JOURNAL OF COMPLEMENTARY MEDICINE RESEARCH, 2020
VOL 11, NO. 5

RESEARCH ARTICLE

Open Access

Antimicrobial, anti-inflammatory and anticancer potential of Microbes mediated zinc oxide nanoparticles

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ABSTRACT

In current days, research on zinc oxide nanoparticles (ZnO NPs) have been added incredible consideration recognized to their distinctive properties. Remarkably, ZnO NPs exhibit the antimicrobial potential, further, it may be depends upon nanoparticle shape and size. Generally ZnO NPs synthesis by different physical and chemical methods and these process are more expensive as well is not environmentally eco-friendly. On the other hand, the microbial mediated ZnO NPs synthesis have been rapidly studied recently since microbial particles are cleaner, nor toxic, eco-friendly and biocompatible nature. Further, ZnO-NPs showed attractive antimicrobial effects due to enlarged particular surface area as the condensed particle size major to improved particle surface reactivity. Therefore, many researchers are interested in microbial ZnO-NPs and their bioactive potential studies. In this review, we have covered the microbial ZnO NPs synthesis and their antimicrobial, anti-inflammatory and anti-cancer prospective.

ARTICLE HISTORY

Received October 03, 2020
Accepted November 15, 2020
Published December 12, 2020

KEYWORDS

metal oxide nanoparticles, biosynthesis, bacteria; Antimicrobial, Characterization

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INTRODUCTION

The zinc oxide nanoparticles have been synthesized using different microbes such as bacteria, fungi, micro algae and etc (Malarkodi et al. 2014, Rajeshkumar et al. 2018, Bharathi et al. 2020, Francis et al. 2020). The different microbes having various biomolecules involved in the zinc oxide nanoparticles with different precursors (Sujatha et al. 2018, Akshaya et al. 2020, Devi et al. 2020, Rajeshkumar et al. 2020). The bacteria such as *Pseudomonas aeruginosa, Rhodococcus pyridinivorans, Aeromonas hydrophila, Lactobacillus sporogens, Serratia ureilytica, Sphingobacterium thalpophilum, Bacillus licheniformis* and *Lactobacillus sporogens* containing biomolecules Enzymes and extracellular proteins actively involved in the zinc oxide nanoparticles with the precursors like Zinc nitrate, Zinc sulfate, Zinc oxide, Zinc chloride, and Zinc acetate ((Singh et al. 2014), (Kundu et al. 2014), (Jayaseelan et al. 2012), (Prasad and K. Jha 2009), (Dhandapani et al. 2014), (Rajabairavi et al. 2017), (Tripathi et al. 2014), (Mishra and Ethiraj 2013). The fungus such as *Aspergillus fumigatus* and *Aspergillus niger* synthesized the zinc oxide nanoparticles by addition of the precursor such as zinc sulfate and zinc nitrate. In this process the biomolecules such as Filtrate protein and Carboxylic acid and the aromatic group (Rajan et al. 2016), (Kalpana et al. 2018). The microalgae *Chlamydomonas reinhardtii* synthesize the zinc oxide nanoparticels from zinc acetate with Hexagonal Wurtzite shape and size with 55-80 nm and proteins are actively involved in the nanoparticles formation (Rao and Gautam 2016)

Biomedical applications of ZnO NPs

Anti-microbial activity of ZnO NPs

Nanoparticles have extensively emerged as an anti-bacterial agent in the past decade (Chan et al. 2010). A plethora of bacteria develop multi-drug resistance in response to commercial drugs and thus, the development of nanoparticles as a potent therapeutic anti-bacterial agent has become the holy grail for the treatment of bacterial infections. Certain nanoparticles have already been reported effective against antibiotic-resistant bacteria (Akhtar et al. 2015, Rudramurthy et al. 2016). Teichoic acid and lipoteichoic acid present in the cell membrane of gram + bacteria chelate Zn^{+2} ion from the nanoparticle and transport it inside the cell while, porins acts as ion channel for the transport of ZnO NPs inside gram- bacteria cell through passive diffusion (Hood and Skaar 2012). Specific targeting of bacteria inside the body could be achieved by complexing ZnO NPs with multiple ligands as they have a high surface area to volume ratio.

ZnO NPs showcase anti-bacterial activity by either disrupting cell membrane of bacteria or generating reactive oxygen species (ROS) within the cell which further induces oxidative stress and alters DNA replication, food metabolism, protein synthesis and induces lipid peroxidation.

Zn^{+2} penetrates the cell membrane and disrupt the integrity of phospholipid bilayer in the bacterial cell membrane. Disruption of the cell membrane is accompanied by blebbing and leakage of cytoplasmic content like intracellular protein, genetic material, ATP and lipopolysaccharide resulting in bacterial cell death. Previous studies have reported the antibacterial effect of ZnO NPs through the cell disruption mechanism on *S. aureus* and *E. coli* cells (Sundrarajan et al. 2015). ZnO NPs inclusion also alters the resting membrane potential by blocking the K^{+} ion channel in the bacterial cell membrane (Xia et al. 2006, Warren and Payne 2015). ZnO NPs also inhibit the efflux pump present in the cell membrane of bacteria which serve to efflux toxic chemicals, antibiotics, and waste material out of the cell (Behlol et al. 2016). Inhibition of efflux pump (P-type ATPase, cation diffusion facilitator) by nanoparticles inhibits the export of excess Zn^{+2} ion out of the cell which leads to cell death when Zn^{+2} ion reaches its toxic concentration (Joe et al. 2016).

The antibacterial effect of ZnO NPs against a broad range of pathogenic bacteria like *Klebsiella aerogenes*, *Escherichia coli*, *Staphylococcus aureus, Proteus mirabilis, Streptococcus pyogenes*, *Mycobacterium tuberculosis, Bacillus subtilis* and *Pseudomonas aeruginosa* has already been reported (Savithramma and Bhumi 2014, Basha et al. 2016, Pandimurugan and Thambidurai 2016, 2017, Murali et al. 2017).

Anti-inflammatory potential of ZnO NPs

Inflammation is the host body response in response to physical and chemical stress or injury in order to restore cellular homeostasis and tissue microenvironment (Gunalan et al. 2014). Inflammatory disorders include asthma, rheumatoid arthritis, pancreatitis and inflammatory bowel disease among many others (Mueller et al. 2010). Non-steroidal anti-inflammatory drugs (NSAIDs) available commercially today in the market showcase various limitations like gastric mucosal layer disruption leading to gastric ulcers, renal issues and cardiovascular strokes (Williams et al. 2000). The development of nanoparticles opens a new therapeutic window for the management of inflammation-based disorders (Ilves et al. 2014, Macrophages et al. 2015). Zn^{+2} ion readily gets absorbed by the biological membranes due to the high reactivity of ZnO NPs owing to their high surface area to volume ratio.

Some of the common anti-inflammatory mechanisms employed by ZnO NPs include inhibition of pro-inflammatory cytokines gene expression, alteration of pro-inflammatory cytokines protein expression, down regulation of nuclear factor kappa B (NF-κβ) pathway, selective targeting of cyclooxygenase (COX-2) enzyme activity, inhibition of mast cell degranulation and down regulation of nitric oxide (NO) release by inhibiting inducible nitric oxide synthase (iNOS) enzyme expression (Klostedudfen and Hauptmann 1996, Cortese-krott et al. 2014, Navaei-nigjeh et al. 2018).

Several models have been used to study the anti-inflammatory mechanism of ZnO NPs. P.C. Nagajyothi et al. reported the anti-inflammatory activity of ZnO NPs in LPS-stimulated RAW 264.7 macrophages by suppressing gene expression and protein expressions of pro-inflammatory mediators like IL-6, IL-1b, iNOS, COX-2, and TNF-α (Nagajyothi et al. 2015). Another study by M. Olbert et al. demonstrated the anti-inflammatory activity of ZnO NPs in the Carrageenan-induced rat paw edema model by inhibition of the NF-κB pathway which further downregulated the release of pro-inflammatory cytokines like IL-1, IL-6, COX enzyme, and nitric oxide synthase activity (Olbert et al. 2017).

Anti-cancer activity of ZnO NPs

Cancer is a medical condition of uncontrolled cell proliferation and is treated by several techniques including radiotherapy, chemotherapy and high profile surgeries. The conventional chemotherapy technique confers non-specific administration of drugs intravenously and sometimes, showcases serious side-effects on surrounding normal tissues limiting its success rate (Menon et al. 2018). Chemotherapy has various side effects like hair loss, weight loss, nausea, skin problem, diarrhea and insomnia. The low solubility of hydrophobic drugs limits their absorption affects drug pharmacokinetics and thus, presents a challenge for the discovery of new therapeutic materials with reduced side effects and limitations. Anti-cancer therapies have undergone rapid technological advancements with the emergence of nanotechnology.

ZnO NPs are biocompatible in nature and allow surface functionalization for targeted therapy of cancer. ZnO NPs demonstrate the anti-cancer activity by employing several mechanisms like induction of cancer cell apoptosis, restraining multiplication of cells that limit their malignancy, stimulation of cell immune system and regulation of cellular redox state (Buerki-thurnherr et al. 2013, Jiang et al. 2018).

Zn^{+2} ions which upregulates hydrogen peroxides (a form of ROS) release by mitochondria through electron transport chain (Guo et al. 2013). Excessive ROS generation leads to mitochondrial damage associated apoptosis of cancer cells (Alrokayan 2012). ZnO NPs also alters caspase activity and JNK, ERK pathway for inducing apoptosis. Zn^{+2} ions also induce oxidative stress-mediated cancer cell death (Deng and Zhang 2013).

Zn^{+2} ions from ZnO NPs downregulates the protein expression of anti-apoptotic molecules such as claspin, phosphorylated P^{53}, apoptosis proteins (IAPs), bcl-2 and hypoxia-inducible factors (HIF)-1α (Alarifi et al. 2013). ZnO NPs also upregulates caspase 3 and 9 expressions for apoptosis induction (Ahamed et al. 2011). ZnO NPs enhances the expression of pro-apoptotic protein bax for inducing apoptosis in a cancer cell.

CONCLUSION

The biologically active compounds obtained from microbes are having double benefit role functional groups in stabilizing and reducing agents. The microbial synthesis methods are simpler, easier and will not involve in any hazardous chemicals. But, there is a challenges in the microbes mediated synthesis to achieve high yield of NPs. Moreover, there is a necessity to discover high potential microbes in the synthesis of ZnO NPs and their biological activities as there are limited potential microbial species that are described in the recent literature. There are different species of microbes present in the environment; therefore, it's needed to evaluate novel groups of microbes and their molecular mechanisms with respect to synthesis process by microbes could be further revealed. Further, biological active of ZnO NPs obtained from microbes can be represent a new alternative source of key betterment in pharmaceuticals and drug delivery industry.

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