume ratios [44], and their distinctive physicochemical properties. However, the precise mechanisms are yet under debate, although several proposed ones are suggested and adopted. Investigations on antibacterial nanomaterials, mostly ZnO NPs, would enhance the research area of nanomaterials and the mechanisms and phenomenon behind nano structured materials. The functional activities of nanoparticles are heavily influenced by the size of the particles against *Staphylococcus aureus*. The data clearly suggest that nanoparticles with smaller particle sizes showed more than 95% growth inhibition at 1 mM of ZnO nanoparticles with concentration, whereas larger particles showed only 40−50% growth inhibition as compared with the control [45].

Synthesis and growth techniques lead to holding numerous active facets in NP. Rod-structures of ZnO have (111) and (100) facets, whereas spherical nanostructures mainly have (100) facets. High-atom-density facets with (111) facets exhibit higher antibacterial activity [46]. The facet-dependent ZnO antibacterial activity has been evaluated by few studies, and nano structured ZnO with different morphologies have different active facets, which may lead to enhanced antibacterial activity [47]. In this regard, the shape of ZnO nanostructures can influence their mechanism of internalisation such as rods and wires penetrating into cell walls of bacteria more easily than spherical ZnO NPs [48]. Whereas, flower-shaped have revealed higher biocidal activity against *S. aureus* and *E. coli* than the spherical and rod-shaped ZnO NPs [49]. In addition to the enhancement of internalisation, it has been suggested regarding the contribution of the polar facets of ZnO nano structured to the antibacterial activity, that the higher number of polar surfaces possess higher amount of oxygen vacancies. Oxygen vacancies are known to increase the generation of ROS and consequently affect the photocatalytic of ZnO [50].

6. CONCLUSION

The review is aimed to discuss and analyse research works carried out by Researchers with references to the nature and potential use of Zinc oxide Nanoparticles (ZnO NPs) for antibacterial activity. The extensive discussion is focused on the mechanism of antibacterial activity of ZnO NPs against various bacterial species specifically pathogenic strains. Further, the review also connected with a number of factors that influencing the nature of antibacterial activity. The influencing factors include the size and shape of the ZnO NPs that is coupled with the mode of action of antibacterial activity. The present review will helpful in the various fields / industries for betterment use of ZnO NPs as a best antibacterial agent.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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