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REVIEW

Green Synthesis of Zinc Oxide Nanoparticles and Their Application in Anticancer Drug Delivery – A Review

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Abstract: Metal and metal oxide nanoparticles have many promising applications in biomedicine and pharmacy. One of the applications that has been widely studied over the last decade is their use as anticancer drug carriers. This review fills a gap in the literature by concentrating exclusively on biosynthesized zinc oxide nanoparticles (ZnO NPs) for targeted anticancer drug delivery. ZnO NPs have been suggested as a feasible prospect, among other metal-based NPs, because of their unique properties and biocompatible nature. The use of ZnO NPs in drug delivery could reduce the dosage of drugs used for cancer treatment and reduce other side effects, by aiming the specific sites of cancer cells. Green methods of synthesis, with the use of natural products and living organisms, have become very popular in last decades due to their numerous advantages. They are not only eco-friendly and less expensive but they also allow to avoid the waste of energy and receive the NPs with well-defined size and morphology. The biosynthesized ZnO NPs have inherent advantages because they are made with the use of bioactive capping agents. Therefore, they show enhanced performance in drug delivery as they have improved stability, biocompatibility and targeting. This review includes a comparative analysis of synthesis methods and a comprehensive survey of their application as nanocarriers for various anticancer drugs. Their development faces several challenges related to synthesis, toxicity, scalability of the process, and limited understanding of the biochemical mechanisms involved in reduction and stabilization of metal ions through biological agents. Although biosynthesized ZnO NPs show a lot of potential as nanocarriers in laboratory conditions, their use in clinical trials is very challenging and requires collaboration between scientists, process engineers, clinicians and regulatory agencies. However, if these challenges are addressed and treated properly, their full commercial value and widespread applications will be enabled.

Keywords: biosynthesis, cancer, targeted drug delivery, nanocarriers, ZnO nanoparticles, green chemistry

Introduction

A diverse application of nanomaterials has opened a new horizon in engineering over the past two decades.[1,2] The term nanomaterial refers to materials with sizes in the range of 1–100 nm. Nanoparticles are manufactured to achieve unique physical and chemical properties that result from their small size, shape, surface area, and conductivity.[3–8] Nanoparticles have been considered as a potential candidate for targeted drug delivery due to their biocompatibility, ease of synthesis, low costs of metal precursors, and successful cellular internalization via endocytosis. The smaller size and larger surface area, as compared to the bulk material, make it easier for NPs to penetrate cell membranes and enable their absorption into cells, that results in better distribution. Different types of NPs are loaded with drugs that reach their targets in strictly defined quantities and then guide the drug release from the nanoparticles.[1,2,9–13] NPs vectors aid in the delivery of hydrophobic drugs, poorly water-soluble drugs, and co-delivery of more than one drug to a specific site due to multiple functionalizations on the NPs surface.[9]

Among the metal and metal oxide nanoparticles, ZnO NPs have been extensively used in various biological applications due to their biocompatibility, biodegradability, nontoxic nature, and unique physico-chemical attributes

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(high surface to volume ratio, crystal structure and wide band gap).[1,4,6,14–16] Numerous studies have established ZnO NPs as one of the most effective antimicrobial and anti-inflammatory agents, as it releases reactive oxygen species (ROS) on its surface.[2,3,17,18] Their biodegradability into Zn^{2+} ions distinguishes them from other NPs (eg gold or silver). Research on the use of ZnO NPs in pharmacy mainly concerns their antibacterial, antifungal, anticancer, antidiabetic, anti-inflammatory, and antioxidant properties.[1,2,7,8,14,19] Humans can be exposed to ZnO NPs through the dermal, oral, and inhalational routes. They can travel throughout the body and penetrate the individual cells, and their nuclei.[7] The use of NPs in targeted drug delivery systems is particularly interesting as traditional cancer treatment (chemotherapy, radiotherapy) have many side effects, including non-specificity and systemic toxicity.[2,8]

The effect of ZnO NPs in drug delivery systems revealed that these NPs aid in the rapid release of the drug and in the next step transition to regulate the release over the treatment period.[2,9] The mechanisms underlying the enhanced cytotoxic potential of anticancer drug-loaded ZnO NPs involve the pH-dependent release of the targeted drug and ZnO NPs in the cytoplasm. Firstly, the drug-loaded ZnO NPs enter the cell through receptor-mediated endocytosis. Then the targeted drugs are released and cause cell death. Additionally, ZnO NPs release Zn^{2+} ions and produce excessive ROS which, subsequently, lead to cancer cell death.[2,20]

The interest in biosynthesized ZnO NPs in drug delivery and cancer treatment is constantly growing (Figure 1). According to the SCOPUS database, there are more than half a thousand publications concerning this topic, and more than 70% of them were published in the last 5 years (data availability: 31 July 2025).

During cancer treatment, ZnO NPs attack specific sites of targeted cells, while almost no harm is experienced by the healthy cells.[4,8] They can also be used as anticancer drug delivery vectors that allow the sustained release of the drug. Nanoparticle vectors aid in the delivery of poorly water-soluble or even hydrophobic drugs and co-delivery of more than one drug to a specific site due to multiple functionalizations on the nanoparticle's surface. Selective targeting reduces the overall concentration of the drug used and consistently the drug release on normal cells, which allows to minimize the negative side effects.[2,9]

Scientists described the role of ZnO NPs in the targeted delivery of anticancer drugs in several articles. However, there are still not many publications about the use of biosynthesized NPs for this purpose.[2,14] The review articles concentrate on the use of different types of metallic NPs in anticancer drug delivery[21] or on the use of ZnO NPs in biomedicine in general.[2–5,18,19] However, to the best of our knowledge, there is no review article focusing on the use of biologically synthesized ZnO NPs as anticancer drug carriers. The presented article focuses on the comparison of the use of biologically synthesized NPs with those synthesized with other methods. Biological synthesis harnesses the natural

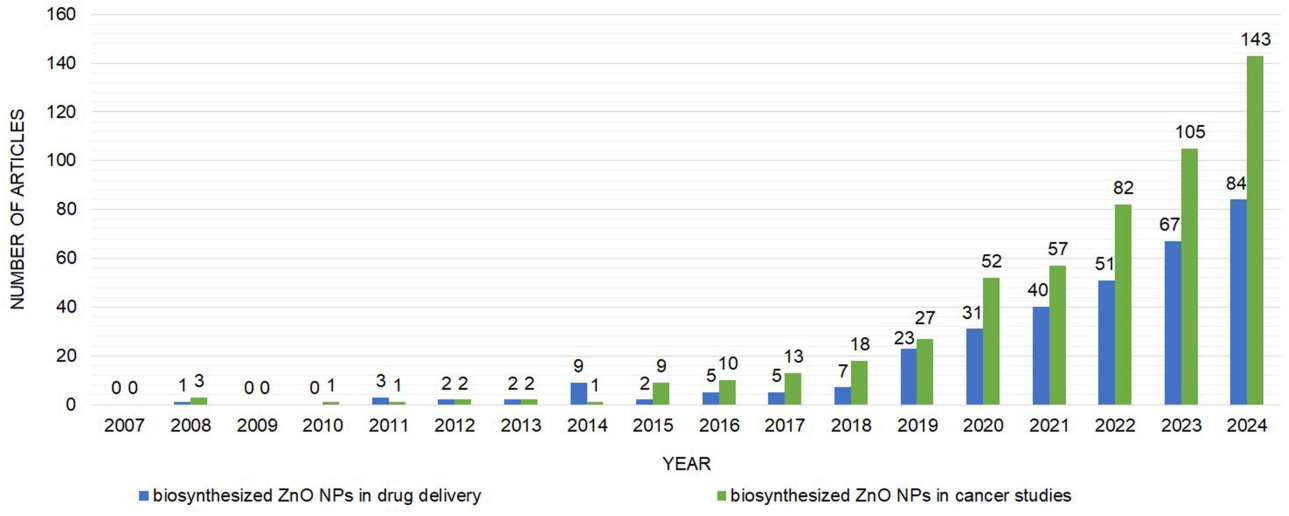

Figure 1 Number of articles on the use of ZnO NPs in anticancer drug delivery over the years (according to SCOPUS database; search phrases: (1) Green OR Biosynthesized AND (Zinc AND Oxide) OR ZnO AND Nanoparticles OR NPs AND Drug AND Delivery; (2) Green OR Biosynthesized AND (Zinc AND Oxide) OR ZnO AND Nanoparticles OR NPs AND Cancer; search in: title, abstract and keywords; data availability: 31 July 2025).

biochemical processes of biological agents (compounds derived from plants, algae, fungi or bacteria) for reduction of metal ions and stabilization of received NPs.[18] This method not only complies with the principles of green chemistry but also enhances the therapeutic potential and biocompability of ZnO NPs. The latest research emphasizes the superior anticancer and antimicrobial properties of ZnO NPs produced via biosynthesis and highlights their potential in biomedical and pharmaceutical applications.[6,18] Biomedical qualities have been improved in biosynthesized ZnO NPs over traditionally produced NPs, which makes them excellent carriers for anticancer drugs.[6]

Despite many advantages of the presented approach, there are still several challenges that need to be addressed before the full benefits of biosynthesis can be achieved, including variability in biosources, difficulties in production scaling, limited understanding of the biochemical mechanisms occurring during synthesis, stability of the product concerns, and regulatory barriers. To overcome these obstacles, advancements in techniques for NPs characterization, integration of biosynthesis with other sustainable technologies (eg novel extraction methods), and interdisciplinary research efforts are required. To ensure the safe and effective use of ZnO NPs in biomedicine and pharmacy, establishing comprehensive regulatory frameworks is essential.[6,18] Undoubtedly, the greatest advantage of biological synthesis of NPs compared to traditional synthesis is its low cost and environmental safety. Traditional chemical methods use toxic solvents and are energy-intensive.[2,6,14]

This review highlights the potential of biosynthesized ZnO NPs in drug delivery systems to remodel current nanopharmacy, providing cost-effective and save for the environment solutions that align with global sustainability goals. It is a comprehensive compilation of recent advances in the use of green ZnO NPs as anticancer drug nanocarriers. The paper will cover methods of ZnO NPs synthesis, their characterization, direct anticancer activity, application in drug delivery, and associated health risks.

Methods of NPs Synthesis

Metallic NPs can be synthesized with the use of top-down (physical) or bottom-up (chemical and biological) methods. These methods are further categorized into various types, depending on the approach adopted. The terms “biosynthesis”, “biological synthesis”, and “green synthesis” are used interchangeably.[2,6,8,18]

Physical Methods

During physical synthesis of NPs, the physical forces are applied as an attraction of nanoscale particles to form well-defined nanoparticles with high stability.[5,19] Physical methods involve breaking down or mechanical crushing of the bulk material into NPs with the use of sonication, laser ablation, mechanical milling, or physical vapor deposition. They are characterized by rapid synthesis, high size variability, and high quantity of impurities. These methods have many disadvantages, including high cost of production, high temperatures, and pressures, large setup spaces for machines, or high time consumption.[3,5,8]

Nanoparticles prepared with the use of mechanical milling include not only contaminants from the milling balls but also from the environment. Moreover, they are irregularly shaped. The most popular physical method is laser ablation. In this technique, metallic ions are removed from metal surfaces by employing a laser beam and a small quantity of liquid (eg methanol, ethanol, and purified water). The main advantages of this method are simplicity and safety from an environmental standpoint, as well as high efficiency. The main disadvantage is the generation of pyrolysis byproducts.[6]

Chemical Methods

The use of chemical methods (NPs synthesized through chemical reactions between atoms, ions, and molecules) allows for to maintenance precise control of size and a low quantity of impurities. Metal ions precursors are used either in solid, liquid, or gas phases to produce metal or metal oxide NPs. Chemical methods include sol–gel process, chemical vapour deposition, and chemical co-precipitation.[3,6] Traditional chemical methods, such as hydrothermal synthesis, chemical precipitation, and the sol-gel method, are well-established and widely used on an industrial scale. They provide controlled size distribution and high purity of received ZnO NPs and are highly effective. Chemical precipitation involves reaction of zinc salts (zinc ion precursors) with alkaline agents to precipitate ZnO NPs, which results in fast reaction rates and high output.[18] It creates metal NPs by simultaneous nucleation, which is followed by growth and then

agglomeration of tiny nuclei. The main drawback is that this method produces NPs that have large quantities of water molecules attached to them.[6]

The most commonly used chemical method is sol-gel synthesis. It uses chemical reagents and zinc ion precursors to regulate the solution pH and prevent the precipitation of $Zn(OH)_2$. Subsequently, the solution is treated thermally to obtain ZnO NPs. During the synthesis, reducing agents like sodium hydroxide or ammonia and stabilizers like citrates or polyvinyl pyrrolidone are usually added to control the morphological properties and to prevent agglomeration of NPs.[2] It produces uniform and pure ZnO NPs that have fine powdered structure through hydrolysis and condensation of zinc ion precursors. The drawbacks of this process include shrinkage, breakage during drying, and an inability to manage proper porosity.[6,8]

Hydrothermal synthesis crystallizes ZnO NPs under high pressure and temperature. This method allows for excellent control over particle size and shape, in addition to high product purity and crystallinity. Moreover, this method has closed system environment, resulting in little pollution. However, it requires expensive equipment (eg autoclave) and it has limitations for research due to the reactor, which cannot be kept open. Another concern is potential safety hazards throughout the autoclave procedure.[6,18]

These traditional methods often require significant energy consumption, contributing to a substantial carbon footprint. The temperature and pH conditions need to be strictly controlled. However, traditional methods have established protocols and infrastructure that ensure consistent and reproducible properties of ZnO NPs across different batches. They are also highly scalable, but the costs associated with energy consumption and residues after synthesis management remain high.[18]

Biological Methods

Recently, eco-friendly biological methods of synthesis, using natural products and living organisms, have become very popular. The main advantages of these methods are lower cost and lower waste of energy. Furthermore, they are scalable for large production and allow to receive NPs that have well-defined size and morphology.[2,4,19] Moreover, nanomaterials synthesized with conventional physical or chemical methods are claimed to play havoc with the environment, as they may employ toxic compounds, including organic solvents, stabilizers, and reducing agents, and result in non-ecofriendly byproducts.[3,4,6,19,22] The green methods of NPs synthesis generally require lower energy consumption that results in a reduced carbon footprint. The difference in the toxicity profile of chemically and biologically synthesized nanoparticles is not yet fully understood. However, it can be confidently assessed that simply switching to a biological synthesis method has a beneficial effect on reducing their environmental toxicity, as it minimizes hazardous chemical waste by utilizing biodegradable or renewable materials.[18]

Biosynthesized ZnO NPs show better biological activity than chemically synthesized NPs. Their surface is coated with various pharmacologically active biomolecules, which allows multiple ligand-based conjugations of NPs with their respective receptors and leads to better bioactivities. These comparisons have suggested that ZnO NPs possess better bioactivities when they are biosynthesized from the potential reducing agents present in the microorganisms, algae, or plants.[2,18] Scientists indicate that functionalization of different types of metallic nanoparticles with phytochemicals or chemical groups leads to steric hindrance and prevents agglomeration.[9] Another key advantage of biosynthesized NPs as compared to the traditionally synthesized is the possibility to manipulate the reaction conditions to optimize the preferred shape and size of the NPs.[23]

Despite being environmentally friendly, green methods of ZnO NPs synthesis face challenges related to scalability and consistency. The main problems with biological methods of NPs synthesis are nanoparticle stability and a lack of understanding of their mechanisms. Moreover, the purification and processing of NPs post-synthesis to remove biological contaminants is often complex and multi-stage. The size and morphology control of ZnO NPs is crucial for their application. However, achieving uniformity still remains challenging with biosynthesis.[18,24,25] To overcome this, it is essential to standardize biological materials and develop robust protocols. Although the initial costs for research and development of biological NPs synthesis methods are high, investing in pilot projects and forming partnerships between public research centers and industry can share the costs and risks and make green methods more economically viable.[18]

Green methods of NPs synthesis involve the use of a variety of natural resources (Figure 2) that include plants,[26–34] bacteria,[35–37] fungi,[24,35,38–46] and algae.[47–51] Active enzymes and phytochemicals of the biotic source act as reducing and capping agents, that allow the mass production of NPs.[2,3] The scheme of NPs biosynthesis is presented in Figure 3, while the mechanism of NPs biosynthesis is presented in Figure 4.

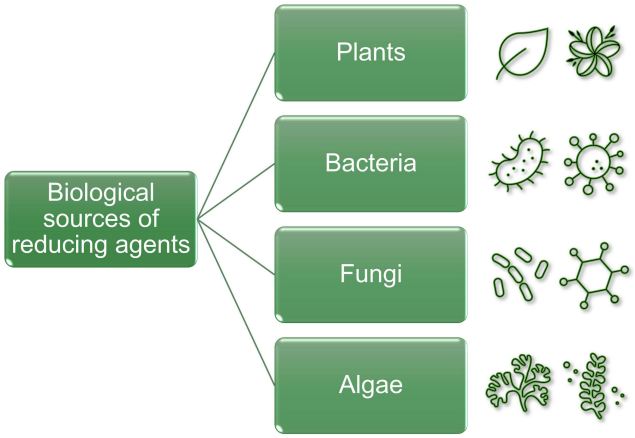

Figure 2 Biological sources of reducing agents used of biosynthesis of ZnO nanoparticles.

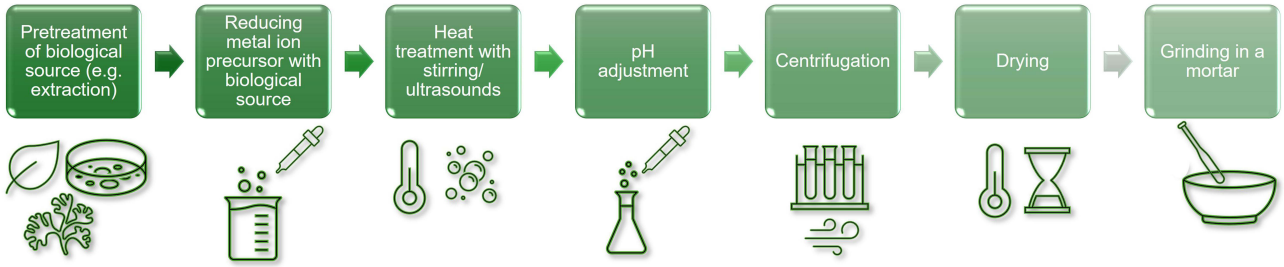

Figure 3 Scheme of ZnO NPs biosynthesis.

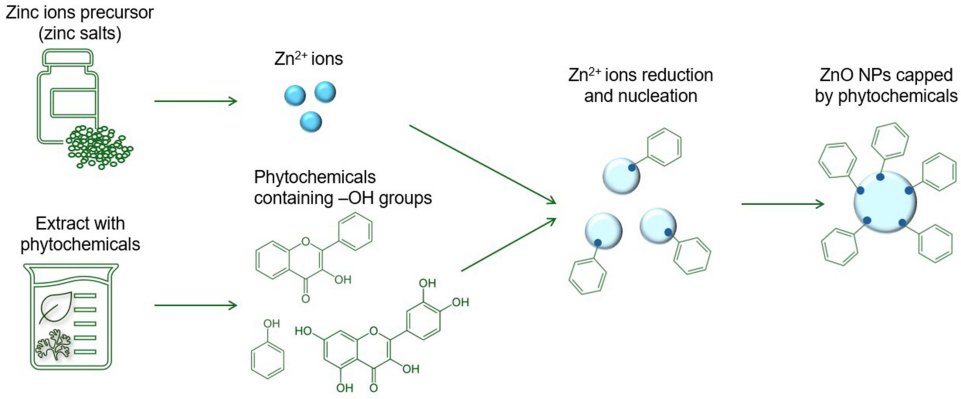

Figure 4 Mechanism of ZnO NPs biosynthesis.

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Plants

Usually, in green methods of NPs synthesis, plant extracts are used.[4] Among the different biotic sources, plants are considered to be the most widely available. They possess phytoconstituents that are reported to be beneficial to human health in various ways. Phytoconstituents can not only act as reducing agents but also play a key role in the capping of nanoparticles. This ability is crucial for their stability and biocompatibility. Moreover, no extra chemical reducing and capping agents are required. Furthermore, they act as a linker molecule between two or more molecules of ZnO NPs, making them self-assemble.[2,25] Additionally, ZnO NPs mediated from plant-based extracts have better antimicrobial potential against human pathogens and various infections caused by bacteria and fungi.[19]

The process of metallic nanoparticle synthesis from plant-based extracts consists of three stages: activation phase, development phase, and process termination phase. In the activation phase, metal ions from precursors are reduced, leading to the creation of reduced metal atoms. During the second phase, the formation of small NPs occurs nearby, resulting in the creation of larger particles. Metal ions undergo heterogeneous nucleation, expansion, and subsequent reduction. The development phase also results in an augmentation of the thermodynamic stability of the NPs. The last phase determines the final morphology and structure of the nanoparticles.[25]

Plant parts such as leaves,[27,30–34,52–65] seeds,[66–69] seed husks,[70] fruits,[26,28] fruit hull,[71] fruit peels,[32,72,73] fruit rough shell,[74] flowers,[29] tree branches,[75] stem barks,[76,77] rhizomes,[78] bulbs,[79] and roots[80–82] have been extensively used for the synthesis of ZnO NPs in the recent past. Synthesized NPs are found to be highly pure, stable, cost-effective to produce, and possess greater biomedical properties, as compared to the NPs synthesized with conventional methods. During this synthesis, metal precursors (metal salts, like zinc nitrate, zinc sulphate, or zinc acetate) are reduced to metal (or metal oxide) NPs by plant phytochemicals such as phenolic acid, polyphenols, terpenoids, alkaloids, and polysaccharides that act as stabilizing agents.[2,3]

Despite numerous advantages, the use of plant extracts in NPs biosynthesis is also associated with certain problems. The main drawbacks of this synthesis method include inconsistent composition of plant-based extracts, the requirement for careful biological material sterilisation, a time-consuming, labor-intensive extraction and synthesis procedure, and possible difficulties in scaling up for commercial usage.[5]

Bacteria

NPs synthesis with the use of bacteria is less explored than with the use of plant extracts. This method of synthesis shows added benefits in comparison to the one with the use of plants due to the microbial reproducibility and the ease of genetic mutation and manipulation.[5] However, it also has many disadvantages, including: the need for screening of microorganisms, the need for a contamination-free environment for the entire biosynthesis process, the requirement for continuous broth culture, the lack of control on NPs size and morphology, and the high cost of nutrient media for microbial growth.[3,5,6] Various enzymes, biomolecules, and proteins in bacteria are recognized as capping agents that are used in the process of forming multiple-sized nanoparticles. Microbial cultures are grown in medium, and metal ion precursor is introduced in the form of metal salts. The reaction time takes around a few hours.[3,35]

Bacteria can create NPs both intracellularly and extracellularly. ZnO NPs are manufactured in the presence of enzymes, ions, cofactors, and other components. Intracellular production is connected with the movement of ions inside the bacteria cell. Zinc interacts with bioactive molecules (like polysaccharides, glycoproteins, and enzymes) produced by bacteria cells during extracellular formation of NPs to produce Zn or ZnO NPs.[5] The participation of bacterial extracellular enzymes and proteins allows to control the size and stability of the NPs. The lactic acid bacteria can also produce exopolysaccharides, which serve as an additional site for metal ions biosorption. They also have electrokinetic potential that allows them to attract Zn^{2+} ions for the NPs synthesis under both oxidative and reductive conditions.[23]

ZnO NPs synthesized with the use of bacteria have not yet been used in anticancer drug delivery. However, ZnO NPs were synthesized with the use of *Lactobacillus* spp.,[37] *Rhodococcus pyridinivorans*[35] and *Streptomyces* sp.[36,83] showed anticancer activity. The mechanism of microbe-mediated ZnO NPs biosynthesis, divided into intracellular and extracellular synthesis, is presented in Figure 5.

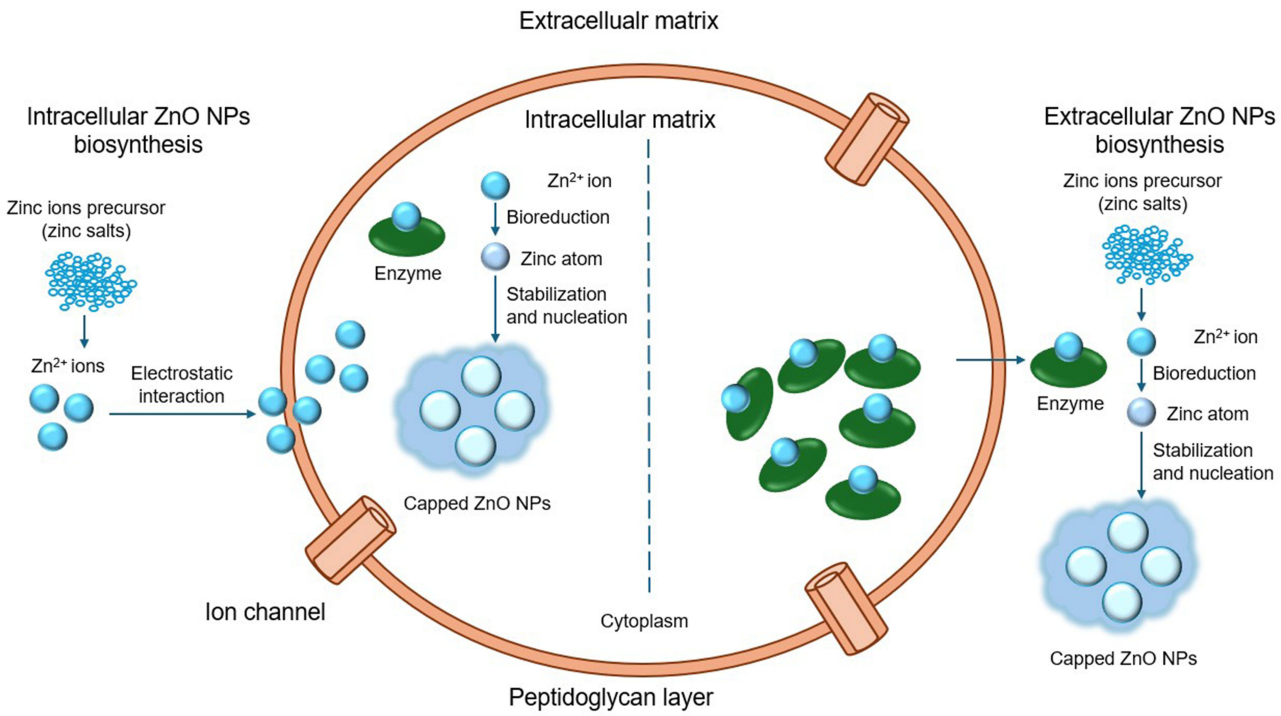

Figure 5 Mechanism of microbe-mediated ZnO NPs biosynthesis.

Fungi

Fungi biomass serves as a renewable and readily available resource for producing ZnO NPs.[18,43] Fungi are preferred more than bacteria for the biosynthesis of NPs because of higher ability to accumulate metals in their bodies. Benefits of using fungus for the green synthesis of ZnO NPs include effective NPs generation and simple processing.[1,5] Generally, during cultivation, the fungal strain is maintained in a sterile environment with a strictly controlled temperature. After a set period, the liquid medium rich in fungal byproducts, is separated by filtration and centrifugation. The received solution is then used to the biosynthesis of ZnO NPs.[18,23,44]

Fungal extracts are cell-free. Their ability to potentially cap and reduce the size of synthesized ZnO NPs was demonstrated in the literature as dependent on the species type. The possible mechanism of biosynthesis of ZnO NPs with the use of fungi involves the initial transformation of zinc ions precursor into the NPs, followed by capping of fungal extracellular proteins on the surface of NPs.[23,42]

The main disadvantage of this method is the unpredictable nature of fungal species, which may affect its scalability and repeatability. Potential problems may also include difficulties involved in growing and extracting from fungal cultures.[5] Biosynthesis with the use of fungi requires specific environmental conditions (precise temperature and pH) and a balanced supply of nutrients. Moreover, extended incubation times are required for fungal cultures, as they grow slower than bacterial cultures. The yield and quality of ZnO NPs are significantly affected by medium composition, aeration and light exposure, which makes their reproducibility difficult. These biological variabilities complicate the scaling up of the process and make it harder to use for industrial applications. Environmental and health concerns must also be addressed, necessitating strict biosafety measures to prevent contamination and mitigate potential health risks associated with handling live fungal cultures.[18]

ZnO NPs biosynthesized with the use of fungi are not yet widely tested as carriers for anticancer drugs.[84] However, they were used in different fields of biomedicine.[23] ZnO NPs synthesized with the use of *Aspergillus niger*,[38,42,43,85,86] *Aspergillus terreus*,[46] *Cordyceps militaris*,[39] *Dictyota dichotoma*,[44] *Fusarium keratoplasticum*,[42] *Lentinula edodes*,[87] *Phanerochaete chrysosporium*,[88] *Pichia fermentans*[89] *Pichia kudriavzevii*,[90] and *Trichoderma viride*[45] were used as an antimicrobial agent

and showed antioxidant activity. Moreover, ZnO NPs synthesized with the use of *Alternaria tenuissima*,[91] *Aspergillus niger*,[38,86] *Aspergillus terreus*,[46] *Fusarium chlamydosporum*,[40] and *Xylaria acuta*[41] showed anticancer activity.

Algae

The utilization of both micro- and macroalgae as the source of reducing agents in the biosynthesis of ZnO NPs is relatively low. The potential of microalgae to break down hazardous metals and transform them into less harmful forms has drawn significant attention.[6,92,93] In case of macroalgae, the use of their extracts for the NPs biosynthesis deserves particular interest because many species of macroalgae are widely considered to be waste resulting from water eutrophication and are even harmful to the environment.[94] Moreover, they are known to hyperaccumulate heavy metal ions and possess the ability to remodel them into different, more malleable forms.[22,50] All types of algae can be used for both intracellular and extracellular biosynthesis of almost all metallic nanoparticles (including ZnO NPs) due to the presence of bioactive compounds such as pigments, polysaccharides, polyphenols, vitamins, lipids, proteins, and antioxidants that act as biocompatible reductants and offer several functional groups such as carboxyl and hydroxyl sulfate and amino, which play important roles in the formation and stabilization of NPs.[22] The intracellular synthesis takes place inside the cell, where the reducing agents may be NADPH. Extracellular synthesis takes place outside the cell and is mainly supported by the exudates of cell metabolism comprising metabolites, enzymes, pigments, ions, lipids and microbial by-products.[22,50]

Moreover, algae contain cytotoxic substances, including laminarians, terpenoids, and fucoidans, which can combat cancer, inhibit proliferation, and suppress tumors. They are highly recommended for green synthesis of different types of NPs for the pharmaceutical and biomedical sector, due to their lack of external reducing or capping agents, high energy efficiency, affordability, and safety for human health and the environment.[18]

Characterization of ZnO NPs

The versatile surface chemistry of ZnO NPs increases their potential as a drug carrier.[20] Usually, to confirm the presence of obtained nanoparticles, UV-Vis spectroscopy is used.[2,3,19] The morphology and surface chemistry of NPs influence their biodistribution, effectiveness in biological systems and biosafety. Characterization of ZnO NPs is the core tool for understanding and successful applications of the NPs. NPs size characterization is complicated by the polydispersity of materials and aggregation. It is very important to determine the morphology since their size's resemblance to biological moieties is assumed to impart their distinct capabilities in nanomedicine.[1] The morphology of the NPs is determined using electron microscopy, such as Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM), or Atomic Force Microscopy (AFM). The crystal structure and chemical composition are calculated using X-Ray Diffraction (XRD), for the determination of the elements present Energy Dispersive X-Ray Spectroscopy (EDS or EDX), is used and to describe the functional groups present on the surfaces of the nanoparticles Fourier transform infrared (FT-IR) spectroscopy is used. The Dynamic Light Scattering (DLS) and Zeta Potential are used to determine the size and dispersion of the nanoparticles in an aqueous suspension.[2,3,19]

UV-Vis Spectroscopy

Interaction of UV–Vis radiation with the tested sample gives a peculiar spectrum for particular chemical species.[8] The biosynthesis of NPs is initiated by mixing the extract (plant or algal) or strain (bacterial or fungal) with a metal precursor under appropriate conditions (including temperature, pH, time, and metal precursor concentration). The initiation of the reaction is usually recognized by a color change or precipitation. UV-Vis spectroscopy is typically used to confirm the appearance of nanoparticles in solution.[8,19,22,95] Synthesized ZnO NPs are scanned in the UV region of the electromagnetic wave around 200–700 nm.[19,22] The interaction between light and the mobile surface electrons of ZnO NPs produced the SPR (surface plasmon resonance).[19] The presence of ZnO NPs in the solution received after the synthesis (before centrifugation) is confirmed by the peak around 350 nm.[95] However, reaction conditions, like type and volume of the extract, can cause a shift in the SPR bands of ZnO NPs (±30 nm).[9,19]

SEM/TEM

Microscopic techniques are an important tool for the characterization and imaging of ZnO NPs. Optical microscopy cannot resolve nanostructures and, therefore, electron microscopy is used to characterize the NPs. Electron microscopy gives exact information about the size, structure, aggregations, shape, spatial resolution, and composition of ZnO NPs.[1,9,19]

SEM is a technique for high-resolution surface imaging, used for obtaining information about the structural details of samples at the nano and micro scale via high-energy electron beam.[5,8] SEM images are useful for ZnO NPs surface topological assessment as they depend on the electron density of the surface and allow for greater depth of field and high magnification. The determination of the morphology using this technique is via direct visualization. ZnO NPs are exposed to electron beams and the signals are generated and recorded by the detector. Information about the morphological identity, crystalline structure, and orientation of the ZnO NPs are deduced from the recorded signal.[19]

TEM is the second most commonly used microscopic technique in ZnO NPs characterization. It allows us to apprehend the chemical and electronic nature of NPs.[8,9] The application of TEM as a characterization tool is based on the interaction of a thin sample of ZnO NPs and the current density electron beam. When the electron beam and tested sample are in contact, the electrons are either transmitted or scattered. The images that reveal the morphological properties of NPs are produced from the transmitted electrons from the TEM machine, and the extent of the interaction between the transmitted electron and the sample influences the size and shape of the ZnO NPs.[19] It can magnify things up to 2 million times.[5] The ZnO NPs have different shapes, including snowflake-like, flower-like, rod-shaped, spherical, hexagonal, and cubic-like.[15,96]

DLS

The size plays an important role in defining ZnO NPs in terms of uniform particle size distribution in formulations and their use for drug release. The most commonly used method for measuring NPs, except for microscopic methods, is DLS.[1,5] Some biological molecules, such as proteins and liposomes, do not deflect the electron beam sufficiently and are invisible to electromagnetic radiation, and therefore, DLS is used to characterize these compounds in suspensions and solutions. It is a non-destructive approach that uses a monochromatic laser and is also known as photon correlation spectroscopy.[1] DLS is used to analyze the hydrodynamic particle size and distribution of the particles over a range of sizes. This method was successfully employed in determining nanoparticle stabilities in various media such as buffers or simulated biological fluids.[5] It shows the zeta potential, conductivity, polarity, and mobility of the synthesized NPs.[8]

Zeta potential analysis is used to quantify the overall surface charge of the tested ZnO NPs and reflects their colloidal stability. The magnitude of the zeta potential value reaches the maximum when the formation of small-sized NPs is complete. The crystallite size decreases at the phase of optimal growth, which leads to an increase in the overall surface charge. The formation of any unstable aggregates in the reaction results in a drop in the Zeta potential.[9] Zeta potential may have an effect on the pharmacokinetic characteristics of biological nanosystems. Its values may vary from −40 to +40 mV.[2,5]

XRD

XRD technique is used to determine the phase and crystallinity of ZnO NPs and crystallite size. During XRD analysis, ZnO NPs are exposed to energetic rays from the X-ray diffractometer, which penetrate through them to provide data about their structure.[8,9,19] Due to the absence of a diffraction peak, this technique cannot be used for estimating the amorphous structure of NPs. A diffraction pattern is formed when surface atoms scatter the light beam incident upon them and these scattered beams show constructive or destructive interference.[9] The broadening of the XRD pattern signifies the nanosize of the particles.[19] XRD pattern is used to comprehend critical crystal features like crystal phase, unit cell dimension, crystallite size, lattice parameter, and phase purity. XRD patterns allow us to assess whether the used synthesis method leads to optimum formation of ZnO NPs in a pure form without interfering intermediates. The pattern of diffraction peaks indicates the structure of synthesized ZnO NPs. Sharp diffraction peaks indicate optimum formation of ZnO NPs with a good degree of crystallinity. A good separation in the peaks indicates a lack of any other complexing intermediates. The absence of any other peaks in the XRD spectrum other than those attributed to ZnO indicates

complete decomposition of all metal ion precursors and the presence of only ZnO with no other intermediate complexes.[5,9] The crystallinity of the product can be indicated by the strong and narrow diffraction peaks.[96]

EDX

Several SEM instruments are equipped with energy-dispersive X-ray spectroscopy.[9] EDX has been reported by many researchers as a suitable technique for the analysis of the elemental composition of ZnO NPs. This analysis is possible as each element has a unique atomic structure that produces distinct peaks on the X-ray spectrum.[19] Each chemical species has a different pattern, and hence this analysis gives the detailed elemental composition of the synthesized NPs.[8] The EDX technique can also be used for the examination of the ZnO NPs purity.[9,19] The chemical constituent of the extracts used as a reducing agent for biosynthesis has been reported to be the source of other elements, eg oxygen or carbon, on the EDX.[19]

FT-IR

FT-IR is used to analyze the surface chemistry of ZnO NPs.[5,9] The investigation of the interaction between zinc ion precursors and biological extracts using FT-IR gives insight into biomolecules responsible for the reduction and stabilization process of ZnO NPs. When ZnO NPs are bombarded with infrared radiation, some of these radiations are absorbed, while some remains unabsorbed. The unabsorbed radiation produces the molecular fingerprint that represents the identity of the biosynthesized ZnO NPs.[5,19] The intensity, position, and shape of an absorption band in the FT-IR spectrum are used to interpret the type of functional groups and chemical bond present.[8,9] Many researchers have pointed out the importance of FT-IR in determining the effectiveness of biological extracts as reducing agents. The use of the FT-IR technique in the characterization of green synthesized ZnO NPs has been helpful in pointing out the biomolecules responsible for the complete formation of ZnO NPs. The sharpness and intensity of the peak corresponding to the ZnO bond leads to the conclusion that there is optimal synthesis of ZnO NPs.[9] FT-IR analysis has shown that extracts containing various biomolecules with functional groups such as C=O, C=C, C-H, C-N, N-H, and –O-H are good reducing agents for the biosynthesis of ZnO NPs.[19] Absence of any other sharp peaks than those attributed to the ZnO bond and the bonds corresponding to the biomolecules indicates a good degree of purity of the biosynthesized ZnO NPs.[9] FTIR scans up to 50 times per minute and gives better resolution than traditional IR.[5]

Anticancer Activity of Biosynthesized ZnO NPs

Anticancer medicines cannot distinguish between cancer cells and normal cells, which results in systemic toxicity and other side effects. For this reason, new drugs with anticancer activity and high selectivity towards cancerous cells are needed. Therapeutic and diagnostic techniques based on nanotechnology are very promising in improving cancer therapy in recent years. Nanomedicine technologies have cleared the path for novel targeted cancer therapies as they allow the therapeutic compounds to be encapsulated in nanomaterials (eg metallic nanoparticles) and delivered selectively to tumors via passive permeation and active internalization mechanisms.[14] Because ZnO NPs have better electrostatic characteristics than other NPs, they are particularly useful for targeting cancer cells.[5] Modern nanomedicine technology has progressed to the point that several nanodrugs for cancer treatment are already on the market. Moreover, there are many more nanomedicines employing various nanosystems in advanced phases of development and clinical testing. These nanomedicines include metal-based NPs (for example, Fe NPs for prostate, colorectal, and hepatic cancer or Au NPs for salivary gland tumor).[14,97]

The small size of ZnO NPs aids in the permeation and retention of NPs within tumorous cells. Moreover, ZnO NPs have special electrostatic properties that aid in the selective targeting of cancer cells. Anionic phospholipids are abundant on the surface of cancer cells, which results in electrostatic attraction with ZnO NPs, that encourages cancerous cells to take up ZnO NPs, resulting in cytotoxicity in cancer cells.[19] Scientists point to two possible mechanisms behind the selective pH-responsive cytotoxicity of ZnO NPs towards cancer cells. The first one is the pH-dependent rapid dissolution of ZnO NPs into the release of Zn^{2+} ions under an acidic intracellular environment that causes ROS production and oxidative stress. Subsequently, it leads to cell damage within DNA, proteins and lipids in cancer cells. The dimensions of ZnO NPs (their crystallinity and surface area) affect their ability to cause oxidative stress, which results in apoptosis and inflammation.[2,5,14,18] Cells undergo apoptosis through distinct pathways, which results in the activation of the caspase-8, mitochondria-dependent path and the caspase-3-dependent pathway. It triggers the

cytoplasmic release of pro-apoptotic mitochondrial proteins.[63] Neutral hydroxyl groups attached to ZnO NPs change their surface charge behavior. At high pH values, protons move away from the surface of the particle, giving the surface oxygen atoms a negative charge. In solutions with lower pH values, positively charged zinc hydroxide ($ZnOH^{2+}$) forms on the particle surface. ZnO NPs have a positive surface charge and an isoelectric point around 6.6 ± 0.2 in healthy conditions. However, cancer cell membranes have a markedly negative potential as they contain many anionic phospholipids. The positive charge of ZnO NPs enhances their interactions with cancer cells, which results in increasing cellular absorption, cytotoxicity, and phagocytosis [18]. The second mechanism is the relatively large production of ROS in cancer cells as compared to normal cells, which causes mitochondrial dysfunction and activates the intrinsic mitochondrial apoptotic pathway.[2,5,14,18] The loss of mitochondrial membrane potential and activation of mitogen-activated protein kinase (MAPK) pathways leads to apoptosis.[20]

Small size of ZnO NPs results in higher anticancer activity as it leads to better cellular uptake and cytotoxicity through apoptosis.[14] The surface sites in the ZnO are the origin of charge trapping states that can be passivated by inorganic shells or by adsorption of organic molecules on the surface of ZnO nanoparticles.[98] ZnO NPs energy band gap falls in a range of a semiconductor. It possesses photocatalytic activity and is correlated with cytotoxic propensity of ZnO NPs.[60,79] The band gap of ZnO NPs is affected by different factors (including size, phase structure, surface functional groups and crystallinity of the NPs) and is lower than the band gap of bulk ZnO.[99] Moreover, Stan et al observed a narrowing of the band gap for biosynthesized ZnO NPs as compared to the NPs synthesized without the use of extract. A lower band gap assures a rapid generation of an electron(e-)-hole(h+) pair in the sample. The generated electron and hole migrate separately to the surface of the catalyst and react with the ROS.[79] Mechanism of anticancer activity of ZnO NPs is presented in Figure 6.

The anticancer activity of biosynthesized ZnO NPs has been validated against a variety of human cancer cell lines. The summary of biological materials used for synthesis of ZnO NPs for treatment of different cancer types is presented in Table 1. The most commonly treated cancer types in these studies were breast cancer,[32,38,54,61,67,68,70,74,76,91,100] colon cancer,[35,37,40,46,48,49,55,69,73,77,78,101] and lung cancer.[28,36,54,57,60,62,65,73,82,99,101]

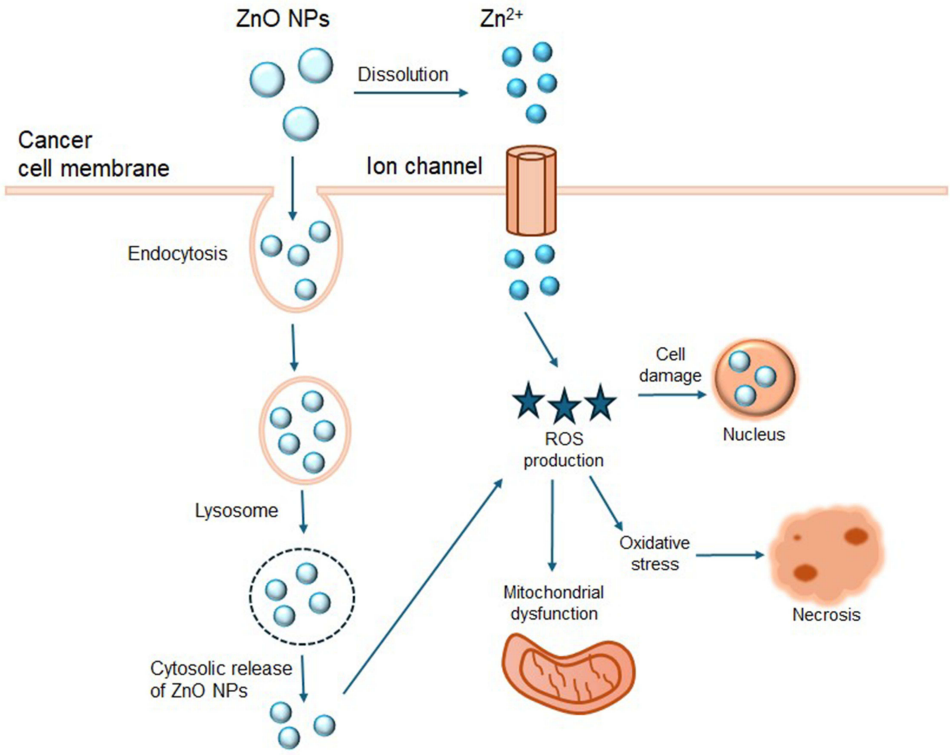

Figure 6 Mechanism of anticancer activity of ZnO NPs.

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According to Al-darwesh et al bioactive compounds from extracts attach on to biosynthesized ZnO NPs surface and improve their bioavailability and cell-killing potential.[104] The research conducted on colorectal cancer resulted in inhibition of Bcl-2, Bax and p53 gene expression by ZnO NPs synthesized with *L. sativum* extract.[69] Despite in-depth research conducted by numerous research groups, more thorough knowledge about the interactions between ZnO NPs and cancer cells is needed.[104]

Table 1 The Use of the Biosynthesized ZnO NPs in Anticancer Therapy

Biological Material for Synthesis	Type of Cancer	Cell Line	Reference
Plants			
Abutilon indicum	Cervical cancer	HeLa	[33]
Albizia lebbeck	Breast cancer	MCF-7	[76]
Albizia lebbeck	Breast cancer	MDA-MB231	[76]
Alhagi maurorum	Osteosarcoma cancer	A141B1	[34]
Alhagi maurorum	Osteosarcoma cancer	G-292	[34]
Alhagi maurorum	Osteosarcoma cancer	HOS	[34]
Alhagi maurorum	Osteosarcoma cancer	Hs 707(A).T	[34]
Alhagi maurorum	Osteosarcoma cancer	MG-63	[34]
Alhagi maurorum	Osteosarcoma cancer	Clone Saos-2	[34]
Amygdalus scoparia	Colon cancer	LS180	[77]
Anacardium occidentale	Pancreatic cancer	AsPC-1	[52]
Annona squamosal	Cervical cancer	HeLa	[56]
Artemisia scoparia	Liver cancer	Huh-7	[102]
Artocarpus heterophyllus	Colon cancer	HCT-116	[55]
Bergenia ciliata	Cervical cancer	HeLa	[78]
Bergenia ciliata	Colon cancer	HT-29	[78]
Cucubrita pepo	Osteosarcoma cancer	MG-63	[53]
Cucurbita sp.	Breast cancer	MDA-MB231	[68]
Cucumis melo inodorus	Breast cancer	MCF-7	[74]
Cynara scolymus	Breast cancer	MCF-7	[61]
Deverra tortuosa	Colon cancer	Caco-2	[101]
Deverra tortuosa	Lung cancer	A549	[101]
Eclipta prostrata	Liver cancer	Hep-G2	[63]
Euphorbia fischeriana	Lung cancer	A549	[82]
Euphrasia officinalis	Breast cancer	MCF-7	[32]
Hyssops officinalis	Prostate cancer	PC3	[59]
Hyssops officinalis	Breast cancer	MDA-MB231	[100]

(*Continued*)

Table 1 (Continued).

Biological Material for Synthesis	Type of Cancer	Cell Line	Reference
Laurus nobilis	Lung cancer	A549	[62]
Lepidium sativum	Colon cancer	Caco-2	[69]
Lepidium sativum	Colon cancer	SW480	[69]
Limonium pruinosum	Epidermoid cancer	A-431	[103]
Lycopersicon esculentum	Cervical cancer	HeLa	[58]
Mangifera indica	Lung cancer	A549	[65]
Marsdenia tenacissima	Laryngeal cancer	Hep-2	[30]
Murraya koenigii	Gastric cancer	MGC803	[31]
Mussaenda frondosa	Lung cancer	A549	[99]
Ocimum sanctum	Breast cancer	MCF-7	[32]
Pandanus odorifer	Breast cancer	MCF-7	[54]
Pandanus odorifer	Liver cancer	Hep-G2	[54]
Pandanus odorifer	Lung cancer	A549	[54]
Piper betle	Breast cancer	MCF-7	[32]
Pongamia pinnata	Breast cancer	MCF-7	[67]]
Punica granatum	Breast cancer	MCF-7	[32]
Punica granatum	Cervical cancer	HeLa	[73]
Punica granatum	Colon cancer	HCT-116	[73]
Punica granatum	Lung cancer	A549	[73]
Raphanus sativus	Lung cancer	A549	[60]
Rehmanniae radix	Osteosarcoma cancer	MG-63	[80]
Rosa canina	Lung cancer	A549	[28]
Scutellaria baicalensis	Cervical cancer	HeLa	[81]
Tecoma castanifolia	Lung cancer	A549	[57]
Vigna mungo	Breast cancer	MDA-MB231	[70]
Ziziphus nummularia	Cervical cancer	HeLa	[64]
Bacteria			
Lactobacillus spp.	Colon cancer	HT-29	[37]
Rhodococcus pyridinivorans	Colon cancer	HT-29	[35]
Streptomyces sp.	Lung cancer	A549	[36]
Streptomyces sp.	Osteosarcoma cancer	MG-63	[83]
Fungi			
Alternaria tenuissima	Breast cancer	MCF-7	[91]

(*Continued*)

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Table 1 (Continued).

Biological Material for Synthesis	Type of Cancer	Cell Line	Reference
Alternaria tenuissima	liver cancer	Hep-G2	[91]
Aspergillus niger	breast cancer	MCF-7	[38]
Aspergillus niger	Liver cancer	Hep-G2	[86]
Aspergillus terreus	Colon cancer	Caco-2	[46]
Fusarium chlamydosporum	Colon cancer	Caco-2	[40]
Fusarium chlamydosporum	Colon cancer	HCT-116	[40]
Xylaria acuta	Mammary gland cancer	MDA-MB-134	[41]
Algae			
Arthrospira platensis	Colon cancer	Caco-2	[49]
Gracilaria edulis	Cervical cancer	SiHa	[47]
Kappaphycus alvarezii	Oral Epidermal cancer	KB	[51]
Sargassum muticum	Acute promyelocytic leukemia	HL-60	[48]
Sargassum muticum	Colon cancer	COLO205	[48]
Sargassum muticum	Ovarian cancer	CaOV-3	[48]
Sargassum muticum	Pancreatic cancer	AsPC-1	[48]
Sargassum muticum	Pancreatic cancer	PANC-1	[48]
Sargassum muticum	Liver cancer	Hep-G2	[50]

Biosynthesized ZnO NPs in Targeted Drug Delivery

The use of ZnO NPs in drug delivery could reduce the dosage of anticancer drugs used for treatment and reduce other side effects, by targeting the specific sites of cancer cells. The biodegradable properties and low toxicity of ZnO NPs have increased their usage in anticancer drug delivery as compared to other NPs.[14,19,104] ZnO NPs also have the capacity to prolong the duration of drug release, which is a significant benefit of using them in drug delivery.[5] Drug delivery with the use of ZnO NPs has emerged as an incredibly efficient approach for treating various types of cancer, including gastric cancer,[98] breast cancer,[105] hepatocellular cancer,[106] lung cancer,[107] cervical cancer,[108] prostate cancer,[109] and colon cancer.[26] Biosynthesized ZnO NPs are characterized by cheap fabrication from inexpensive metal ion precursors, biocompatibility, and efficient cellular absorption via endosomes.[110] Their bioactivity may be due to their morphology, size, larger band gap, higher surface area to volume ratio.[99] For these reasons, they have been suggested as an interesting prospect in targeted drug delivery.

The ZnO NPs have an isoelectric pH of around 9, which means that they exhibit a net positive charge throughout the physiological pH. They have hydroxyl groups attached to their surface. At low pH, the surface moieties get protonated to form $ZnOH_2^+$ ions that give a positive charge to the particle. At high pH, the surface gets deprotonated to form negatively charged ZnO^- ions. This property is widely explored for their application in drug delivery. Moreover, ZnO NPs possess a large surface area (high surface to volume ratio) that provides more sites for surface functionalization. Their smaller size (as compared to the bulk material) helps in increasing the drug retention time, which reduces the drug load.[20,110] Mechanism of drug delivery with the use of green synthesized ZnO NPs is presented in Figure 7.

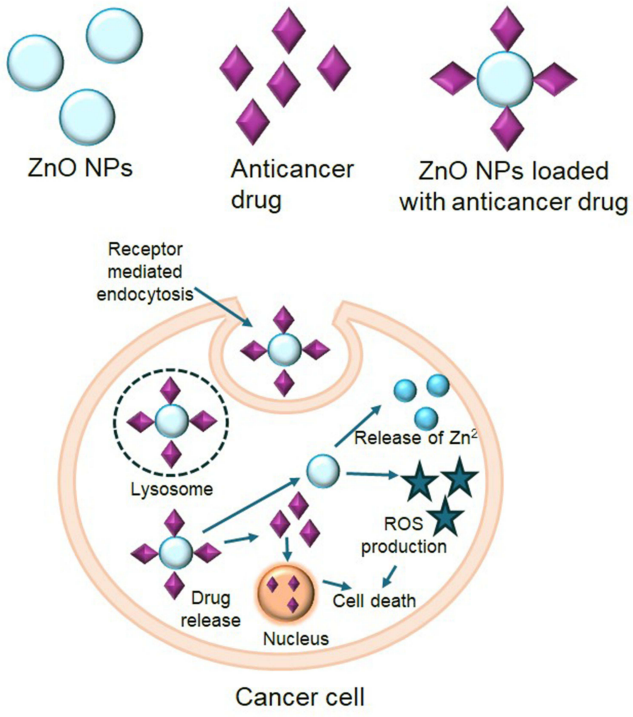

Figure 7 Mechanism of drug delivery with ZnO NPs.

Biosynthesized NPs have so far been used much less frequently as drug carriers than nanoparticles synthesized with the use of chemical methods. A summary of the ZnO NPs synthesized with the use of different methods in anticancer drug delivery is presented in Table 2. The summary concerns research performed on human cell lines.

ZnO NPs for targeted anticancer drug delivery so far have only been synthesized with the use of plant extracts and fungi. The drugs used for these studies were curcumin, doxorubicin, naringenin, paclitaxel, and quercetin. They were used against breast cancer, colon cancer, lung cancer, neuroblastoma, and skin cancer. Tested concentrations range from 0.1 to 500 μg/mL.

One of the possibilities for the anticancer drug to be delivered efficiently is surface functionalization of biosynthesized ZnO NPs. It can be achieved with the use of various agents, eg ligands, drugs, markers, and linker chains. Through specific molecular interactions, including receptor-ligand-based interactions, ZnO NPs accumulate in cells. The drug is released and its cognate target is destroyed through endo/lysosomal escape on receiving an appropriate stimulus. Various types of internal and external stimuli are also involved in the targeted delivery of anticancer drugs.[8,18,124] Moreover, according to Sun et al, NPs can be potentially functionalized with erythrocytes and used in combined anticancer therapy.[125]

Another interesting novelty in ZnO based nanomaterials is multifunctional nanocarriers that can be fabricated as a platform for drug delivery.[116,126] One example of such nanocarriers is nanoplatforms like ZnO@MXene that were used by Yin et al for elimination of drug resistant bacteria and acceleration of infected wound healing. The authors proved that the nanoplatforms showed antimicrobial properties and improved ROS generation, which are the reasons for their possible use in drug delivery.[116] Another example is poly(ethylene glycol)-coated mesoporous nanocomposite ZnO@Fe_2O_3 developed by Alavi and Meshkini for methotrexate delivery. The nanocomposite showed capacity for the adsorption of chemotherapy drug – methotrexate. The developed nanocarrier resulted in mitochondrial membrane disruption and caspase activation, followed by apoptosis. Their use is very promising as they showed selective cytotoxic effects, only towards cancer cells.[126]

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Table 2 The Use of the Synthesized ZnO NPs in Anticancer Drug Delivery

Method of Synthesis	Concentration of The Drug [μg/mL]	Anticancer Drug	Type of Cancer	Effects	Reference
Chemical methods					
Heating with zinc acetate, trisodium citrate, and sodium acetate	0.0001, 0.001, 0.01, 0.05, 0.1, 0.25, 0.5, 1.0	CUR	Gastric cancer cells AGS	Co-polymer encapsulated ZnO NPs loaded with CUR showed pH-dependent drug release and higher cytotoxicity than nanocurcumin	[98]
Heating with zinc acetate, magnesium acetate, KOH and APTES	5, 10, 20, 30, 40	CUR	Breast cancer MCF-7	PBA conjugated ZnO NPs loaded with CUR showed pH dependent drug release and exhibited higher cytotoxicity as compared to drug used without NPs	[105]
Co-precipitation with zinc chloride and chitosan	5; 10; 15; 20; 30; 40; 50; 60; 100	CUR	Breast cancer MDA-MB-231	Chitosan-conjugated ZnO NPs showed efficient curcumin loading, pH-responsive drug release, and exhibited higher cytotoxicity as compared to the drug used without NPs	[111]
Co-precipitation with alkaline medium and LDH encapsulation	-	CUR and DOX	Hepatocellular carcinoma HEP G2	DA-LAC-NH_2-ZnO/DOX/CUR/LDH demonstrated enhanced cytotoxic properties towards HepG2 cells in comparison to L929 (normal) cells as a result of the targeted delivery mechanism of DOX and CUR to cancer cells	[106]
Heating and precipation with zinc chloride, NAC and NAOH	20, 40, 60, 80, 100	CPT	Lung cancer A549	NAC capped ZnO NPs conjugated with CPT showed higher cytotoxicity as compared to drug used without NPs	[107]
Heating with zinc acetate, KOH, and methanol	3.125, 6.25, 12.5, 25, 50, 100	DNR	Lung cancer A549	ZnONPs-incorporated liposome nanocomplexes exhibited superior DNR loading and pH-responsive drug release property, as well as synergistic chemo-photodynamic anticancer activity	[112]
Co-precipitation with zinc nitrate hexahydrate and NaOH	1.56, 3.12, 6.25, 12.5, 25, 50, 100	DOX	Breast cancer MCF-7	DOX-ZnO-PMMA nanocomposites resulted in cancer cell viability significant decline at the highest concentration (100 μg/mL) – less than 30% as compared to the control group	[113]
Solvothermal method with zinc acetate and triethylene glycol	3.125, 6.25, 12.5, 25, 50	DOX	Cervical cancer HeLa	ZnO-DOX@ zeolitic imidazolate frameworks core-shell NPs loaded with DOX showed pH-dependent drug release and exhibited higher cytotoxicity as compared to the drug used without NPs	[114]
Sonification and reflux with zinc acetate, triethylene glycol, and ethyl acetate	0.5, 1.0, 2.0, 4.0, 8.0	DOX	Cervical cancer HeLa; glioblastoma multiforme U87MG	RGD peptide conjugated ZnO NPs loaded with DOX showed targeted and pH responsive drug release, and exhibit higher cytotoxicity as compared to non-targeted nanocarriers and drug used without NPs	[108]
Chemical synthesis with zinc acetate, magnesium acetate and ethanol	0.1, 0.5, 1.0, 2.5, 3.0 (ZnO QDs modified with NH_2, PEG and HA)	DOX	Lung cancer A549	HA functionalized ZnO QDs loaded with DOX showed targeted and pH responsive drug release, and exhibit higher cytotoxicity as compared to non-targeted nanocarriers	[115]
Heating with ethanol, dried zinc methacrylate, poly(ethylene glycol) methyl ether methacrylate and azobis (isobutyronitrile)	1, 2, 3, 4, 5, 6, 8, 10	ISO	Breast cancer MCF-7; cervical cancer HeLa; lung cancer A549; prostate cancer DU145	Core-shell ZnO-polymer NPs loaded with ISO showed pH dependent drug release and exhibited higher cytotoxicity as compared to drug used without NPs	[109]

Seed mediated method with α-Fe_2O_3 seeds, CTAB, zinc acetate, and ammonia	16, 32, 64, 128	MTX	Breast cancer MCF-7 and T47D	Folic acid conjugated mesoporous ZnO@Fe_2O_3 nanocomposite showed superior MTX loading and pH/UV light responsive MTX, pH dependent release properties as well as synergistic chemo-photodynamic anticancer activity	[116]
Stirring of zinc nitrate solution and sodium carbonate solution	25, 50, 100, 200	MTX	Breast cancer MCF-7	Cationic cellulose-based ZnO nanocomposites loaded with MTX showed pH-dependent drug release and exhibit higher cytotoxicity than free MTX	[117]
Boiling and sonication with zinc acetate dihydrate and ethanol	12.5, 25, 50	PAX	Breast cancer MDA-MB-231	Nanoscarrier exhibited significantly higher cytotoxicity towards cancer cells as compared to drug used without NPs	[118]
Heating with zinc acetate, magnesium acetate, KOH and APTES	1.5, 3.0, 6.0, 9.0, 12.0, 15.0	QE	Breast cancer MCF-7	PBA conjugated ZnO NPs loaded with QE showed pH dependent drug release and exhibited higher cytotoxicity as compared to drug used without NPs	[119]
Biological methods					
Borassus flabellifer fruit extract	0.125, 0.25, 0.5, 1.0, 2.0, 4.0, 8.0	DOX	Breast cancer MCF-7; colon cancer HT-29	Dose-dependent cytotoxicity MCF-7 and HT-29 cell lines with an inhibitory concentration of 0.125 μg/mL	[26]
Camellia sinensis ethanolic leaf extract	0.045, 0.225, 1.125 (chitosan-coated NPs)	PAX	Breast cancer MCF-7	Acytotoxic (anticancer) effect on MCF-7 cell lines and reduced cytotoxic effect on normal fibroblast cell lines	[27]
Cucumis melo seed extract	7.8, 15.6, 31.2, 62.5, 125, 250, 500	CUR	Skin cancer A431	A nanocomposite hydrogel with ZnO NPs showed efficient CUR loading, pH dependent drug release and exhibit higher cytotoxicity as compared to drug used without NPs	[120,121]
Cucumis melo seed extract	7.8, 15.6, 31.2, 62.5, 125, 250, 500	CUR; QE; NRG	Skin cancer A431	A nanocomposite hydrogel with ZnO NPs showed efficient drug loading for all 3 drugs, pH-dependent drug release, and exhibited higher cytotoxicity as compared to the drug used without NPs	[120,122]
Grewia flavescens leaf extract	250	CUR	Neuroblastoma	Significant cytotoxicity against cancer cells as compared to drug used without NPs	[123]
Aspergillus niger fungus	0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8	DOX	Lung cancer A549	Strongly inhibited proliferation of the A549 cell line with the concentration of 0.34 μg/mL; better results than for the NPs or DOX used separately; increased nuclear condensation, enhanced ROS generation in cytosol, and reduced mitochondrial membrane potential	[84]

Abbreviations: APTES, (3-Aminopropyl)triethoxysilane; CPT, camptothecin; CTAB, cetyltrimethylammonium bromide; CUR, curcumine; DA-LAC, dialdehyde lactose; DOX, doxorubicin; DNR, daunorubicin; HA, hyaluronic acid; ISO, isotretinoin; LDH, layered double hydroxides; MTX, methotrexate; NAC, N-acetyl-L-cysteine; NRG, naringenin; PAX, paclitaxel; PBA, phenylboronic acid; PEG, polyethylene glycol; QDs, quantum dots; QE, quercetin; RGD, arginine-glycine-aspartate.

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Stability within the body is crucial for successful use of ZnO NPs in drug delivery systems. For this reason, metallic NPs are often modified with biodegradable and biocompatible materials to ensure sustained release of the therapeutic agent and prevent premature degradation.[18]

Although biosynthesized ZnO NPs show a lot of potential as nanocarriers in laboratory, their use in clinical trials is a great challenge, as there is a significant "translational gap" in nanomedicine. One of the main reasons behind this, is a lack of focus on advanced formulation strategies required to transform the biosynthesized ZnO NPs into functional drug carriers. Another challenge is standardization of protocols for toxicology and long-term safety assessments for metal-based nanomaterials. Introducing the use of ZnO NPs in clinical trial requires collaboration between scientists, process engineers, clinicians and regulatory agencies.[2,127]

Health Risks of ZnO NPs

ZnO NPs biosynthesis faces challenges in reproducibility and consistency due to environmental sensitivity, which affects the performance of NPs in their applications. The main challenge of the ZnO NPs lies in their toxicity and impact on the environment. Regulatory and safety concerns complicate the application of biosynthesized NPs in biomedicine considerably. Although eco-friendly, described biosynthesis methods still require extensive testing for biocompatibility, toxicity, and long-term safety for humankind and the environment to gain regulatory approval. The regulatory landscape for the use of nanomaterials in biomedicine and pharmacy is continually evolving with stringent safety standards necessary for clinical use.[7,18]

Despite various medical applications, including anticancer therapy, gene therapy, tumor imaging, and drug delivery systems, ZnO NPs have deleterious effects on several key organs, including lungs, liver, kidneys, and reproductive systems. However, the toxicity induced by ZnO NPs is multifactorial, and it is yet unknown how toxic they are for these organs.[1] Enhanced understanding of NPs' toxicity (both environmentally and biologically) has prompted nanotoxicologists to call for deeper insights into the atomic interactions between NPs and organic structures. Despite being typically considered insoluble in water, ZnO NPs can release zinc ions, which highlights their potentially hazardous nature. Their surface, shape, size, and properties may be affected by the pathways through which NPs are taken up by cells.[18]

ZnO NPs exhibit differential effects on cancer cells versus healthy cells. This is crucial for their safe therapeutic use. In cancerous cells, ZnO NPs cause increased ROS production and an altered redox state, which induces oxidative stress and apoptosis more effectively. This targeted effect enhances their potential as anticancer agents. Healthy cells are generally more resilient to oxidative stress and less susceptible to toxicity induced by ZnO NPs. Nevertheless, it is still important to remember that high concentrations or prolonged exposure can harm also healthy cells, potentially causing cellular damage and inflammation. Therefore, precise dosage and targeted delivery are essential to optimize therapeutic benefits and, at the same time, minimize toxicity risks to healthy tissues.[7,18,106]

Conclusion and Future Perspective

The biological synthesis of ZnO NPs represents a major advancement in biomedical nanotechnology. Over the past two decades, their unique properties have been widely explored in different biomedical and pharmaceutical applications. While traditional chemical and physical methods are effective, they pose significant environmental and economic challenges. In contrast, biosynthesis methods offer a sustainable and eco-friendly alternative that reduces impact on the environment, minimizes health risks, and lowers production costs, making the green synthesis more suitable for industrial-scale production.[3,18,20]

Biosynthesized ZnO NPs represent a paradigm shift towards sustainable nanomedicine but require interdisciplinary efforts to mature. They have a promising anticancer potential, but more study is required to completely comprehend their mechanisms of action in drug delivery systems, evaluate their safety profiles, and maximize their therapeutic efficacy. Important factors to take into account include assessment of possible adverse effects of NPs, making sure cancer cells are precisely targeted, and looking into ways to improve their administration and efficacy in clinical trial.

The green synthesis of ZnO NPs faces several challenges that must be overcome for effective application in drug delivery. The biochemical compositions of biorsources used as a reducing agent for biosynthesis vary significantly, which affects the size, morphology, and functionality of the NPs and complicates standardization, which is essential for

ensuring consistent quality in biomedical applications. Another challenge is the limited understanding of the mechanisms involved in reduction and stabilization of zinc ions through biological agents. Moreover, scaling up green synthesis to industrial production still remains a significant obstacle.[18] The cost-effectiveness of green synthesis relies on the accessibility and availability of biological material sources. Additionally, geographical limitations and seasonal variations can impact the supply of raw materials, affecting production quality and cost.[18] If these challenges are addressed properly, it is possible to unlock their full commercial value.[8] Advancements in characterization techniques, including FTI-R, XRD, and TEM, are offering deeper insights into the mechanisms of synthesis. These techniques enable better control over NPs production by revealing the interactions between biological molecules and metal ions.[18]

One of the latest innovations and an area for future development in the study of anticancer properties of ZnO NPs is their ability to trigger ferroptosis. Ferroptosis is a type of Fe-dependent cell death characterized by excessive ROS levels and the inhibition of glutathione peroxidase 4 (GPX4). GPX4 is a key antioxidant enzyme that suppresses ferroptosis through the CREB/cAMP signalling pathway. Mechanistically, ferroptosis can be triggered by disrupting the intracellular redox homeostasis, causing excessive ROS levels to burden antioxidant defences. Consequently, it leads to lipid peroxidation and cell death. The cyclic AMP response element binding protein (CREB) is a stimulus-induced transcription factor that promotes the expression of GPX4. CREB activates GPX4[128,129] transcription by directly binding to its promoter through the coactivator EP300, maintaining redox homeostasis and preventing ferroptotic cell death. The research on use of ZnO NPs for triggering ferroptosis offers great potential for treating aggressive, resistant, and invasive cancer cells. Therefore, it has emerged as a crucial cancer treatment strategy. The next stage of this research may be its implementation using nanoparticles synthesized by biological methods.[129]

Another interesting topic for future research is also differences in ROS generation by biosynthesized ZnO NPs. Some nanomaterials are responsive to elevated ROS levels in inflamed regions and capable of mimicking antioxidant enzyme activity. This strategy has the potential to overcome the limitations of single-mechanism targeted drug delivery and enable multi-functional treatment approaches, resulting in significantly enhanced efficiency of delivery.[130]

The use of biosynthesized metal-based NPs as nanocarriers in targeted drug delivery is undoubtedly the future of drug delivery systems. Green ZnO NPs are extensively used for different biomedical applications. However, studies into their use in this field are still in their preliminary stage. Future research in this area should focus on functionalizing ZnO NPs with specific biomolecules, ligands, or polymers, as that could enhance targeted delivery of anticancer drugs. Exploring a wider variety of biological sources, such as rare plants, freshwater and marine algae, fungi, bacteria, or yeast, could also open new avenues for green synthesis of NPs with unique and desirable properties. Another interesting topic worth considering may be the combination of the use of novel extraction methods of biotic sources with the synthesis of nanoparticles, which could ultimately pave the way for more effective, sustainable, and accessible cancer therapies.

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Disclosure

The author(s) report no conflicts of interest in this work.

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