United Journal of Nanotechnology and Pharmaceutics

Synthesis of ZnO Nanoparticles Using Biological Substrates: A Review

Nefeli Lagopati[1, 2], Maria-Anna Gatou[1], Alexandra Gogou[1], Evangelia A. Pavlatou[1*]

[1] Laboratory of General Chemistry, School of Chemical Engineering, National Technical University of Athens, Zografou Campus, 9, Iroon Polytechniou str., GR-15780, Zografou, Athens, Greece.
[2] Laboratory of Histology-Embryology, Molecular Carcinogenesis Group, Faculty of Medicine, School of Health Science, National and Kapodistrian University of Athens, 75, Micras Asias Str., GR-11527, Goudi, Athens, Greece.

*Corresponding Aurthor:

Evangelia A. Pavlatou, a Laboratory of General Chemistry, School of Chemical Engineering, National Technical University of Athens, Zografou Campus, 9, Iroon Polytechniou str., GR-15780, Zografou, Athens, Greece, Email: pavlatou@mail.ntua.gr, Phone No: 00302107723110

Article Information
Article Type: Review Article
Article Received: 22-11-2020
Article Accepted: 13-12-2020
Article Published:
Vol:1, Issue:1

OPEN ACCESS

Keywords:
Zinc Oxide Nanoparticles, Biosynthesis, Biogenic Synthesis, Green Synthesis, Antimicrobial Properties, Microorganisms, Plant Extracts, Nanomedicine.

Abstract

During the last few decades, the utilization of nanotechnology is exponentially increasing in biomedical engineering applications, such as antibiotics, antimicrobial agents, and anticancer therapies. It is known that a large number of diseases caused by pathogenic microorganisms originate from the fact that these pathogens have developed resistance in commercially available drugs. Thus, the development of novel, effective, non-toxic, and low-cost therapy for better treatment of diseases is imperative. Nanoparticles based on metals and metal oxides have emerged as a promising means of therapy due to their exceptional properties. Among these nanoparticles, zinc oxide nanoparticles (ZnO NPs) have drawn significant attention owing to their eminent biomedical properties. A variety of physical as well as chemical methods is utilized for the ZnO NPs synthesis. However, many of them include the use of hazardous reagents or are energy-consuming. For this reason, green methods are proposed to synthesize ZnO NPs using biological substrates. These methods possess significant benefits, as the extracts contribute positively to the formation and improvement of the antimicrobial activity of ZnO NPs, also acting as reducing and stabilizing agents. In this review, an integrated approach of ZnO NPs bio-synthetic techniques using microorganisms, such as bacteria, fungi and algae, plants and plant extracts, is discussed, shedding light on their comparative advantages.

Citetion: N. Lagopati, et al, et al. / United Journal of Nanotechnology and Pharmaceutics 1(2020): 1-7

Introduction

Nowadays, due to the combined effect among engineering and medical sciences, nanotechnology constitutes an ever–growing novel domain in the field of biological research, aiming at the synthesis and application of nanoparticles (NPs) with controlled morphologies and remarkable features. The Development of nanoparticles characterized by diverse sizes and shapes is of great interest because of their exceptional physicochemical properties, compared to their equivalent bulk materials; thus, this leads to considerable differences in their biological activity [5]. Nanoparticles can be produced through several approaches, which involve both physical and chemical methods, electrochemical and photochemical reaction, as well as heat evaporation methods [13]. Although these techniques have shown high efficiency in the production of nanoparticles with desirable properties, they are associated with some drawbacks regarding the release of harmful by-products posing a high risk to living systems, and the high cost of the synthetic procedure [5,56]. Therefore, to overcome such constraints, the main focus of both science and technology is the design of nanoparticles utilizing environmentally benign approaches.

Taking the aforementioned into consideration, during the last decade, researchers have been developing methods to improve the production of nanoparticles, such as metal and metal oxide NPs, using greener energy saving and cost–effective technologies [8,39,74].

The syntheses of metal and metal oxide nanoparticles via a green-route involve the utilization of non – toxic chemical substances as reducing and stabilizing agents [18].

Among metal and metal oxide NPs, zinc oxide nanoparticles (ZnO NPs) have drawn considerable attention owing to their excellent biomedical properties, as they exhibit tremendous anti–bacterial, anti–fungal and anti–inflammatory properties [1]. Moreover, ZnO NPs are also utilized for bio – imaging, wound healing and as a potential drug delivery vehicle for standard drugs, as it provides synergistic effects for the treatment [1,7].

Various methods, including physical and chemical, are employed for the production of ZnO nanoparticles [35,45]. However, as stated above, the majorities of them either employ noxious compounds or require large amounts of energy during the synthesis process. In light of this, biological methods based on bacteria, Fungus algae, plant extracts, and organic products [2,32] have proven to be extremely promising for the ZnO NPs production, without negative impact neither on human health or the environment.

This review summarizes the latest developments regarding the green synthesis of zinc oxide nanoparticles with antimicrobial properties, through the utilization of different biological extracts.

Synthesis of Zinc Oxide Nanoparticles (ZnO NPs):

Researchers worldwide have developed a plethora of semiconductor nanoparticles, such as TiO2, SiO2, SnO2, GaAs, etc. that is extensively demanded different applications due to their unique properties. Among these semiconductor NPs, those of zinc oxide (ZnO) are at great economic and industrial interest because of a quite vast range of properties, owing to their wide bandgap (3.37eV), high excitonic binding energy (~60meV), non-toxic nature, and low cost [12,19]. This wide range of properties allows the employment of ZnO NPs in many different areas, such as agriculture, cosmetics, metal surface treatment, gas sensors, solar cells, photocatalysts [8,54].

Given that nanotechnology and its implication in various pharmaceutical fields is the area of focus in modern material science, ZnO nanoparticles have gained researchers' attention, as they also possess excellent biomedical properties, which make them potential candidates for novel biomedical engineering application, such as tissue regeneration, implant coatings, bio-imaging, bio-sensors, wound healing antibiotics, antimicrobial and anti-inflammatory agents, development of cancer therapies, etc. [8,20,26,33-35]. In particular, zinc oxide nanoparticles are able to produce reactive oxygen species (ROSs), which lead to their antibacterial and anticancer properties [35,60].

It is known that zinc (Zn) constitutes an important micronutrient, which is included in the structure of more than 300 enzymes comprising a crucial part of several bioprocesses, including the retention of the body's metabolism through hematopoiesis, enzyme regulation, maintenance of the cell redox balance and both DNA and protein synthesis machinery regulation [1]. Zinc also plays an important role in hepatic glycogenesis; particularly, hepatic glycogenesis is through its involvement in the signaling pathway for improved uptake of glucose [35]. In addition, zinc is also essential for the synthesis, secretion, as well as signaling of a very important hormone, insulin, affecting subsequently its action on metabolism [6,35].

In general, several methods to synthesize ZnO NPs, such as physical, chemical, and biological. Chemicals methods include various techniques, like direct precipitation, solution evaporation, hydrothermal, wet chemical reduction, microemulsion, and sol-gel [8,9,12,17,37,53,54]. Among chemical methods, sol-gel comprises the most frequently used synthesis for the fabrication of zinc oxide nanoparticles. Although chemical methods are efficient, they may result to high energy consumption, when condition of high temperature or pressure are required during the production process [8,27,40]. Additionally, there is a possibility of the adsorption of noxious residues over the nanoparticles' surface due to the utilization of stabilizers, which can adversely affect their application for biomedical purposes.

Zinc oxide nanoparticles can also be fabricated through physical methods, such as vapor deposition, plasma, and ultrasonic irradiation, interferometric lithography, physical fragmentation, and amorphous crystallization, although these techniques are less used than the chemical methods [8,27] and also require a high amount of energy and sophisticated equipment.

However these methods have led to ZnO nanoparticles with desired properties, size, and shape, the main focus is to design zinc oxide NPs using environmentally benign approaches. These provide solutions to the use of ZnO NPs in biological and medical applications.

1.Bio-synthesis of Zinc oxide Nanoparticles:

Biogenic fabrication of zinc oxide nanoparticles proves to be an effective alternative to the conventional physical and chemical synthetic routes. The demand for green synthesis of ZnO NPs has increased considerably during the last decade as awareness regarding green chemistry is on the rise. The development of this new approach and the significant interest in it is mainly related to the absence of toxic chemicals or a high amount of energy applied to the biological synthesis, which makes the process more cost-effective and eco-friendlier [8,23,27,40]. More specifically, the biosynthetic route for the fabrication of zinc oxide nanoparticles utilizes biological substrates, such as plants, plant parts, and cellular microorganisms (bacteria, fungus, and algae) in order to replace chemical solvents and stabilizers to decrease the toxicity of both produced nanoparticles and synthetic procedure [2,8,27,33].

The bio-synthesis of zinc oxide nanoparticles constitutes a quite simple procedure in which a zinc salt, such as zinc chloride, zinc acetate, etc., is added to a biological extract previously prepared. After the reaction, this solution is submitted to thermal treatment, and the ZnO powder is obtained [8,27,33,58].

In general, zinc oxide NPs synthesized through bio-synthetic route tend to exhibit enhanced antibacterial activity than those being synthesized through the physical or chemical techniques, due to coating various pharmacologically active biomolecules on their surface that allow multiple ligands-based conjugations of nanoparticle with a reception on bacterial membranes.

A large number of ligands can be hosted over nanoparticles for imposed targeting of pathogenic microorganisms, owing to their large surface area to volume ratio. These are mainly organic flavones, aldehydes, ketones, amides, polysaccharides, and quinones, which are known to have a significant therapeutic effect against a wide range of human pathogen [1,2,72].

Namely, either bacteriostatic or bactericidal effect of ZnO NPs is expressed by preventing bacteria from receiving the necessary nutrients or by disrupting their cell membrane [2,47].

Perveen [44] compared the antibacterial activity of ZnO NPs prepared by both the aforementioned sol-gel and green synthetic procedures. For the green synthesis method, vegetable seeds from Brassicaceae plants (red radish, white radish, turnip, sarson, and cauliflower) were used. The antimicrobial activities were assessed against three bacterial strains, including Bacillus subtilis (B. subtilis), Staphylococcus aureus (S. aureus) and Salmonella typhimurim (S. typhimurim) and against three fungal strains, including Aspergillus niger (A. niger), Fusarium oxysporum (F. oxysporum) and Penicillium digitatum (P. digitatum). The NPs might be able to pass readily through the cell membrane of peptidoglycan polymer and thus exert antibacterial action. Antibacterial activity is assigned to the destruction or inhibition of bacterial growth. S. aureus was the most actively inhibited strain by all the samples. The antifungal activity was low compared to the antimicrobial activity of these samples. A. niger was not inhibited. It was therefore concluded that red radish, white radish, turnip, sarson and cauliflower could possibly be used for the fabrication of ZnO as active antimicrobial agents [44]. Furthermore, Ahmad and Kalra (2020) investigated the extract of Euphorbia hirta leaf for the construction of ZnO NPs and applied them on human bacteria such as Streptococcus mutans, Streptococcus aureus, Clostridium absonum, and Escherichia coli [3] and fungus strains such as Arthogrophis cuboida, Aspergillius fumigates and Aspergillius nigar. The result of the antibacterial study clearly indicated that the antibacterial activity (in terms of Zone of Inhibition) increases as the concentration of ZnO nanoparticles (20, 40, 60, 100 mg/ml) increases too, which may be due to the increase of H2O2 concentration from the surface of ZnO nanoparticles. The zone of inhibition was found to be highest in the case of Streptococcus aureus (29 mm) when compared to other bacteria, like Streptococcus mutans (28 mm), Clostridium absonum (27 mm), Escherichia coli (24 mm). It is also found that comparing the obtained antifungal result of the synthesized nanoparticles; the best result is obtained in the case of Arthogrophis cuboida (zone of inhibition 29 mm). In the case of Aspergillius nigar, the minimum zone of inhibition (ZoI) was reported (zone of inhibition 20 mm).

1.1 Bio-synthesis of ZnONPs using plants and plant extracts:

The plant-based synthesis of metal and metal oxide nanoparticles comprises an emerging field of nanotechnology in the present era, given the fact that plants constitute the most commonly used biological substrate for the biosynthesis of nanoparticles with metallic ions [8]. Plant extracts, deriving from different parts of the plant, like leaves, roots, stems, barks, flowers, seeds, and fruits, are abundant in various phytochemicals or active compounds in different concentrations, such as polyphenols, flavonoids, methylxanthines, terpenoids, quinones, fatty acids, and saponins, which render them suitable candidates to act as reducing and stabilizing agents [5,8,16,38,71]. These compounds are also known as antioxidants, as they can neutralize reactive oxygen species (ROS) and free radicals and chelate metals [8]. Phytochemicals coating onto the surface of green synthesized nanoparticles makes them biologically benign and compatible, offering very interesting applications in biomedicine and related fields [1,32,56].
The bio-synthetic route of metal and metal oxide nanoparticles utilizing both plants and their extracts provides additional benefits compared to the use of microorganisms for several reasons: (i) it is non-pathogenic, as there is no exposure to health risks or concerns regarding safety issues related to dangerous microorganisms during the synthetic process, (ii) it does not demand any complicated protocol or methodology; plant extracts can be easily obtained through the exposure of the plant to a solvent that is usually distilled water or ethanol [4,8], (iii) it is cost-effective and relatively easy for scaling up and production in industrial level [11] and finally, (iv) it is characterized by a higher bio-reduction potential, compared to microorganisms culture filtrates [4,59]. In the case of microorganisms, the synthetic process consists of multiple stages, including isolation of the potential microorganism, specific culture preparation, aseptic culture conditions maintenance, etc. [11].

Zinc oxide nanoparticles can be synthesized using either the whole plant or its extract; thus, the availability of the reducing and stabilizing agents is greater in their extract than in the plant itself, so as a result, the majority of the studies have focused on the use of plant extracts for the ZnO NPs synthesis. In general, the plant-based method for the synthesis of zinc oxide nanoparticles involves the reaction of the active compounds present in the plant extract with a zinc salt to reduce or form complexes with the metal [8,11,31,57].

Several researchers have reported the synthesis of ZnO NPs with antimicrobial properties using a plant-based methodology. In 2017, Murali and his co-researchers synthesized ZnO NPs from the leaf extract of Ceropegia candelabrum, a medicinal plant endemic to India, with zinc nitrate as a precursor using a simple hydrothermal process. The as-synthesized ZnO NPs exhibited significant antibacterial and antioxidant potential in comparison to the standard drugs; as a result, they could be used as an alternative to current chemical compounds. Also, in 2017, Santhoshkumar and his research team bio-synthesized zinc oxide nanoparticles using Passiflora caerulea fresh leaf extract and zinc acetate. The team tested the antimicrobial effect of the as-prepared zinc oxide nanoparticles against urinary tract infection pathogens, like E. coli, Streptococcus sp., Enterococcus sp., and Klebsiella sp. The results indicated that the ZnO NPs exhibited considerable antibacterial activity and they could comprise a potential antibacterial agent towards urinary tract infection. Malaikozhundan [30], taking into account that the overuse of antibacterials and drugs has led to the development of resistance in a number of pathogens and parasites and that breast cancer constitutes the second most frequent cause of death due to cancer among women, they assumed that the development of novel, effective, low-cost and environmentally friendly drugs are of high importance. Thus, the team developed zinc oxide nanoparticles from Pongamia pinnata seed extract, and they tested them against Bacillus licheniformis, Pseudomonas aeruginosa, Vibrio parahaemolyticus, C. albicans, as well as breast cancer MCF-7 cells. They concluded that the as-prepared green ZnO NPs could be utilized as effective antimicrobial and anticancer agents. Moreover, Sathishkumar [52] reported a facile route to bio-synthesize zinc oxide nanoflakes using leaf extract of C. guianensis Aubl., which is commonly known as cannonball tree and possesses great biological properties, such as antimicrobial, antiseptic, antitumor, immunomodulatory, etc. [51]. These zinc oxide nanomaterials presented an excellent bactericidal effect towards human pathogens and demonstrated minimum hemoglobin release that clearly reveals their suitability to be used in diverse nanomedicinal applications.

During 2018, Khatami and his team utilized a fast, clean and green synthesis method of zinc oxide nanoparticles using Stevia (natural sweetener) extract. They examined the antimicrobial activity of the bio-synthesized nanoparticles against Leishmaniasis major, Staphylococcus aureus and Escherichia coli and they concluded that low concentrations of the as-prepared zinc oxide nanoparticles could inhibit the in vitro growth of the aforementioned microorganisms. Additionally, in 2018, Singh and co-researchers, developed a green and sustainable synthesis of zinc oxide quantum dots using zinc acetate as precursor and Eclipta alba, a medicinally important herb, leaf extract as reducing, capping and stabilizing agent. The as-biosynthesized ZnO quantum dots exhibited significant antibacterial activity against E. coli. Khan [24] synthesized ZnO NPs from aqueous extract of Abutilon indicum, as well as Cu-doped ZnO NPs from aqueous extracts of Clerodendrum infortunatum and Clerodendrum inerme, through a straightforward green method. The fabricated zinc oxide nanoparticles possessed potent biological properties, such as antimicrobial, antifungal, anticancer and antioxidant.

Moreover, in 2019, Vijayakumar and co-workers, successfully prepared zinc oxide nanoparticles from ethyl acetate leaf extract of Acalypha fruticosa through a facile, green and low-cost technique. They concluded that the biosynthesized ZnO NPs were excellent potential candidates to be used as antimicrobial agents towards a variety of pathogenic microorganisms. Also, during 2019, Madhumitha [29] fabricated zinc oxide NPs utilizing Pithecellobium dulce peel extract. The phytochemicals present in the peel act as capping and stabilizing agents. The biosynthetic process led to ZnO NPs that exhibited great antifungal properties after being tested against Aspergillus flavus and Aspergillus niger. Lingaraju [28] proposed a Euphorbia heterophylla leaves extract mediated preparation of zinc oxide nanoparticles. The researchers stated that the biosynthesized ZnO NPs presented significant antibacterial activity towards Gram positive (Staphylococcus aureus) and Gram negative (Escherichia coli, Pseudomonas desmolyticum and Klebsiella aerogenes) bacteria. The cytotoxicity of the zinc oxide nanoparticles was evaluated as well, towards lung (A549) and hepatocellular carcinoma (HepG2) cell lines. The overall assumption of the research team's observations was that the aforementioned green synthesis approach had effectively led to the formation of ZnO NPs with excellent antibacterial and cytotoxicity properties.

Nilavukkarasi [41] described the synthesis of ZnO NPs using Capparis zeylamica leaf extract. The antimicrobial activity of these nanoparticles was examined against bacteria (S. epidermidis, E. faecalis, S. paratyphi, S. dysenteriae) and fungi (C. albicans, A. niger) through the agar well diffusion method. Cytotoxicity analysis was also conducted against A549 cancer cell lines. Nilavukkarasi and his co-researchers assumed that the novel as-biosynthesized ZnO NPs presented excellent antimicrobial and anticancer properties and as a result they could be used in various nanomedicine applications.

Loquat seed extract was also recently used for the optimization of green synthesis of ZnO NPs, by Shabaani [55], through response surface methodology (RSM) [55]. The researchers studied the behavior of the ZnO NPs in five food spoilage bacterial pathogens, including Bacillus cereus, Staphylococcus aureus, Enterococcus faecalis, Listeria monocytogenes and Salmonella typhimurium. The ZnO NPs showed a large zone of inhibition against Gram-positive bacteria, especially S. aureus strain. It is noteworthy that biosynthesized NPs showed significant antibacterial activity against S. typhimurium as a Gram-negative bacterium, while the applied antibiotic was not effective, which leads to the conclusion that the ZnO NPs can be utilized as antibacterial agents in food packaging.

1.2 Bio-synthesis of zinc oxide nanoparticles using microorganisms:

The green synthesis of metal and metal oxide nanoparticles utilizing bacterial culture or biomass can take place in an extracellular or intracellular environment, in which the nanoparticles are formed or synthesized based on their location in the bio-reducing system [8,42,46]. Regarding the extracellular synthesis, it is proposed from various researches that both enzymes and proteins produced and released by the microorganisms have the ability to reduce the metal and metal oxide ions and, subsequently, stabilize the particles [8,46].

In the case of the intracellular bio-synthesis, the metal and metal oxide development mechanism is more complicated owing to the intricacy of the cells' composition and processes. Despite this, several studies suggest that cells incorporate the metal or metal oxide ions, which will be then reduced by proteins and enzymes present within the cell in order for the nanoparticles to be synthesized [8].

According to several studies, microorganisms are capable of incorporating Zn2+ ions [2,8]. Although the intracellular synthesis could be a feasible route to obtain zinc oxide nanoparticles, the extracellular synthesis route constitutes the most commonly utilized for the fabrication of zinc oxide nanoparticles through bacteria cultures [8,10]. Furthermore, the intracellular bio-synthesis demands an additional process in comparison to the extracellular synthesis route, that of cell lysis, in order to release the nanoparticles from inside the microorganisms [36]. Therefore, the former is more time consuming and expensive than the latter one, in which the metal and metal oxide ions are directly reduced or chelated by proteins and enzymes present outside the cells [8]. Busi and his co-researchers in 2016, bio-synthesized zinc oxide nanoparticles utilizing the culture supernatant of A. schindleri SIZ7. The researchers mentioned that the formed ZnO NPs exhibited antimicrobial activity towards food-borne pathogens (E. coli and S.enterica) and as a result, the aforementioned bacterial system owns the potential for the realization of an environmentally friendly, effective, and low-cost fabrication of zinc oxide nanoparticles. Rauf [46] presented the potential of S. aureus culture medium to be used as an agent for inducing the synthesis of zinc oxide nanoparticles. The proposed method was facile, green, and low-cost, ZnO nanoparticles possessed significant antibacterial properties towards various pathogens. Furthermore, Jayabalan [21] suggested a green synthesis of zinc oxide nanoparticles utilizing Pseudomonas putida (MCC 2989), a Gram-negative, rod-shaped, soil bacterium broth culture. The produced ZnO NPs presented good antibacterial activity that has constrained the growth of Gram-negative and Gram-positive bacteria. Summarizing, the study of Jayabalan and his co-researchers proposed a possible route for synthesizing zinc oxide NPs conjugated antibiotics, which may in the future improve the activity of commercially available antibiotics.

The synthesis of metal and metal oxide nanoparticles utilizing fungal culture or biomass follows a similar route as the one presented for the biosynthesis of nanoparticles using bacteria [8]. Compared to the bacteria-mediated synthesis, the fungal synthesis of nanoparticles is believed to feature the enhanced potential for the biosynthesis of NPs, as it has the ability to release higher concentrations of metabolites to the culture media than bacteria cells. Additionally, fungus cells appear to be more resistant in conditions variations during the synthetic process, such as stirring, pressure, pH that increases their potential use for industrial synthesis [8,73]. [22] presented the extracellular synthesis of zinc oxide nanoparticles using culture filtrates of Aspergillus niger. They examined the antimicrobial properties of the produced nanoparticles against E. coli and S.aureus, and they observed a significant reduction of both microorganisms. Finally, in 2020, Ganesan and his co-research team utilized a facile and effective approach for the biosynthesis of ZnO

NPs using an aqueous extract of Periconium sp (a fast-growing endophytic fungus) through the sol-gel process. The mycochemical constituents that are present within the fungal extract play a crucial part in the sol-gel process as chelating and gelling agents. The as-synthesized ZnONPs presented great antimicrobial activity against two pathogenic bacteria, Staphylococcus aureus, and Escherichia coli and the fungus Candida albicans.

Another type of microorganisms used for the biosynthesis of metal and metal oxide nanoparticles is that of algae. Algae constitute one of the most primitive biological entities and conduct more than 50% of photosynthesis on the planet [25]. They are simple organisms, and their phytochemical composition can be associated with the plant extracts' composition. Some of the reasons that render algae eminent microorganisms for the green synthesis of metal and metal oxide nanoparticles are: (i) their fast-doubling time, (ii) the fact that they constitute well-developed systems, (iii) their cells can be easily disrupted, (iv) they are low-cost, suitable for large scale synthesis and (v) the nucleation and crystal growth of nanoparticles are accelerated owing to the presence of negative charge on the surface of the cell [25].

The development mechanism of biosynthesized ZnO NPs utilizing algae substrates can be related to the plants' mechanism already described, where various phytochemicals act as reducing and stabilizing agents [8]. In 2018, Sanaeimehr and his team synthesized ZnO NPs via Sargassum muticum algae extract and assessed their cytotoxicity, and apoptotic properties on human liver cancer cell line (HepG2). The research's results confirmed that zinc oxide nanoparticles presented apoptotic, anti-angiogenic, and cytotoxic effects, and they could be used as a supplemental drug in cancer treatment for decreasing angiogenesis and induce apoptosis. Lastly, another novel recent research used marine red macroalga Kappaphycus alvarezii for the green synthesis of ZnO and MgO nanoparticles, prepared by biogenic co-precipitation technique [43]; the obtained results pave the way for the green production of these nanoparticles in a large scale, as crystallinity, purity, surface morphology and chemistry are considered acceptable.

Conclusions

Zinc oxide nanoparticles (ZnO NPs) have drawn considerable attention due to their significant biomedical properties. A plethora of physical and chemical techniques are employed for the synthesis of ZnO NPs. Nevertheless, the majority of them either involves the utilization of noxious reagents or requires large amounts of energy. Taking the aforementioned into consideration, several researches report the fabrication of zinc oxide nanoparticles through a bio-synthesis route process instead of the conventional methods. The biogenic synthesis of ZnO NPs can be distinguished into two main categories, the green synthesis based on the use of plants and their extracts and the approach based on the utilization of microorganisms, such as bacteria, fungus, and algae. These methods use biological resources as reducing, capping, and stabilizing agents, and present significant benefits since the extracts contribute positively to the synthesis of ZnO NPs and improvement of their antimicrobial activity.

Overall, in this review, an integrated approach of zinc oxide nanoparticles bio-synthetic techniques utilizing microorganisms, plants, and plant extracts were discussed in order to highlight the significance of the incorporation of green-synthesized nanoparticles in basic and applied research, as well as in nanomedicine applications.

Acknowledgments

This research is implemented through IKY scholarships program and co-financed by the European Union and Greek national funds through the action entitled "Reinforcement of Postdoctoral Researchers", in the framework of the Operational Program "Human Resources Development Program, Education and Lifelong Learning" of the National Strategic Reference Framework 2014-2020-MIS5001552.

Conflicts of Interest

The authors declare no conflict of interest.

References

[1] Agarwal H, Shanmugam V. A review on anti-inflammatory activity of green synthesized zinc oxide nanoparticle: mechanism-based approach. Bioorganic Chemistry. 2019; 94.

[2] Agarwal H, Menon S, Kumar S V, Rajeshkumar S. Mechanistic study on antibacterial action of zinc oxide nanoparticles synthesized using green route. Chemico-Biological Interactions. 2018; 286: 60 – 70.

[3] Ahmad W, Kalra D. Green synthesis, characterization and anti-microbial activities of ZnO nanoparticles using Euphorbia hirta leaf extract. Journal of King Saud University- Science. 2020; 32(4): 2358 - 2364.

[4] Ahmed S, Ahmad M, Swami B L, Ikram S. A review on plants extract mediated synthesis of silver nanoparticles for antimicrobial applications: A green expertise. Journal of Advanced Research. 2016; 7(1): 17 – 28.

[5] Altemimi A, Lakhssassi N, Baharlouei A, Watson D, Lightfoot D. Phytochemicals: extraction, isolation, and identification of bioactive compounds from plant extracts. Plants (Basel). 2017; 6(4): 42.

[6] Asani S C, Umrani R D, Paknikar K M. In vitro studies on the pleotropic antidiabetic effects of zinc oxide nanoparticles. Nanomedicine (Lond), 2016; 11(13): 1671 – 1687.

[7] Bala N, Saha S, Chakraborty M, Maiti M, Das S, etal. Green synthesis of zinc oxide nanoparticles using Hibiscus subdariffa leaf extract: effect of temperature on synthesis, anti-bacterial activity and anti-diabetic activity. RSC Advances. 2015; 5(7): 4993 – 5003.

[8] Bandeira M, Giovanela M, Roesch-Ely M, Devine D M, da Silva Crespo J. Green synthesis of zinc oxide nanoparticles: A review of the synthesis methodology and mechanism of formation. Sustainable Chemistry and Pharmacy. 2020; 15: 100223.

[9] Bekkari R, laânab L, Boyer D, Mahiou R, Jaber B. Influence of the sol gel synthesis parameters on the photoluminescence properties of ZnO nanoparticles. Materials Science in Semiconductor Processing. 2017; 71: 181 – 187.

[10] Busi S, Rajkumari J, Pattnaik S, Parasuraman P, Hnamte S. Extracellular synthesis of zinc oxide nanoparticles using Acinetobacter schindleri SIZ7 and its antimicrobial property against foodborne pathogens. Journal of Microbiology, Biotechnology and Food Sciences. 2016; 5(5): 407 – 411.

[11] Chandra H, Kumari P, Bontempi E, Yadav S. Medicinal plants: Treasure trove for green synthesis of metallic nanoparticles and their biomedical applications. Biocatalysis and Agricultural Biotechnology. 2020; 24: 101518.

[12] Chennimalai M, Do J Y, Kang M, Senthil T S. A facile green approach of ZnO NPs synthesized via Ricinus communis L. leaf extract for biological activities. Mater Sci Eng C Mater Biol Appl. 2019; 103:

109844.

[13] Dubey S P, Lahtinen M, Sillanpaa M. Tansy fruit mediated greener synthesis of silver and gold nanoparticles. Process Biochemistry. 2010; 45(7): 1065 – 1071.

[14] Fazlzadeh M, Khosravi R, Zarei A. Green synthesis of zinc oxide nanoparticles using Peganum harmala seed extract, and loaded on Peganum harmala seed powdered activated carbon as new adsorbent for removal of Cr(VI) from aqueous solution. Ecological Engineering. 2017; 103(part A): 180 – 190.

[15] Ganesan V, Hariram M, Vivekanandhan S, Muthuramkumar S. Periconium sp. (endophytic fungi) extract mediated sol-gel synthesis of ZnO nanoparticles for antimicrobial and antioxidant applications. Materials Science in Semiconductor Processing. 2020; 105: 104739.

[16] Guldiken B, Ozkan G, Catalkaya G, Ceylan F D, Yalcinkaya I E, et al. Phytochemicals of herbs and spices: health versus toxicological effects. Food and Chemical Toxicology. 2018; 119: 37 – 49.

[17] Hasnidawani J N, Azlina H N, Norita H, Bonnia N N, Ratim S, et al. Synthesis of ZnO nanostructures using sol-gel method. Procedia Chemistr. 2016; 19: 211 – 216.

[18] Hernández-Morales L, Espinoza-Gómez H, Flores-López Z L, Sotelo-Barrera L E, Núñez-Rivera A, et al. Study of the green synthesis of silver nanoparticles using a natural extract of dark or white Salvia hispanica L. seeds and their antibacterial application. Applied Surface Science. 2019; 489: 952 – 961.

[19] Inamdar H K, Sasikala M, Agsar D, Ambika Prasad M V N. Facile green fabrication of ZnO nanopowders: their antibacterial, antifungal and photoluminescent properties. Materials Today: Proceedings. 2018; 5 (10): 21263 – 21270.

[20] Iqbal J, Abbasi B A, Mahmood T, Kanwal S, Ahmad R, et al. Plant-extract mediated green approach for the synthesis of ZnONPs: Characterization and evaluation of cytotoxic, antimicrobial and antioxidant potentials. Journal of Molecular Structure. 2019; 1189: 315 – 327.

[21] Jayabalan J, Mani G, Krishnan N, Pernabas J, Devadoss J M, et al. Green biogenic synthesis of zinc oxide nanoparticles using Pseudomonas putida culture and its In vitro antibacterial and anti-biofilm activity. Biocatalysis and Agricultural Biotechnology. 2019; 21.

[22] Kalpana V N, Kataru B A S, Sravani N, Vigneshwari T, Panneerselvam A, et al. Biosynthesis of zinc oxide nanoparticles using culture filtrates of Aspergillus niger : Antimicrobial textiles and dye degradation studies. OpenNano. 2018; 3: 48 – 55.

[23] Khalid A, Khan R, Ul-Islam M, Khan T, Wahid F. Bacterial cellulose-zinc oxide nanocomposites as a novel dressing system for burn wounds. Carbohydrate Polymers. 2017; 164: 214 – 221.

[24] Khan S A, Noreen F, Kanwal S, Iqbal A, Hussain G. Green synthesis of ZnO and Cu-doped ZnO nanoparticles from leaf extracts of Abutilon indicum, Clerodendrum infortunatum, Clerodendrum inerme and investigation of their biological and photocatalytic activities. Materials Science and Engineering: C. 2018; 82: 46 – 59.

[25] Khanna P, Kaur A, Goyal D. Algae-based metallic nanoparticles: Synthesis, characterization and applications. Journal of Microbiological Methods. 2019; 163.

[26] Khatami M, Alijani H Q, Heli H, Sharifi I. Rectangular shaped zinc oxide nanoparticles: green synthesis by Stevia and its biomedical efficiency. Ceramics International. 2018; 44(13): 15596 – 15602.

[27] Król A, Pomastowski P, Rafińska K, Railean-Plugaru V, Buszewski B. Zinc oxide nanoparticles: synthesis, antiseptic activity and toxicity mechanism. Advances in Colloid and Interface Science. 2017; 249: 37 – 52.

[28] Lingaraju K, Naika H R, Nagabhushana H, Nagaraju G. Euphorbia heterophylla (L.) mediated fabrication of ZnO NPs: Characterization and Evaluation of antibacterial and anticancer properties. Biocatalysis and Agricultural Biotechnology. 2019; 18: 100894.

[29] Madhumitha G, Fowsiya J, Gupta N, Kumar A, Singh M. Green synthesis, characterization and antifungal and photocatalytic activity of Pithecellobium dulce peel–mediated ZnO nanoparticles. Journal of Physics and Chemistry of Solids. 2018; 127: 43 – 51.

[30] Malaikozhundan B, Vaseeharan B, Vijayakumar S, Pandiselvi K, Kalanjiam M A R. Biological therapeutics of Pongamia pinnata coated zinc oxide nanoparticles against clinically important pathogenic bacteria, fungi and MCF-7 breast cancer cells. Microbial Pathogenesis. 2017; 104: 268 – 277.

[31] Matinise N, Fuku X G, Kaviyarasu K, Mayedwa N, Maaza M, (2017). ZnO nanoparticles via Moringa oleifera green synthesis: Physical properties & mechanism of formation. Applied Surface Science. 2017; 406: 339 – 347.

[32] Menon S, Kumar S V, Agarwal H, Gopalakrishnan D. Characterization and optimization of bacterium isolated from soil samples for the production of siderophores. Resource-Efficient Technologies. 2017; 3(4): 434 – 439.

[33] Mirzaei H, Darroudi M. Zinc oxide nanoparticles: Biological synthesis and biomedical applications. Ceramics International. 2017; 43(1): 907 – 914.

[34] Mishra P K, Mishra H, Ekielski A, Talegaonkar S, Vaidya B. Zinc oxide nanoparticles: a promising nanomaterial for biomedical applications. Drug Discovery Today. 2017; 22(12): 1825 –1834.

[35] Mohammadi Arvanag F, Bayrami A, Habibi-Yangjeh A, Rahim Pouran S. A comprehensive study on antidiabetic and antibacterial activities of ZnO nanoparticles biosynthesized using Silybum marianum L seed extract. Materials Science and Engineering: C. 2019; 97: 397 – 405.

[36] Molnár Z, Bódai V, Szakacs G, Erdélyi B, Fogarassy Z,et al. Green smynthesis of gold nanoparticles by thermophilic filamentous fungi. Scientific Reports. 2018; 8(1): 3943.

[37] Morandi S, Fioravanti A, Cerrato G, Lettieri S, Sacerdoti M, et al. Facile synthesis of ZnO nano-structures: morphology influence on electronic properties. Sensors and Actuators B: Chemical. 2017; 249: 581–589.

[38] Mosaviniya M, Kikhavani T, Tanzifi M, Tavakkoli Yaraki M, Tajbakhsh P, et al. Facile green synthesis of silver nanoparticles using Crocus Haussknechtii Bois bulb extract: catalytic activity and antibacterial properties. Colloid and Interface Science Communications. 2019; 33: 100211.

[39] Murali M, Mahendra C, Nagabhushan, Rajashekar N, Sudarshana

M S, et al. Antibacterial and antioxidant properties of biosynthesized zinc oxide nanoparticles from Ceropegia candelabrum L. – An endemic species. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2017; 179: 104 – 109.
[40] Muthuvinothini A, Stella S. Green synthesis of metal oxide nanoparticles and their catalytic activity for the reduction of aldehydes. Process Biochemistry. 2019; 77: 48 – 56.

[41] Naveed Ul Haq A, Nadhman A, Ullah I, Mustafa G, Yasinzai M, et al. Synthesis approaches of zinc oxide nanoparticles: the dilemma of ecotoxicity. Journal of Nanomaterials. 2017; 1 – 14.

[42] Nilavukkarasi M, Vijayakumar S, Prathipkumar S. Capparis zeylanica mediated bio-synthesized ZnO nanoparticles as antimicrobial, photocatalytic and anti-cancer applications. Materials Science for Energy Technologies. 2020; 3: 335-353.

[43] Ovais M, Khalil A, Ayaz M, Ahmad I, Nethi S, et al. Biosynthesis of Metal Nanoparticles via Microbial Enzymes: A Mechanistic Approach. International Journal of Molecular Sciences. 2018; (12): 4100.

[44] Pachiyappan J, Gnanasundaram N, Lakshmana Rao G. Preparation and characterization of ZnO, MgO and ZnO-MgO hybrid nanomaterials using green chemistry approach. Results in Materials. 2020; 7.

[45] Perveen R, Shujaat S, Qureshi Z, Nawaz S, Khan MI, et al. Green versus sol- gel synthesis and antimicrobial activity evaluation against panel of pathogens. Journal of Materials Research and Technology. 2020; 9 (4): 7817 – 7827.

[46] Pirhashemi M, Habibi-Yangjeh A, Rahim Pouran S. Review on the criteria anticipated for the fabrication of highly efficient ZnO-based visible-light-driven photocatalysts. Journal of Industrial and Engineering Chemistry. 2018; 62: 1 – 25.

[47] Rauf M A, Owais M, Rajpoot R, Ahmad F, Khan N, et al. Biomimetically synthesized ZnO nanoparticles attain potent antibacterial activity against less susceptible S. aureus skin infection in experimental animals. RSC Advances. 2017; 7(58): 36361 – 36373.

[48] Rudramurthy G, Swamy M, Sinniah U, Ghasemzadeh A. Nanoparticles: alternatives against drug-resistant pathogenic microbes. Molecules. 2016; 21(7): 836.

[49] Sanaeimehr Z, Javadi I, Namvar F. Antiangiogenic and antiapoptotic effects of green-synthesized zinc oxide nanoparticles using Sargassum muticum algae extraction. Cancer Nanotechnology. 2018; 9(1): 3.

[50] Santhoshkumar J, Kumar S V, Rajeshkumar S. Synthesis of zinc oxide nanoparticles using plant leaf extract against urinary tract infection pathogen. Resource-Efficient Technologies. 2017; 3(4): 459 – 465.

[51] Saratale R G, Karuppusamy I, Saratale G D, Pugazhendhi A, Kumar G, et al. comprehensive review on green nanomaterials using biological systems: Recent perception and their future applications. Colloids and Surfaces B: Biointerfaces. 2018; 170: 20 – 35.
[52] Sathishkumar G, Pradeep K J, Vignesh V, Rajkuberan C, Jeyaraj M, et al. Cannonball fruit (Couroupita guianensis, Aubl.) extract mediated synthesis of gold nanoparticles and evaluation of its antioxidant activity. Journal of Molecular Liquids. 2016; 215: 229 – 236.

[53] Sathishkumar G, Rajkuberan C, Manikandan K, Prabukumar S, DanielJohn J, et al. Facile biosynthesis of antimicrobial zinc oxide (ZnO) nanoflakes using leaf extract of Couroupita guianensis Aubl. Materials Letters. 2017; 188: 383 – 386.

[54] Senthilkumar N, Nandhakumar E, Priya P, Soni D, Vimalan M, et al. Synthesis of ZnO nanoparticles using leaf extract of Tectona grandis (L.) and their anti-bacterial, anti-arthritic, anti-oxidant and in vitro cytotoxicity activities. New Journal of Chemistry. 2017; 41(18): 10347 – 10356.

[55] Senthilkumar N, Vivek E, Shankar M, Meena M, Vimalan M, et al. Synthesis of ZnO nanorods by one step microwave-assisted hydrothermal route for electronic device applications. Journal of Materials Science: Materials in Electronics. 2018; 29(4).

[56] Shabaani M, Rahaiee S, Zare M, Jafari S M. Green synthesis of ZnO nanoparticles using loquat seed extract; Biological functions and photocatalytis degradation properties. LWT. 2020; 134: 110133.

[57] Sharma D, Kanchi S, Bisetty K. Biogenic synthesis of nanoparticles: A review. Arabian Journal of Chemistry. 2015; 12 (8): 3576 –3600.

[58] Singh J, Dutta T, Kim K H, Rawat M, Samddar P, et al. Green synthesis of metals and their oxide nanoparticles: applications for environmental remediation. Journal of nanobiotechnology. 2018; 16(1): 84.

[59] Singh P, Kim Y J, Zhang D, Yang D C. Biological synthesis of nanoparticles from plants and microorganisms. Trends in Biotechnology. 2016; 34(7): 588 – 599.

[60] Souza T A, Rosa Souza L R, Franchi L P. Silver nanoparticles: An integrated view of green synthesis methods, transformation in the environment and toxicity. Ecotoxicology and Environmental Safety. 2019; 171: 691 - 700.

[61] Tiloke C, Anand K, Gengan R M, Chuturgoon A A. Moringa oleifera and their phytonanoparticles: Potential antiproliferative agents against cancer. Biomedicine & Pharmacotherapy. 2018; 108: 457–466.

[62] Vijayakumar S, Arulmozhi P, Kumar N, Sakthivel B, Prathip KumarS, et al. Acalypha fruticosa L. leaf extract mediated synthesis of ZnO nanoparticles: Characterization and antimicrobial activities. Materials Today: Proceedings. 2020; 23(1): 73 – 80.

[63] Xu D P, Li Y, Meng X, Zhou T, Zhou Y, et al. Natural antioxidants in foods and medicinal plants: extraction, assessment and resources. International Journal of Molecular Sciences, 2017; 18(1): 96.

[64] Yadav J P, Kumar S, Budhwar L, Yadav A, Yadav M. Characterization and antibacterial activity of synthesized silver and iron nanoparticles using Aloe vera. Journal of Nanomedicine & Nanotechnology. 2017; 7(3): 1000384.

[65] Zielonka A, Klimekochab M. (2017). Fungal synthesis of size-defined nanoparticles. Advances in Natural Sciences: Nanoscience and Nanotechnology. 2017; 8(4): 043001.

[66] Zikalala N, Matshetshe K, Parani S, Oluwafemi O S. Biosynthesis protocols for colloidal metal oxide nanoparticles. Nano-Structures & Nano-Objects. 2018; 16: 288 – 299.