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A review on biosynthesis of Zinc Oxide Nanoparticles using plant extracts and its potential Bio Applications

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Abstract
Zinc oxide nanoparticles (ZnO NPs) are one of the vital metal oxide nanoparticles with key applications in antimicrobial, anticancer, anti-inflammatory, antidiabetic and agriculture. The ecological impacts and economic challenges associated with most mechanisms of ZnO NPs are result in the search for other substituted with environment and productive benefits. The specific features of ZnO NPs synthesised using plant extracts have enhanced its used in agriculture for the production of fertilizers, fungicides and pesticides. In the field of pharmacology such as anticancer, antidiabetic biosynthetized ZnO NPs have found significant use in the manufacture of bactericides, fungicides, and anti-inflammatory agents. Despite the listed benefits of biosynthesized ZnO NPs, the struggling associated in clarifying the formation mechanism and reactions survive unresolved. This review article demonstrates that the recent development in the synthesized and applications of biosynthesized ZnO NPS in antimicrobial, anticancer, antidiabetic, anti-inflammatory and agricultures.

Keywords: Bisynthesis, ZnO NPs, antimicrobial, anticancer, antidiabetic activity

Introduction

Zinc oxide nanoparticles are one of the most key metal oxide materials and are broadly used in the science of materials owing to its distinctive physical, chemical and biological properties such as biocompatibility, ecological friendliness, low cost and non-toxic nature (Salahuddin *et al*., 2015; Ruszkiewicz *et al*., 2017) [1-2]. Due to its exceptional properties, ZnO nanoparticles are used as a functionally advanced material, especially in the field of cosmetics and antimicrobial additives (Ruskievich *et al*., 2017) [2]. The wurtzite structure is most common because of its stability to ambient conditions in which each zinc atom is consolidated with four oxygen atoms (Barhom *et al*., 2019) [3]. It has such advantages as stabilization in the substrate, chiefly in the form of zincblende with a cubic lattice structure (Parihar *et al*., 2018) [4]. Food and Drug Administration (FDA) Zinc oxide is one of the safest metal oxides to use in the food industry (Bettini *et al*., 2016) [5].

ZnO has unique chemical and physical properties; for example, higher photosynthesis, higher chemical stability, naturality, paramagnetism, wider range of radiation absorption and higher electrochemical coupling coefficient (Parihar *et al*., 2018) [4]. Due to the distinguished performance of ZnO nano-structured materials in photonics, optics and electronics, it attracted much attention. The lack of symmetry center in the wurtzite structure, combined with excellent electro-mechanical coupling, strong pyroelectric and piezoelectric properties are the reasons for the use of ZnO in piezoelectric detectors and mechanical actuators.

Furthermore, zinc oxide contains a wide energy gap, which is characteristics for a compound semiconductor, sufficient for various types of applications; for instance, solar cells, in power generators, ultraviolet (UV) lasers (Wang *et al*., 2017) [6], gas detectors (Tomchenko *et al*., 2003) [7], photo catalysts, field emission devices, capacitors(Marcı *et al*., 2001; Singh *et al*., 2017) [8-9]. It can also be used for clear UV resistance coating, photo-printing, electrochemical, electrophotography, electromechanical nano-devices, antibacterial agents, anti-hemorrhoids, sun blockers, cosmetics, wound healing, and human medicine (Serpone *et al*., 2007; Ozgur *et al*., 2007) [10-11]. Zinc oxide powder is widely used as an additive in numerous products and materials involving ceramics(Sabir *et al*., 2014) [12], rubber, lubricants, cement, paints, adhesives, ointments, plastics, pigments, food, ferrites, glass, sealants, batteries and fire retardants(Serpone *et al*., 2007) [10]. ZnO-based coating can be utilized as a safety layer against moisture in woody samples (Makarona *et al*., 2018) [13]. Metal and metal oxide nanoparticles have shown broad applications in many fields, including agriculture, medicine, textile, pharmaceuticals, catalysts, heavy industry dealing and antimicrobial evaluation(Vaishali *et al*., 2018; Akintelu *et al*., 2019; Jay *et al*., 2016; Senthilkumar and Sivakumar, 2014; Sivakumar *et al*., 2015; Sivakumar, 2019)[14–19]. In specific, the uses of ZnO NPs in coatings, medical purposes, antimicrobial treatments, cosmetics, photocatalysis, pesticides, sunscreen products, agriculture and antimicrobial agents are notable (Jay *et al*., 2015; Devatha and Thalla, 2018)[20-21]. The outstanding antimicrobial powers of ZnO NPs have aided its many uses in surgical tapes antiseptic creams, shampoos and calamine lotions. ZnO NPs have been reported to exhibited broad spectrum against bacterial growth at low concentrations (Chen *et al*., 2019) [22]. ZnO NPs receive its significant antimicrobial use and biosafety features in medical applications approved by the United States Food and Drug Administration (21, CFR 182, 8991). The use of ZnO NPs in the electronics, rubber fabrication, biosensors, Transducers, pharmaceutical and biomedical field is growing rapidly during this era (Khatami *et al*., 2018) [23]. Among the different approaches and protocols used for the synthesis of ZnO NPs, the use of biosource as a reducing agent is commonly accepted by researchers Because of its eco-friendliness, nonhazardous reagents, simple-to-operate processes, low energy consumption and cost effectiveness

(Khatami *et al*., 2018) [23]. Biomolecules and secondary metabolites present in plant extracts such as tannins, flavonoids, saponins, polyphenols, alkaloids and terpenoids are said to be responsible for effectively reducing zinc precursors; the effectiveness of plant extracts in reducing zinc precursors was relatively higher than that of microorganisms. ZnO NPs mediated from plant extracts have excellent antimicrobial potential against human pathogens and bacterial and fungal infections (Asghari *et al*., 2016) [24]. Various plants including Trifolium, *Physalis alkekengi, Justicia adhathoda, Cassia auriculata, Aloe barbadenis, Pongamia pinnata, pretense flowers, Limonia acidissima, Plectranthus amboinicus, Sedum alfredii Hance, Cochlospermum religiosum, Aspidoterys cordata, and Bauhinia racemosa*, Green tea have been reported as better sources for the synthesis of NPs (Krol *et al*., 2017; Prashant *et al*., 2019) [25–26]. A previous study demonstrated that the morphological identification of nanoparticles and ZnO NPs influence their different uses; the following techniques, such as UV visible spectroscopy, scanning tunneling microscope, atomic force microscope, scanning electron microscope, transmission electron microscope, dynamic light scattering, differential scanning calorimetry, Fourier transmission infrared spectroscopy, energy dispersive x-ray, and particle size analysis, had been used in characterization of ZnO NPs to determine their various properties (Iqbal *et al*., 2019) [27]. In this review articles provide detailed scientific information on the latest developments in the synthesis and applications of ZnO NPs using plant materials. Furthermore, recent developments in the applications of antimicrobial activity, anticancer activity, anti-inflammatry activity, anti-diabetic activity, medicine, agriculture of biosynthesized ZnO NPs have been well presented.

Green synthesis of ZnO NPs

Biosynthesis includes the biological and green synthesis method, which is an option for both physical and chemical methods, with environmental benefits and natural capping agents that control the agglomeration of nanoparticles, this type of synthesis does not require an artificial capping agent. The biosynthesis of ZnO nanoparticles is a bottom up approach, which often involves reduction and oxidation reaction. The synthesis reaction takes place at one step, so a molecule with dual properties such as reducing and capping agents are preferred. Environmental sources are considered to be the resources for the biosynthesis of nanoparticles, which are the primary sources of plant extract, bacteria, and fungi (Senthilkumar and Sivakumar, 2014; Senthil Kumar *et al*., 2016; Singh *et al*., 2016) [28-30]. NPs are immediately coated with a protein molecule to form a natural cap, thus preventing the formation of accumulations. Capping for nanoparticles with biological components increases long shelf life and stability (Kaushik *et al*., 2010) [31]. Plants for the synthesis of ZnO NPs, plants are considered to be green nano factories in the genesis of NPs. The green synthesis of ZnO NPs using plants and their use in the associated field has become a preferred pursuit of all scientists, including biologists, chemists and engineers. The advantage of ZnO nanoparticles synthesis using plant extracts is that they are very easy to obtain, safe and contain numerous reducing agents that reduce nontoxic, metal ions. Plant extract reduces time, and cost, waste, etc. and implements sustainable procedures for the development of environmentally friendly and simple methods of production.

Green nanotechnology is also known as photobiological approach, which uses the plant to extract and capping agents for the synthesis of ZnO NPs (Singh *et al*., 2011) [32].

Applications of ZnO NPs

ZnO has various chemical and physical properties and also used in many fields. Zinc oxide is significant in a broad range of applications, from medicine to agriculture, from paints to chemicals and tires to pottery. Figure 1. Shows the global consumption of ZnO through via area (Kolodziejczak-Radzimska and Jesionowski, 2014) [33]. Clinical applications Zinc oxide NPs have specific properties that are suitable for applications associated with the central nervous

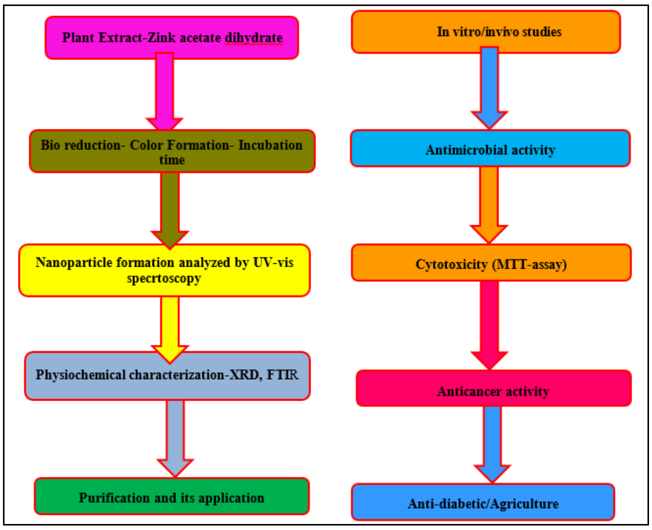

Fig 1: Flow chart illustrating the biological method of ZnO NPs synthesis and applications.

System (CNS), and developmental therapies for the treatment of disease (mediating neuronal excitability) or (even the release of neurotransmitters). Various studies have shown that zinc oxide affects homogeneous tissues, cells, or functions, as well as neural tissue engineering and biocompatibility (Osmond *et al*., 2010; Sivakumar, 2021) [34-35].

Antimicrobial applications

The antimicrobial activity of ZnO NPs can be traced to its distinctive features (Ishwarya *et al*., 2018) [36]. Several researchers have studied the antibacterial and antifungal properties of biosynthesized ZnO NPs, versus many bacteria and fungi have been notable antimicrobial efficiency have been recorded (Rekha *et al*., 2010; Sharma *et al*., 2013; Bhuyanetal., 2015) [37-39]. The effect of variation in the concentrations of phytosynthesized ZnO NPs on the growth of Escherichia coli and Staphylococcus aureus using the Shake flask method examined that ZnO NPs may inhibit bacterial cell growth because the growth of bacterial cells in the presence of ZnO NPs was extensively decrease when compared with bacterial cells of the control group. The reduced in bacterial growth was 5.1–100% and 23.43–99.48% for *E. coli* and *S. aureus* respectively as concentration of ZnO NPs increases (Singhal *et al*., 2020) [40]. Investigation into the antibacterial activity of synthesized ZnO NPs against *Escherichia coli* and *Clostridium apsonum, Streptococcus aureus*, and *Streptococcus mutants* showed a higher bacterial resistance based on the inhibitory zone using the disk diffusion method, which increased as the concentration of ZnO NPs used increased. An increase in antibacterial activity has been associated to an increase in the concentration of H2O2 on the surface of ZnO NPs (Bayrami *et al*., 2020) [41]. Evaluation of antifungal potency of synthesized ZnO NPs using Euphorbia hirta leaf extract evaluated the unique antifungal efficacy against the growth of Aspergillus nigger, Arthogrophis cuboida, and Aspergillius fumigates. Various study reported high antifungal activity of ZnO NPs against the growth of Alternaria alternate, Botrytis cinerea, and Fusarium oxysporum with corresponding inhibition zones of 64, 128, and 64 mm respectively(Jamdagni *et al*., 2016; Zeinab *et al*., 2017) [42-43].

Anticancer Activity.

Cancer is a condition of uncontrolled malignant cell proliferation that has been treated with chemotherapy, radiotherapy and surgery for the past several decades. Even though, all of these therapies appear to be effective in killing cancer cells in theory, these unselected therapies introduce many serious side effects (Sharma *et al*., 2016) [44]. Recently, nanomaterial based nanomedicine, with its high biocompatibility, easily of surface function, cancer targeting and drug delivery capability, has proven its ability to deal with these side effects. $Zn2^{+}$ is an vital nutrient for adults, and ZnO nano products are considered safe in vivo. Taking these benefits into account, ZnO NPs can be selected as biocompatible and biodegradable nanoplatforms and explored for cancer treatment (Zhang *et al*., 2013; Martinez-Carmona *et al*., 2018) [45-46].

Anti-diabetic activity

Diabetes is a serious public health problem, and in 2014, the WHO estimated that there were more than 400 million adults worldwide with diabetes (Seclen *et al*., 2017) [47]. Diabetes is a metabolic disease caused by the body's inability to produce insulin or the ineffective use of insulin produced (Nazarizadeh and Asri-Rezaie, 2016; Umrani and Paknikar, 2014) [48-49]. Zinc is a trace element and a mineral abundant in all human tissues and tissue fluids. Zinc is well known for its insulin structure and plays a vital role in the secretion of insulin by pancreatic cells. It also participates in insulin synthesis, storage and secretion (Malizia *et al*., 1998) [50]. Therefore, ZnO NPs have been developed as a new agent for the supply of zinc and have been evaluated for their antidiabetic potential. Kittur *et al*. working natural extract of red sandalwood (RSW) has been used as an effective antidiabetic agent in combining ZnO NPs. Antidiabetic activity was evaluated with the help of α-amylase and α-glucosidase inhibitors in murine pancreatic and small intestinal extracts (Kitture *et al*., 2015; Sivakumar, 2021)[51-52].

Anti-Inflammatory Activity

Inflammation is fragment of the complicated biological response of body tissues to harmful stimuli such as pathogens, damaged cells or irritants (Ferrero-Miliani *et al*., 2006) [53]. Considering the advent of nanoparticles and these biological functions of zinc ions, the anti-inflammatory efficacy of ZnO NPs has also attracted much attention. Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by a deficiency of the skin's immune function, which is associated with complex interactions between genetic and environmental factors (Boguniewicz and Leung, 2001; Jurakic Toncic and Marinovic 2016) [54-55]. Textiles have a very long and intense contact with human skin. Weighing and exploring the role of ZnO active textile fibers in regulating antioxidant stress in AD in vitro and in vivo (Wiegand *et al*., 2016)[56]. Studies have shown that AD patients show distinct improvement in AD pruritus and subjective sleep quality when wearing ZnO textiles overnight for 3 consecutive days. ZnO may be due to the high antioxidant and strong antibacterial ability of textiles.

Agricultural Applications

ZnO NPs have the potential to augmented the growth of food crops. Seeds determined by different ZnO NP concentrations improved seed propagation, seed dispersal, seed strength and plant growth. ZnO NPs have been shown to be active in the growth of rootstocks and seeds (Prasad *et al*., 2012) [57]. The importance of zinc oxide NPs in the field of biotechnology was observed (Paul and Ban, 2014) [58]. They observed the efficacy of the biological structure of chemically produced ZnO NPs and also used in various concentrations from zinc oxide (*Streptococcus pneumonia*, *Bacillus subtilis, E. coli* and *Pseudomonas aeruginosa*). Rapid increase in enzymatic activity was detected by high concentrations of zinc oxide (Paul and Ban, 2014) [58].

Conclusion

ZnO NPs have demonstrated promising applications based on its antimicrobial, anticancer, anti-inflammatory, antidiabetic and agricultural applications. Owing to the intrinsic toxicity of ZnO NPs, they have strong inhibitory effects against cancer cells and bacteria, inducing intracellular reactive oxigen species generation and activating the apoptotic signaling pathway, making ZnO NPs a potential candidate for reactive and antibacterial agents. Furthermore, with the potential to lower blood glucose and increase insulin levels, ZnO NPs have shown promising potential in the treatment of diabetes and in resolving its complications, which can be further evaluated.

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