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Antibacterial and Anticancer Properties of Zinc Oxide Nanoparticles: A Review of Current Advances and Future Directions

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A B S T R A C T

Zinc oxide Nanoparticles (ZnO-NPs) have a promising potential in antibacterial and anticancer treatments because of their ease of production, low toxicity, and versatility in application. This review encompasses recently developed synthesis, characterizing and biomedical applications of ZnO-NPs. Green synthesis methodologies, sol-gel, and precipitation influence the biological effectiveness of ZnO-NPs, these methods particularly affect key characteristics such as particle size, shape and surface charge. These properties play crucial roles in antibacterial effectiveness, which facilitates their ability to generate reactive oxygen species (ROS) and bacterial cell membrane disruption, leading to bacterial cell death. The efficiency of ZnO-NP in cancer treatment is also reviewed because the nanoparticles selectively affect cancer cells, which generate apoptosis and cease cell proliferation. Additional novel applications of ZnO-NPs further highlight their benefits because they improve the precise delivery of the drug and enhance its bioavailability. Additionally, ZnO-NPs had future uses in photodynamic therapy as their light-triggered ROS generation results in localized and selective bactericidal and anticancer effects without affecting normal cells. This review provides a comparative evaluation of recent findings on the antibacterial and anticancer properties of ZnO-NPs, as well as exploring the possible directions for futural research; in addition, it emphasizes improving the functional characteristics of ZnO-NPs for enhancing the therapeutic impact and reducing the unfavorable influences that may expand the list of possible clinical uses of ZnO-NPs.

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1. Introduction

Nanomaterials have received considerable academic concentrations as substances and elements for various uses owing to their desired physical and chemical features [1]. The emergence of nanoparticles in resisting infectious microorganisms has revived the hope of the biomedical fields. Zinc oxide (ZnO) is extensively utilized in physical and biological applications owing to its significant band gap (3.27 eV), excellent chemical stability, non-toxicity, and significant absorbance in the UV range [2, 3].

Zinc oxide nanoparticles (ZnO-NPs) have drawn significance in the biomedical context because of their physicochemical features and biological activity, especially antibacterial and anticancer properties. Some general characteristics of ZnO-NPs include Nanomaterial characterization, Nanoscale size, Surface area to volume ratio, and producing reactive oxygen species (ROS) that synergistically enhance the ZnO-NPs ability to target and kill bacterial and cancer cell pathogens [4, 5]. The ZnO-NPs utilized in clinical applications as therapeutic structures and carriers of drugs have accelerated the advancement of ZnO-NPs in biomedicine. These antibacterial features of ZnO-NPs make them more effective in addressing the resistance challenges of bacteria in the current healthcare and medicine field [6]. Moreover, ZnO-NPs have antifungal and antibacterial properties, which can disturb bacterial cell membrane formation, and fractured bacterial cells, and interfere with the development of both positive and negative bacterial cell walls [7]. Its uses include wound covering, medical equipment ensoulment, and food packaging, as well as inhibiting Gram-positive and Gram-negative bacteria. ZnO-NPs also exhibit anticancer activity, suggesting that they might be utilized as a complementary or even an alternative to standard chemotherapy [8, 9]. Based on these observations, ZnO-NPs can selectively induce apoptosis and inhibit cell proliferation in cancerous tissues more efficiently. Nevertheless, as the current literature shows, synthesizing new antimicrobial and anticancer agents remains a topic of great interest. ZnO-NPs have demonstrated remarkable versatility in these research domains. ZnO-NPs have received immense attention in healthcare; hence, this review will discuss their synthesis, properties, antibacterial activity, and anticancer effects.

2. Fundamental Properties of ZnO-NPs

Zinc oxide (ZnO) occurs naturally due to the crusting of the mineral zincite in the earth, while the majority is manufactured through synthetic commercial processes. ZnO is characterized as a functional, strategic, promising, and versatile inorganic material with various utilizations. It is referred to as an II-VI semiconductor, as zinc and oxygen are classified in groups two and six of the periodic table, respectively [10]. ZnO possesses distinctive optical, chemical sensing, semiconducting, electrical conductivity, and piezoelectric characteristics [11]. It features a relatively wide band gap (3.27 eV) in the near-UV spectrum, a high excitonic binding energy (60 meV) at ambient temperature [12–16], and inherent n-type electrical conductivity [17]. These attributes allow ZnO to possess significant applications throughout various domains [15]. The extensive band gap of ZnO significantly influences its characteristics, including electrical conductivity and optical absorption. Excitonic emission can persist at elevated temperatures even at ambient conditions [15], and conductivity is enhanced when ZnO is doped with other metals [12]. Despite exhibiting a slight covalent nature, ZnO possesses extensive ionic bonding in the Zn–O connection. Additionally, ZnO demonstrates superior durability, selectivity, and thermal resistance compared to those of organic and inorganic materials [18]. The production of nano-sized ZnO has prompted the exploration of its potential as a novel antibacterial agent. Besides their distinctive antibacterial and antifungal characteristics, ZnO-NPs exhibit elevated catalytic and photochemical activity. ZnO exhibits significant optical absorption in the UVA (315–400 nm) and UVB (280–315 nm) spectra, which is advantageous for antibacterial efficacy and utilized as a UV protector in cosmetics [19]. Moreover, owing to the significant UV absorption characteristics of ZnO, these particles are increasingly used in consumer products, including anti-dandruff shampoos, fabric therapies for UV protection, and baby powders [20, 21]. The US Food and Drug Administration (USFDA) classified ZnO as a widely recognized safe chemical [22]. However, they are typically known to potentially develop new characteristics that may generate harmful effects.

Many comparison investigations demonstrated that ZnO exhibits superior antimicrobial properties compared to many metal oxides. Dasari et al. [23] examined the toxicity of metal nanoparticles (CuO, ZnO, TiO_2, and Co_2O_3) on *E. coli*. The antibacterial activity ranking based on lethal concentrations (LC_{50}) for *E. coli* among the examined MNPs was ZnO < CuO < TiO_2 < Co_3O_4 in light environments and ZnO < CuO < Co_3O_4 < TiO_2 in dark conditions, respectively. Metal ion release was found in *E. coli* cells exposed to ZnO and CuO NPs, whereas the release from Co_3O_4 and TiO_2 was negligible. Likewise, the research conducted by Jones et al. [24] indicated that ZnO-NPs exhibit markedly superior antibacterial efficacy against *S. aureus* compared to TiO_2, Al_2O_3, CuO, CeO_2, and ZnO-NPs, under standard laboratory lighting conditions. ZnO exhibits superior photocatalytic effectiveness compared to other metal oxides. The mean concentration of total reactive oxygen species generated during a defined irradiation duration (48 hours) ranked as follows for nanoparticles: TiO_2 > ZnO > Al_2O_3 > SiO_2 > Fe_2O_3 > CeO_2 > CuO, and for bulk oxides: ZnO > TiO_2 [25]. The quantity of ROS produced from the ZnO surface should rise proportionately with higher concentrations of nanoparticles. The survival rate of bacteria diminishes when the

average concentration of reactive oxygen species (ROS) increases. Due to their specific structure and content, nanoscale ZnO-NPs demonstrate biological behaviors and hold a potential possibility of therapeutic application. Understanding the behavior and synthesis of ZnO-NPs is essential for effective utilizations to eradicate bacteria and cancer cells. ZnO exhibits substantial antibacterial and anticancer effects, which are primarily attributable to the production of reactive oxygen species (ROS) that are responsible for inducing cell death in pathogenic bacteria and cancerous cells [7, 26]. ZnO serves a dual purpose in therapeutic applications by acting as an antibacterial agent and inducing apoptosis in unhealthy cells, while simultaneously promoting tissue repair in healthy cells. This duality of destroying detriments and boosting healthy cell propagation makes ZnO an excellent candidate for medical therapies [27–29]. Additionally, because of both low toxicity and biocompatibility, ZnO is extensively applied in different biomedical fields in the form of coatings, nanoparticles, and drug delivery systems. Ongoing research is unlocking the full therapeutic potential of ZnO, including combination therapies to counteract resistant bacteria strains and numerous types of cancer. Also, researchers are exploring the behavior of ZnO within biological systems to realize its therapeutic effects and create standardized clinical protocols. This study outlines the potential of ZnO and the requirements for continued research to improve treatment across diverse areas of healthcare [30–32].

3. Physical and Chemical Properties of ZnO-NPs

3.1. Surface Area and Particle Size

A high surface area to volume ratio is a significant factor of ZnO-NPs in their interaction with cell and biological membranes, influencing their physicochemical properties. A larger surface area means adequate apposition with a bacterial or malignant tumble, which results in proper adhesion, higher cell penetration, and enhanced ROS possibility [33]. This can be attributed to their higher reactivity and impressive ability to pass through cell membranes [34]. For example, it is noted that particles within this size can pass through the cell membrane and, thus, can enter the intra-cellular area, resulting in a higher ZnO-NPs concentration to enhance the therapeutic effects [35]. Conversely, when the size of particles is large, this may not be very effective in the uptake by the cells which reduces their effectiveness in the treatment process [36].

3.2. Surface Charge and Zeta Potential

Another essential characteristic of ZnO-NPs is the surface charge, which determines the stability of ZnO-NPs in the biological environment and their adhesion to the negatively charged cells' membranes. The zeta potential that describes the potential at the surface of the nanoparticles plays a major part in their behavior within biological environments [37]. Thus, positive-charged ZnO-NPs interact better with bacterial membranes since they are negatively-charged by lipopolysaccharides in the gram-negative bacteria or teichoic acids in the gram-positive bacteria. The charge-based interaction promotes adhesion and amplifies the ZnO-NP capability to degrade the cell membrane of bacteria and cause bacterial cell death [38]. Likewise, cationic ZnO-NPs have shown sufficient compatibility with cancer cells that mostly have negatively charged phospholipids in their outer cell membrane. This improved biocompatibility raises the death rate of cancer cells, thereby making ZnO-NPs potent anticancer agents [39].

3.3. Crystal Structure and Morphology

ZnO generally exhibits a hexagonal quartzite crystal phase, regarded as the most thermodynamically stable phase with high surface energy. A particular crystalline form enhances the generation of photocatalytic ROS, which is particularly relevant as it defines ZnO antibacterial and anticancer activities. The shape of ZnO-NPs also contributes significantly to the sustenance of therapeutic features [40]. Thus, spherical, rod-like, or sheet-like changes to the structure of ZnO-NPs are significant in determining the capacity of the nanoparticles to generate ROS. For instance, ZnO-NPs in the form of rods had a higher potential production of ROS than spherical NPs [41]. This enhanced ROS production is beneficial in such processes that require the destruction of bacteria and cancer cells since the increased oxidative stress on the target cells produces free radicals that lead to their death.

3.4. Stability and Solubility

The stability of ZnO-NPs is a significant factor as they directly impact their behavior in biological systems when applied to Biomedical applications. ZnO-NPs are stable across a different range of pH levels in the immediate surroundings, which is essential for use in various biological settings. However, the dissolution, available with a

decrease of pH below three, can effectively precipitate Zn^{2+} ions from ZnO-NPs [42]. Releasing of ions helps the antibacterial and anticancer activity required for the microbiocidal. However, increased dissolution also can lead to cytotoxicity, which must be well-controlled to ensure safety and effectiveness for application [37]. To counter these challenges, other subsequent surface modifications, like polymer coatings, can stabilize ZnO-NPs in physiological conditions and reduce unnecessary dissolutions. These changes also improve the general safety properties of ZnO-NPs and the duration of their effectiveness in biological systems, which will lead to improved treatment outcomes [43].

3.5. Optical Properties

ZnO-NPs have optical behavioral properties, such as better ultraviolet (UV) absorption. This characteristic makes them particularly suitable for Photodynamic Therapy (PDT) applications. When ZnO-NPs undergo light, UV absorption produces ROS that can eliminate bacteria and cancer cells. Due to generating ROS on light activation of ZnO-NPs, it makes them valuable for developing light-sensitive therapies to destroy the targeted cells while minimizing damage to the surrounding healthy cells [44]. In addition, owing to the optical characteristics of ZnO-NPs, it is helpful for diagnosis, including imaging and biosensing [5]**.** It becomes clear that researchers can use the fluorescence properties of ZnO-NPs to design better imaging systems, enabling them to monitor some processes or diseases as they occur in the body. Integrating ZnO-NPs into diagnostic tools raises early diagnosis and treatment management standards, thus decreasing patient mortality [45].

4. Methods of ZnO Synthesis

The synthesis methods of ZnO-NPs include physical, chemical, biological, and sonochemical techniques known to influence the physicochemical characteristics of the ZnO-NPs, such as size, shape, surface charge, and crystal structure. Nanosized structure manufacturing processes are categorized as top-down approaches (successive reduction of bulk substance) or bottom-up approaches (assembly of particles from smaller components) [46]. **Fig. 1** illustrates a schematic comparing the two methodologies. The methodologies employed to fabricate nanoparticles are often categorized under physical fabrication, biological preparation, and chemical manufacturing. Nonetheless, the advancement of novel fabrication and processing technologies, coupled with a comprehensive view to understand the correlation among the structures and features of the produced material powders, has continually generated diverse opportunities to produce nanostructured materials in the forms of coatings, composites, films, and powders [47]. **Table 1** summarizes various ZnO-NP synthesis methods, including their benefits and drawbacks.

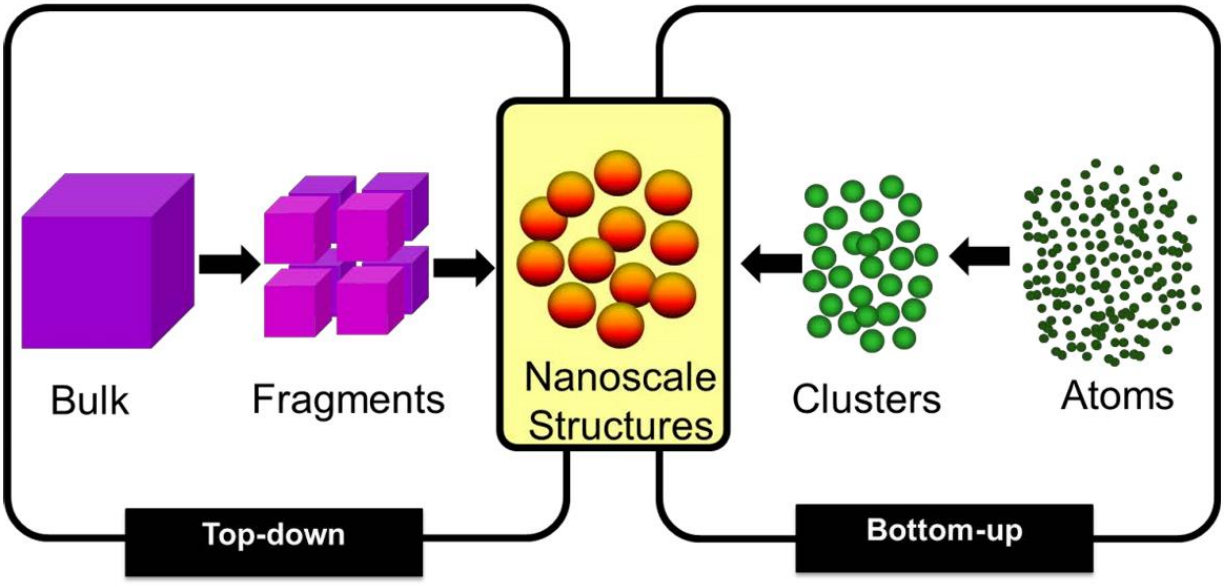

Figure 1: A conceptual illustration of top-down and bottom-up manufacturing methodologies [48].

Table 1: Comparison of Synthesis Methods for ZnO-NPs

Method	Process Overview	Advantages	Disadvantages	Reference
Green Synthesis	It uses plant extracts, bacteria, or fungi.	Eco-friendly, low toxicity, cost-effective.	Potential for inconsistent particle size.	[49]
Sol-Gel Method	Hydrolysis and condensation of zinc salts.	Fine control over particle size and shape.	Requires precise temperature control.	[50]
Precipitation	Reaction of zinc salts with precipitating agent.	Simple and scalable, suitable for large-scale production.	It often involves calcination to improve purity.	[51]
Thermal Evaporation Technique	involves heating a material to vaporize it, followed by rapid cooling to condense the vapor into nanoparticles	Simple, Produces high-purity nanoparticles	High energy consumption Possible agglomeration of nanoparticles	[52]
Solid-state method	It involves grinding or mixing solid precursors, followed by heating to induce chemical reactions	Eco-friendly, solvent-free, Energy-efficient	Requires high temperatures, Longer processing time	[53]
Electrochemical method	It involves using an electric current to reduce metal ions in a solution	Simple and cost-effective , Scalable for large production	Limited to conductive materials, Agglomeration risk	[54]
Hydrothermal	High-pressure reaction in water.	Produces highly crystalline particles with controlled size.	Longer processing times and energy requirements.	[55]
Laser ablation	Generation of a plasma plume and the formation of nanoparticles	Controlled particle size and shape and high purity.	Low production rate	[56]

4.1. Precipitation Method

The precipitation method is not complex, without high-temperature requirements, and overall savings in energy [57]. This method entails the process of ZnO precipitation from a zinc salt solution with the presence of a precipitating agent, including sodium hydroxide and ammonia. **Fig. 2a** depicts an exploded view of the precipitation method. The precipitate is then collected using a separating funnel as the ZnO particles form and are washed [58, 59]. The precipitation method is beneficial mainly because it is essential and quickly forms massive particles, which are advisable for bulk manufacturing. However, one disadvantage of the precipitation method is that the size and shape of the particles cannot be largely controlled compared to the sol-gel process [51, 60]. This uncontrolled causes a broader and less uniform distribution of particles, which may be disadvantageous in some instances. The possible addressing of these challenges can be overcome by adjusting the synthesis parameters or by incorporating some stabilizers or surfactants during the synthesis**.** Noteworthy instances include the research conducted by Costenaro et al. [61], who synthesized spherical ZnO-NPs with a particle size between 2 and 10 nm via a co-precipitation method utilizing a zinc acetate solution in methanol. In contrast, Purwaningsih et al. [62] produced ZnO-NPs through a precipitation method employing zinc acetate dihydrate, hydrochloric acid, and ammonia as reactants. The shape and structure of the ZnO-NPs exhibited a pseudo-spherical form, with an average particle size ranging from 11 to 20 nm. Similarly, Adam et al. [63] manufactured homogenous ZnO-NPs via a co-precipitation technique, achieving a mean size of approximately 140 nm. The characteristics of ZnO-NPs can be adjusted to enhance their applicability within the biomedical discipline.

4.2. Sol-Gel Method

The technique of sol-gel is considered a common method for producing ZnO-NPs because of its easy operation and good particle size and size distribution controllability [64]. **Fig. 2b** presents a comprehensive view of the sol-gel method. In one method, a zinc precursor like zinc acetate or zinc nitrate is dissolved in a solvent and hydrolyzed using a base, usually a sodium hydroxide solution. The formed zinc hydroxide precipitate is then transformed into ZnO-NPs using calcination. The sol-gel synthesis method has several advantages; based on that, it is possible to

accumulate specific properties in nanoparticles depending on the selection of the synthesis parameters like temperature, acidity, and concentration of precursors [65]**.** This flexibility can be used in synthesizing nanoparticles with various forms; it transforms into rod-like from spherical. However, this procedure involves post-synthesis heat treatment, and the crystallinity and stability characteristics of the obtained ZnO-NPs are affected [66]. The sol-gel technique for producing ZnO-NPs was initially established by Spanhel et al. [67] and subsequently refined by Meulenkamp [68]. Zinc acetate dihydrate is typically employed as the precursor due to its facilitation of hydrolysis control. Sodium hydroxide is utilized to regulate the pH of the product of the reaction, as the pH influences the rate of ZnO production and impacts the size and stability of the resultant nanoparticles [69]. This approach has four phases: solvation, hydrolysis, polymerization, and transformation. Zinc acetate dihydrate is dissolved in a solvent like methanol or ethanol and subsequently hydrolyzed, facilitating the elimination of any intercalated acetate ions. This results in the creation of a zinc hydroxide colloidal gel [70]. Zinc hydroxide dissociates into Zn^{2+} cations and OH^- anions, then undergoes polymerization of the hydroxyl group to create 'Zn–O–Zn' bridges, transforming sol into a gel. The gel is subsequently converted into ZnO [70, 71]. Hayat et al. [72] produced 25 nm ZnO-NPs via a modified sol-gel process and effectively employed nanoparticles for the photocatalytic degradation of phenol.

4.3. Hydrothermal Synthesis

Hydrothermal synthesis utilizes high temperature and high pressure to cause the precipitation of ZnO out of the zinc salt solution, leading to highly purified ZnO-NPs with some defects. **Fig. 2c** depicts the simplified structure of the hydrothermal procedure. This method produces highly stable NPs with proper structural characteristics [5]. Many solvents are utilized in these reactions. When water is used, the method is referred to as a hydrothermal strategy, but the usage of organic solvents, like polyols or ethanol, is termed a solvothermal technique [73]. Hydrothermal procedures featured some benefits such as elevated purity and crystalline structure of the product [74], precise control over the final nanostructure size, shape, and crystal phase [73], along with less contamination due to the enclosed system circumstances. This is exactly why this strategy is frequently classified as an environmentally sustainable methodology for the manufacturing of ZnO-NPs. However, this technique has some limitations, including a slower rate of reaction at any level of temperature [75], the necessity for costly autoclaves, constraints in reaction observation (as the reactor must remain sealed) [76], and possible safety risks during the autoclave process [57].

The hydrothermal/solvothermal methods are regarded as simple and easy to implement, as noted with the sol-gel technique. Prominent instances encompass the research conducted by Bharti and Bharati, who produced ZnO-NPs via a hydrothermal technique, exhibiting a size range of 16 to 25 nm and various morphologies [77]. Likewise, Wirunmongkol et al. produced ZnO-NPs via a hydrothermal method utilizing an autoclave, incorporating $Zn(NO_3)_2.6H_2O$ and NaOH as the initial precursors. The synthesized nanoparticles exhibited a morphology resembling short prisms and flower-like structures, with widths ranging from 30 to 80 nm and lengths between 0.5 and 1 μm [78]. Microwave-assisted synthesis uses microwave radiation to heat the reaction mixture, producing ZnO-NP quickly and efficiently. Hydrothermal and microwave-assisted methods provide the same advantage of controlling the particle size and morphology. Still, hydrothermal synthesis is more suitable for obtaining ZnO nanostructures with larger sizes and higher stability which indicates ZnO is ideal for drug delivery applications since the particles need high surface area and stability [79]. These synthesis techniques affect the properties of ZnO-NPs, which are utilized in antibacterial and anticancer activities. However, sol-gel and precipitation methods are helpful when preparing nanoparticles of varying sizes and shapes, which is essential in drug delivery and biological applications. Self-assembly has the advantage of incorporating bio-friendly agents, hence enhancing biocompatibility**.** Laser ablation guarantees the high purity of the samples, and hydrothermal synthesis provides stability for the synthesized materials, so these methods are more suitable for specific medicinal and clinical applications.

4.4. Solid-State Pyrolytic Method

The solid-solid reaction method provides a simple and low-cost method of producing ZnO-NPs. **Fig. 2d** provides an exploded diagram of the solid-state pyrolytic procedure. For this approach, two solid precursors, usually zinc salts, e.g., zinc acetate or zinc nitrate, and a solid base, e.g., sodium hydroxide (NaOH) or potassium hydroxide (KOH), are well mixed [53, 80]. This reaction takes place via mechanical grinding or mixing at room temperature

or under mild heating conditions [81]. The precursors react when ground produce ZnO, while subsequent heating can aid in the decomposition of by-products and increase crystallinity. Interestingly, the reaction can be conducted under solvent-free conditions. The product obtained after the reaction was washed, dried, and calcined sometimes to obtain highly pure and crystalline ZnO-NPs [82]. This is beneficial because the approach is simple, scalable, and does not require expensive equipment or energy inputs. Moreover, it offers excellent nanoparticle size modulation via grinding time, temperature, and precursor concentration control [83]. Wang et al. [84] produced ZnO-NPs of varied diameters, from 8 nm to 35 nm, by adjusting the pyrolysis heat of the reactant combination. Synthesized nanoparticles possessed hexagonal-wurtzite forms and demonstrated powerful UV emissions, related to the higher purity of the generated ZnO.

4.5. Thermal Evaporation Technique

Thermal evaporation involves a solid-state thermal sublimation procedure when the source materials, in powdered form, are positioned at the center of the tube furnace. The source elements are sublimated by increasing the temperature, and the resulting vapor phase produces novel nanostructures under specific circumstances. By manipulating growth kinetics, temperature, substrate placement, and catalyst, diverse ZnO structures can be synthesized. These subsequently formed ZnO-NPs possess distinctive properties that suit different applications such as electronics, catalysis, and biomedical fields. They are especially appreciated for their large surface area and optical properties that improve their function in sensors, drug delivery systems, and photocatalysis [52, 85]. **Fig. 2e** illustrates a conventional thermal chemical vapor deposition apparatus comprising a horizontal quartz pipe and a resistant heating furnace.

4.6. Electrochemical Method

Electrochemical deposition offers the potential for high-throughput, controlled synthesis of ZnO-NPs. The concept of "electrodeposition" can be used to describe either electroplating (which is based on a solution of ionic species in water) or electrophoretic (which is centered on in-suspension particles) deposition [86]. Both methods utilize an electric current to facilitate the nucleation of crystallites on the surface of a substrate and their subsequent development. **Fig. 2f** depicts a diagram of the electrochemical deposition procedure. In this technique, an electrochemical cell is created with a conductive substrate as the cathode and a solution of zinc salt (zinc nitrate or zinc sulfate) as the anode. At the cathode, Zn^{2+} ions in the electrolytic solution are captivated by the potential applied, which reduces and forms the ZnO-NPs [87]. The ZnO-NPs then precipitate from the solution to the substrate surface. By this method, the time of deposition, current density and electrolyte constituents can be adjusted so that the size, shape, and crystallinity of ZnO-NPs are regulated [88]. This method has the benefits of producing monodisperse and homogenous ZnO nanostructure and thin films which can be used in ZnO fabrication in semiconductors, photocatalytic, solar cells, and gas sensors. The electrochemical deposition of ZnO is low-cost, suitable for scale-up, rapid growth rate, elevated purity, commercial use, and the versatility of utilizing various substrate types therefore achieving a cost-effective ZnO-NPs formation process with desirable properties [89, 90]. To improve the regulation of nanoparticle formation, it is essential to investigate the transfer of charge at the electrode surface and the outer diffusion of the adsorbed ions, which are significantly influenced by these parameters. This method's advantage is in the direct production of nanostructures within the final substrate, hence eliminating the need for additional consolidation procedures for the nanoparticles. This will also resolve difficulties such as inadequate bonding of the nanoparticles or porosity concerns [47]. Numerous authors have described the utilization of electrodeposition for fabricated metal oxide nanostructures, enabling the growth of nanostructures with various morphologies. Hassan et al. documented the electrodeposition of ZnO nanoflakes [91], whereas Li et al and Yang et al. reported the electrodeposition of ZnO nanotubes [92, 93].

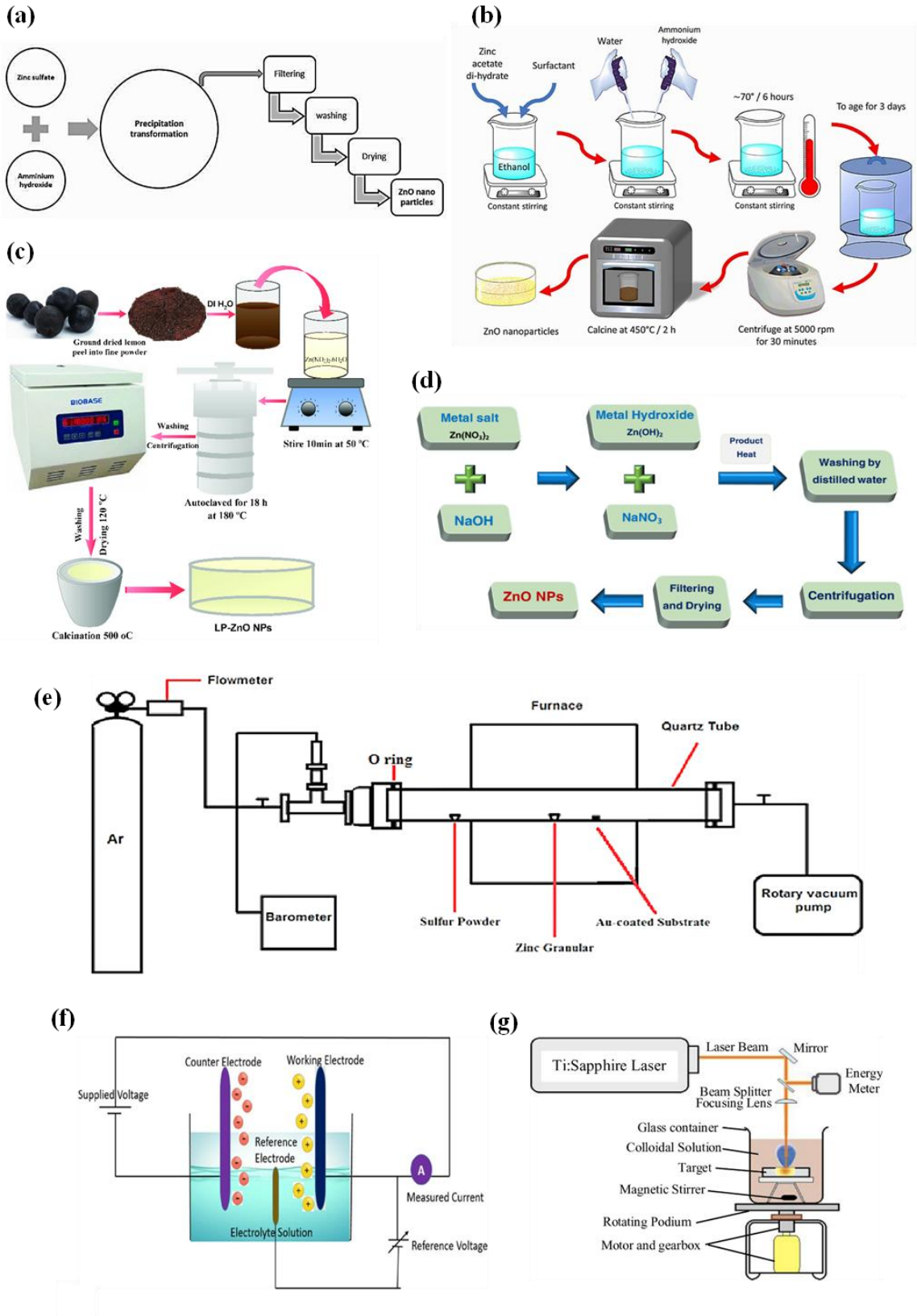

Figure 2: A schematic illustration to produce ZnO-NPs using (a) precipitation [94], (b) sol–gel [95], (c) hydrothermal [96], (d) solid-state reaction, (e) thermal chemical vapor deposition [97], (f) electrochemical deposition [98] , and (g) laser ablation methods [99].

4.7. Biosynthesis

There are essentially two primary methods of synthesizing ZnO-NPs. The first is biosynthesis, which involves using plant extracts, bacteria, or fungi to synthesize the NPs. The following environmentally friendly approach is a sustainable solution to conventional chemical treatment methods, often involving toxic reagents [100, 101]**.** Phytochemical compounds present in plant extracts can chelate zinc ions and help in the development of less poisonous nanoparticles, for example, the use of *Crotalaria verrucosa* leaf extract for the synthesis of ZnO-NPs that possess a high degree of stability, as well as antibacterial and exhibits anticancer properties [102]**.** Vidhya et al. [101] reported that ZnO-NPs derived from *Ocimum americanum* leaves possess antibacterial and anticancer activities. They were efficacious against bacteria, fungus, and malignant skin cell lines. Demissie et al. [103] noticed that the nanoparticles had efficacy against both Gram-positive and Gram-negative bacteria, achieving maximum inhibition zones of 14 mm and 12 mm, respectively. Aldeen et al. [30] extracted ZnO-NPs from *Phoenix Roebelenii* palm leaf extract, exhibiting bactericidal efficacy against four bacterial strains. Mousa et al. [4] utilized green tomato extract to synthesize ZnO-NPs, demonstrating inhibitory zones towards *Staphylococcus aureus* and *Escherichia coli*. ZnO-NPs demonstrated cytotoxic effects on human ovarian cancer cells, with an inhibition dosage of 27.45 µg/ml. In most cases, biosynthesized ZnO-NPs are known to exhibit high biocompatibility compared to the chemically synthesized ZnO-NPs, making them most appropriate for use in therapeutic applications where minimizing toxicity is essential.

4.8. Pulsed Laser Ablation

The pulsed laser ablation method involves directing a high-energy laser beam on a zinc target that melted in a liquid environment to produce nanoparticles [104]. The mechanism of this process is dependent on the interaction of the high-density light of the laser with the target zinc, which results in its material ablation in the solution; this ablation subsequently facilitates nucleation and synthesizes ZnO-NPs in the solution. Rashid et al. [105] synthesized Zn-NPs and ZnO-NPs using the laser ablation of a zinc substrate in ethanol. The nanoparticles were experimented against *Escherichia coli, Pseudomonas aeruginosa, Streptococcus mutans*, and *Staphylococcus aureus*. Elsayed et al. [29] found that a ZnO-Ag nanocomposite, synthesized using laser ablation with a diameter of 30-130 nm, exhibits anticancer properties against HCT-116 and HELA cancer cell lines. **Fig. 2g** presents the arrangement for obtaining suitable ZnO-NPs suspension. Using a laser, the colloidal solution's particle size, degree of purity, and morphology can be easily regulated and controlled by varying the pulse duration and energy. One of the great values of pulsed laser ablation is that the synthesized ZnO-NPs are not contaminated with chemical substances, which may be crucial for biomedical applications [106]. Furthermore, this method offers flexibility that allows the synthesis of ZnO-NP in many solvents, such as water and organic, to obtain nanoparticles of desired surface properties.

5. Photocatalytic Activity of ZnO-NPs

ZnO-NPs exhibit photocatalytic efficacy because of the capability of electron-hole pair generation when exposed to light with energy above their bandgap. These electrons transition from the valence band to the conduction band, creating holes in the valence band. The excited electrons interact with oxygen on the ZnO surface, forming superoxide radicals ($O_2^{-\bullet}$). These superoxide anions generate hydrogen peroxide (H_2O_2), which interacts with valence electrons to generate active hydroxyl radicals ($OH^{\bullet}$) [107]. The photogenerated holes can directly interact with organic pollutants or oxidize OH^- and H_2O to generate hydroxyl radicals ($OH^{\bullet}$) [108]. The active species, $OH^{\bullet}$ and $O_2^{-\bullet}$, decompose dye molecules on the nanocatalyst's surface into nontoxic compounds [28, 109, 110]. **Fig. 3** illustrates the degradation mechanism of an organic pollutant applying the ZnO nanocatalyst. The photocatalytic activity of a catalyst is influenced by its physical properties, including surface area, shape, band gap energy, and crystallinity. As the diameters of the particles reduce, the surface area of reactive sites increases, leading to improved adsorption and degradation of dye molecules. The degradation process's ability relies on the quantity of electrons in the conduction band and holes in the valence band [5, 82, 111].

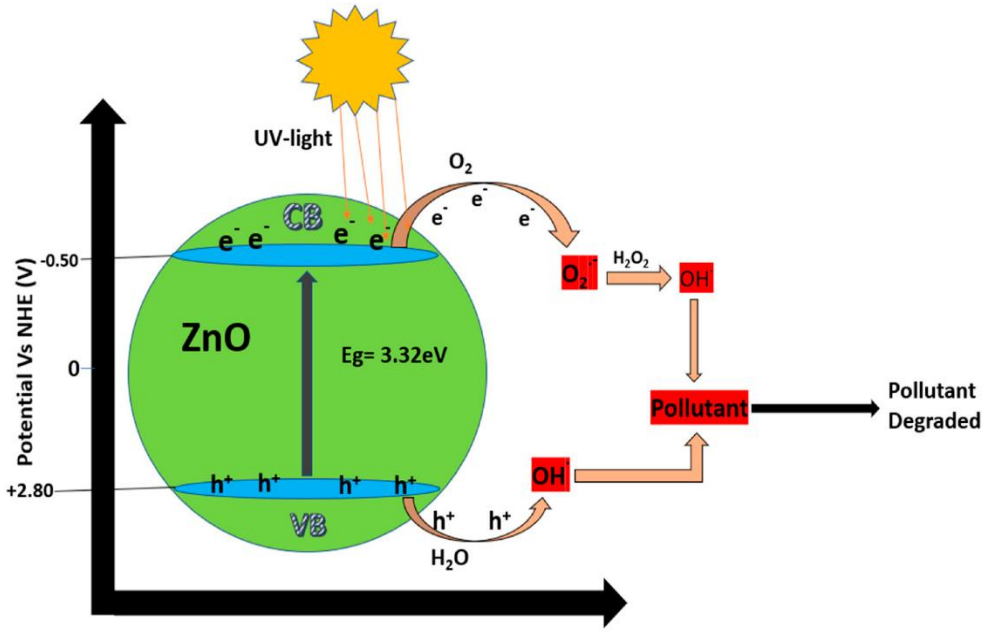

Figure 3: Degradation mechanism for an organic pollutant by the ZnO nanocatalyst [112].

6. Antibacterial Mechanisms of ZnO-NPs

6.1. Direct Contact Mechanism

ZnO-NPs have shown high antibacterial activity predominantly through direct contact, where the cell surface of the nanoparticles meets the bacterial cell membrane. The antimicrobial activity of ZnO-NPs is attributed to their small size and high surface area-to-volume ratio, which increases reactivity with the microbial cells. ZnO-NPs are predominantly positively charged and thus could firmly attach to the negatively charged bacterial cell membrane, causing disorganization and commensurate apoptosis [113]. This contact results in several effects that destabilize the bacterial membrane and contribute significantly to the antibacterial action of these nanoparticles.

6.1.1. Membrane Permeabilization

When ZnO-NPs interact with bacterial membranes, they adhere to the surface and exert mechanical pressure that causes rupture of the phospholipid bilayer, leading to increased membrane permeability. This alteration facilitates the passage of critical intra-cellular contents like ions and metabolites vital for cell balance. It was established that small-size ZnO-NPs, with high surface charge density and rod shape, can elicit significant bacterial toxicity and cell death within the shortest time possible for both Gram-positive and Gram-negative bacteria [114]. Membrane permeability increases with the concentration of ZnO-NPs, meaning the higher the concentration of ZnO-NPs, the enhanced disruption, and increased leakage of intracellular contents [38]. This suppression is significant in treating bacterial infections from antibiotic-resistant strains whereby conventional antibiotics cannot effectively achieve the intended effects.

6.1.2. Physical Disruption and Cell Lysis

The high pointy structure of ZnO-NPs facilitates the creation of pores on bacterial cell walls, making them susceptible to physical attack. This mechanical disruption is keenly observed in Gram-negative bacteria, whose two membrane layers have a thin peptidoglycan layer compared to Gram-positive microbes. Erythrocytes on lysis release enzymatic cytoplasm, nucleotide, and ribosomal content into solution, which destructed the cell's structural integrity and is nonreversible [114, 115]. Research indicates that higher inclinations of ZnO-NPs enhance this lytic process since the combined activity of nanoparticles surpasses the antibacterial response. Furthermore, a surface comparison of ZnO-NPs indicates that the roughness of these nanomaterials and the sharpness of their crystal facets tend to increase the probability of interfering physically with bacterial integuments [116].

Another vital feature in which ZnO-NPs inhibit bacterial growth is ion exchange and charge disruption. ZnO-NPs can bind with membrane-bound ions and, due to this mechanism, cause disturbance of ionic gradient across the

cell membrane. The replacement of Zn ions for the required metal ions like Mg^{2+} or Ca^{2+} affects the binding of essential metal ions, thereby causing imbalances in metal ion equilibrium, which is vital for the normal functioning of enzymes needed for cell survival and functioning [115, 117]. Most bacterial cells preserve ion gradients in the cells for transport and metabolic activities, which, when disrupted by ZnO-NPs, the cells disintegrate and finally die. Notably, the imbalance of these ionic balances also induces oxidative stress signal transduction in bacterial cells, thus reducing viability [118].

6.1.3. Protein Denaturation

Besides the distortion of cell organelles, ZnO-NPs can bind to the actual membrane proteins, causing structural change and consequent loss of function [119]. There are various types of proteins, but the key is an integral part of cells' membranes, which plays a significant role in cell signaling, nutrient transportation, and waste disposal [120]. These proteins are essential in enhancing bacterial sensitivity because distortion of these proteins' functions affects the overall metabolic processes necessary for survival. For instance, proteins generating adenosine triphosphate (ATP) or transport across membranes can be particularly impaired, resulting in energy deficits and toxic metabolite buildup [121]. It is essential to recognize that this combined effect disrupts the bacterial membrane and impairs other critical cellular components.

6.2. Reactive Oxygen Species (ROS) Generation

ROS play a critical role in the antibacterial activity of ZnO-NPs primarily by enhancing ROS generation. Several mechanisms have been identified in the scientific field to clarify how nanoparticles may fight bacteria and fungi. The generation of reactive oxygen species (ROS) by metal oxide nanoparticles, including superoxide anion hydroxyl (O_2^-), hydroxyl radicals (HO_2^-) and hydrogen peroxide (H_2O_2), which results in damaging cellular constituents such as DNA, proteins, and lipids, is one of the most frequently documented mechanisms of antimicrobial activity in previous studies [18, 122, 123]. The generation of ROS is considered a primary cause of oxidative damage in bacterial cells and their subsequent death [124, 125]. This process is incredibly efficient because ZnO-NPs have inherent photocatalytic characteristics activated by UV and Visible light, which boosts ROS generation [126]. Consequently, ZnO-NPs can highly locate and eliminate bacterial pathogens, including multiple antibiotic-resistant ones. Doping ZnO-NPs with different elements has further expanded their potential applications by enabling fine-tuning of their properties. **Fig. 4** illustrates how doping ZnO-NPs with different elements (like Ag and Fe) enhances antibacterial efficacy, supporting the discussion of ROS generation and its impact on antibacterial properties.

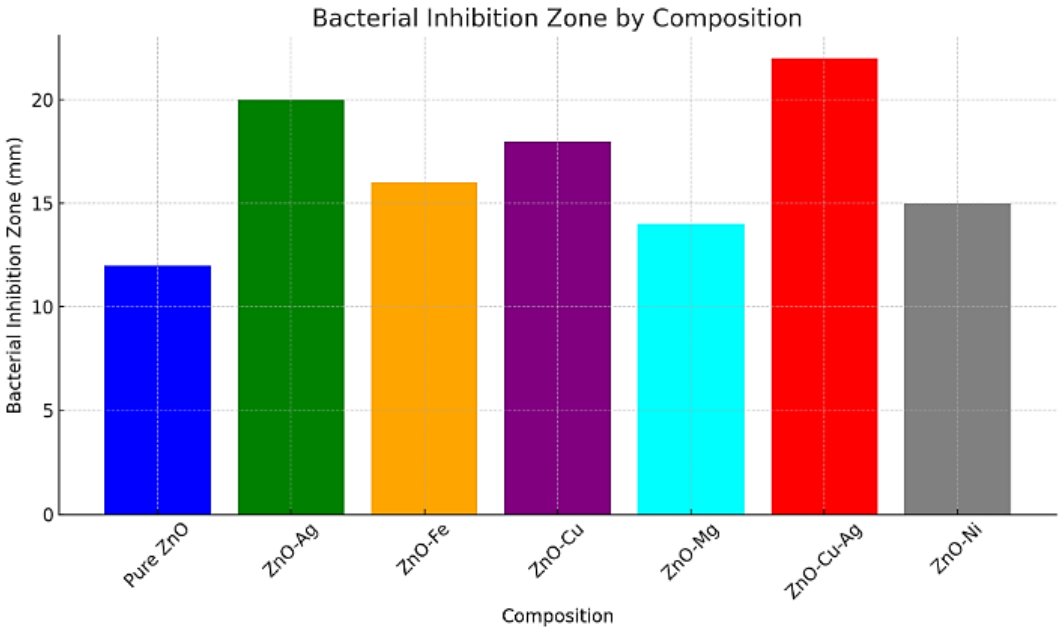

Figure 4: Antibacterial efficacy of ZnO-NPs with different compositions.

6.2.1. Release of Zn^{2+} Ions

A further mechanism involves the extraction of Zn^{2+} ions after the decomposition of ZnO-NPs. Zn^{2+} may inhibit amino acid metabolism and disrupt the enzymatic system [40]. The toxicity of ZnO-NPs was linked to the disruption of cellular integrity due to their interaction with the cell wall and subsequent uptake. The increased toxicity of smaller nanoparticles may arise from the requirement of many particles to envelop the bacterial surface, hence producing elevated amounts of reactive oxygen species (ROS) generated by ZnO on the cell surface. Furthermore, Zn^{2+} ions may contribute to antimicrobial behavior, and the dissolution of ZnO-NPs producing Zn^{2+} ions can be confirmed to be size-dependent [127, 128]. Moreover, smaller nanoparticles can more readily traverse the bacterial barrier owing to their elevated interfacial area [40]. Consequently, all mechanisms of ZnO NP toxicity in bacteria and fungi, as currently understood, are contingent upon size. Consequently, the diminutive nanoparticle size enhances antibacterial action [7]. **Fig. 5** displays a simplified mechanism of the antibacterial behavior of ZnO-NPs.

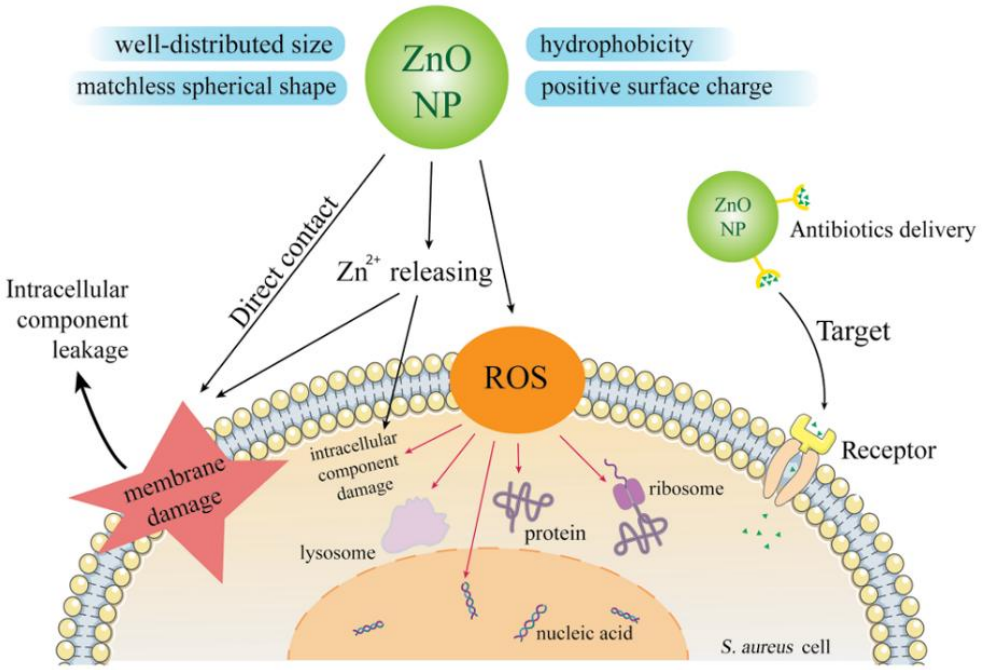

Figure 5: Representation of the antibacterial mechanism of ZnO-NPs [129].

6.2.2. Oxidative Stress and Lipid Peroxidation

The generation of ROS by ZnO-NPs has one of the foremost consequences, oxidative stress, which results in lipid peroxidation in bacterial membranes. This disrupts the steady state nature of the membrane and causes poration for ions and metabolite leakage out of the cell. Lipid peroxidation alters the structure of the membrane phospholipid bilayer and finally promotes the imbalance of cellular ions and cell dysfunction, leading to cell death [42, 130]. This effect is mainly manifested in oxidation-sensitive bacteria, which have low antioxidant protection and are especially vulnerable. The capacity of ZnO-NPs to generate ROS involved in lipid peroxidation is a very effective antibacterial mechanism since the bacterial membrane is a cellular structure that functions as a primary barrier against external aggression [131].

6.2.3. Protein and DNA Damage

Besides inducing lipid peroxidative changes, ROS led to severe protein and DNA damage in bacteria. The reactive oxygen alterations that occur due to ROS damage the body's metabolic processes and slow the growth of bacteria. For example, ROS produced by ZnO-NP can modify the shape of bacterial proteins due to the redox alteration of the critical thiol group, thereby inactivating the enzyme and promoting the aggregation of misfolded proteins [125]. These alterations affect essential aspects of bacterial life, such as energy metabolism and nutrient assimilation. Moreover, ROS can cause DNA strand breaks and several changes that negatively affect replication and

transcription. This helps to cause the death of bacterial cells because the cellular damage that cannot be repaired affects almost every important metabolic function essential for bacterial survival and the bacteria's genetic makeup [131, 132].

6.2.4. ROS Synergy with Direct Contact

The ZnO-NPs exhibit an enhanced antibacterial performance from the production of ROS and direct interactions with bacterial cells. The transmission electron microscopic images also illustrate that the physical contact between ZnO-NPs and bacterial membranes leads to the disturbance of cell wall layers and exposes the inner cell organelles to ROS. This exposure increases this oxidative damage and accelerates the rate at which cells die. The integration of these mechanisms is especially vital in UV or visible light irradiated conditions, as ZnO-NPs are more photocatalytically active and produce more ROS [42, 133]. This synergy highlights the uses of ZnO-NPs in different contexts, including sterilization steps and BBC application in health care and food hygiene practices [113]. The combined approach of direct contact and reactive oxygen species (ROS) activity makes ZnO nanoparticles a powerful tool for developing effective antimicrobial strategies, regarding the exponential rise in bacterial resistance and the constant requirement for controlling infections.

6.3. Comparative Properties of ZnO-NPs in Antibacterial and Anticancer Applications

The following tables provide a comprehensive comparison of the properties, mechanisms, and ROS production of ZnO-NPs in antibacterial and anticancer applications. **Table 2** compares the key features of ZnO-NPs for these two important applications, while **Table 3** outlines the distinct mechanisms by which ZnO-NPs maintain their impact. Finally, **Table 4** examines the ROS production capabilities of ZnO-NPs under different light conditions, which is a critical factor in their efficacy. Together, these tables offer valuably documented the versatile and targeted applications of ZnO-NPs in the fields of antimicrobial and antitumor therapies.

Table 2: Comparison of ZnO-NPs Properties for Antibacterial and Anticancer Applications

Property	ZnO-NP Characteristics	Effect on Antibacterial Activity	Effect on Anticancer Activity	Reference
Shape	Spherical	Provides uniform interaction with bacterial surfaces; effective ROS generation due to high surface-to-volume ratio	Enables effective cellular uptake, enhancing apoptosis and ROS generation	[32, 43]
	Rod-shaped	Better penetration into bacterial membranes, increased surface interaction	Enhanced mitochondrial disruption and selective apoptosis in cancer cells	[100]
	Sheet-like	Large contact area increases membrane damage but may reduce internalization.	Effective in PDT applications; high ROS production under light exposure	[134]
Composition	Pure ZnO	High antibacterial activity, ROS generation, ion release	Significant ROS-mediated apoptosis; selectively toxic to cancer cells	[135]
	Doped ZnO (e.g., Ag-doped, Fe-doped)	Enhanced antibacterial efficacy through synergistic effects, improved ROS	Increased cytotoxicity and ROS production, improved selectivity and apoptosis	[135]
	Surface-functionalized (e.g., PEG-coated)	Increased biocompatibility, reduced cytotoxicity in non-target cells	Enhanced stability in biological systems, targeted delivery potential	[38]
Size	< 20 nm	High reactivity, penetrates bacterial membranes effectively	Rapid cellular uptake, strong ROS production, DNA damage in cancer cells	[100]

	20–50 nm	Optimal balance between reactivity and stability for bacterial cell damage	Enhanced drug-loading potential, suitable for drug-delivery systems	[100]
	> 50 nm	Lower antibacterial effectiveness, limited internalization	Limited cell penetration, but valuable in surface applications (e.g., coatings)	[100]
Concentration	Low (≤ 10 µg/mL)	Minimal antibacterial impact; sub-lethal, potentially resistance-inducing	Lower cytotoxicity, minimal ROS, generally safer but less effective in treatment	[5]
	Moderate (10–50 µg/mL)	Significant bacterial cell death, effective membrane damage	Effective apoptosis induction, suitable for controlled cancer cell targeting	[5]
	High (> 50 µg/mL)	The potent bactericidal effect, risks of cytotoxicity in non-target organisms	Strong cytotoxic effects, practical aggressive cancer therapies, but potential off-target toxicity	[5]

7. Anticancer Mechanisms of ZnO-NPs

The fundamental technique toward the cytotoxicity of ZnO-NPs is the intracellular release of dissolved Zn ions, subsequently producing reactive oxygen species (ROS). This process induces zinc-mediated protein activity unbalance and oxidative stress, ultimately resulting in cell death. Soluble extracellular zinc has minimal cytotoxicity. In recent years studies indicate that extracellular soluble zinc, when introduced to cell culture and media, generates weakly soluble amorphous zinc-carbonate phosphate precipitates (with phosphate originating from the media). This precipitation is intended to keep the cell from the damaging consequences of zinc [137]. Conversely, the release of free zinc ions within the cell initiates an interconnected cascade of pathways that mediates the cytotoxic reaction of ZnO-NPs.

Table 3: ZnO-NPs Mechanisms in Antibacterial and Anticancer Applications

Mechanism	Antibacterial Action	Anticancer Action
ROS Generation	Creates oxidative stress, damaging bacterial cell components	Induces oxidative stress, leading to apoptosis in cancer cells [100]
Direct Contact with Cell Membrane	Disrupts cell wall integrity, causing cell lysis	Increases cell membrane permeability, promoting drug uptake [9, 115]
Ion Release	Zn ions disrupt bacterial metabolism	Zn ions interfere with tumor cell signaling pathways [36, 136]
Photodynamic Activation (PDT)	Enhances ROS under UV/visible light for sterilization	Increases cytotoxic effects on cancer cells when exposed to UV light [44, 115]

Table 4: ROS Production by ZnO-NPs Under Different Light Types

Light Type	ROS Level Generated	Antibacterial Effectiveness	Anticancer Effectiveness	Reference
UV Light	High	High	High (Surface-level)	[120]
Full-Spectrum Light	Moderate	Moderate	Moderate to High	[35]

Fig. 6 depicts the three mechanisms of cytotoxicity associated with ZnO-NPs. The graphic illustrates that zinc-dependent protein activity imbalance and increased ROS production result in cytotoxicity. Investigations into reactive oxygen species (ROS) have demonstrated that the application of antioxidants and ROS quenchers does not significantly diminish the cytotoxicity of ZnO-NPs [137–140]. This indicates that ROS generation might not be the only mechanism of cytotoxicity of ZnO-NPs, but rather the resultant cytotoxic response. While ROS is generated when ZnO interacts with the cell, the primary source to generate ROS can result from the cytotoxic reaction associated with the imbalance of zinc-dependent protein activity, exemplified by the permeabilization of

mitochondria that releases large quantities of ROS within the cell. This suggests that the main mechanism of ZnO-NPs cytotoxicity is the disruption of zinc-dependent protein activity due to the elevated release of free zinc ions within the cell [116, 137–139].

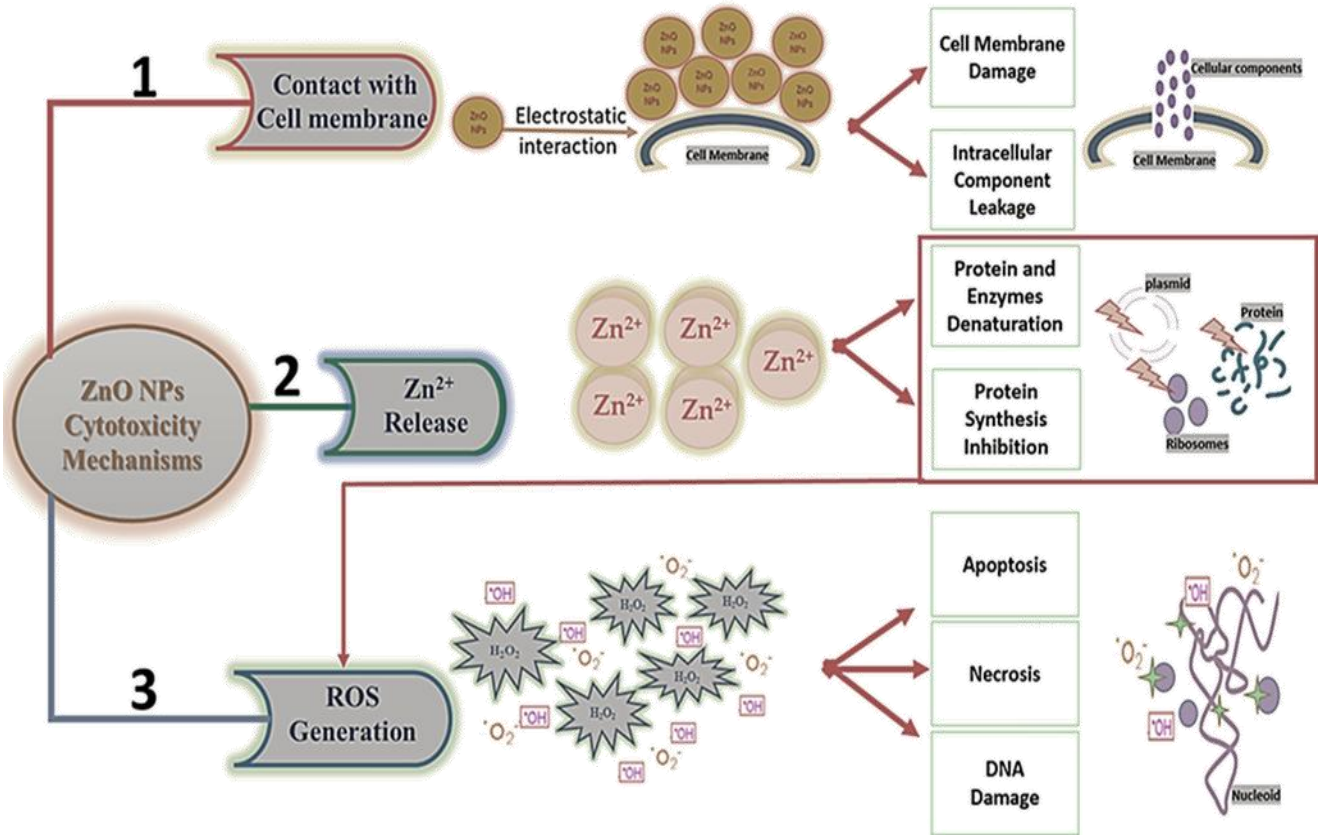

Figure 6: The three pathways contributing to the cytotoxicity of ZnO-NPs: (1) direct interaction with the cell membrane, (2) release of Zn^{2+}, and (3) production of reactive oxygen species (ROS) [140].

7.1. Induction of Apoptosis

ZnO-NPs have attracted concentrations for their capability to be toxic to cancer cells while saving normal cells through ROS production, damage to mitochondria, and targeting cancer cells' apoptosis regulatory proteins. This section will explore how ZnO-NPs cause apoptosis, specifically oxidative stress, mitochondrial disorder, and the regulation of apoptotic proteins [6].

7.1.1. ROS Generation and Oxidative Stress

ZnO-NPs generated ROS, which causes oxidant stress indices within cancer cells beyond cellular antioxidant defenses. High ROS levels amplify multiple cellular processes, culminating in apoptosis [141]. This oxidative stress causes the activation of the mitochondrial apoptotic pathway, and cytochrome C is released into the cytoplasm [116]. The released cytochrome C combines with apoptotic protease activating factor 1 (Apaf-1) and pro-caspase-9 to form an apoptosome complex [142]. This complex further activates the caspase-3, the primary effector caspase involved in the execution of apoptosis and thus causes cell death. Besides, they alter the delicate mitochondrial membrane potential, so high levels of ROS contribute to further oxidative damage to lipids, proteins, and DNA. This disruption can activate the intrinsic apoptotic pathway, causing cancer cell death. Furthermore, the ROS involvement in activating pro-apoptotic signaling pathways like the p53 pathway mainly participates in the ZnO-NPs cytotoxicity. High ROS levels activate other pathways such as p53, which instigates cell cycle arrest and apoptosis, enhancing the ZnO-NPs impact in cancer cells [143].

7.1.2. Mitochondrial Disruption and Cytochrome Release

ZnO-NPs accumulate within mitochondria, decreasing the mitochondrial membrane potential and releasing cytochrome C, which is pivotal towards apoptosis. It has been reported that most cancer cells have mitochondrial dysfunction and are usually resistant to apoptosis. The relevance of the cytosolic cytochrome C movement from mitochondria in the intrinsic pathway of apoptosis is essential [102]. In the cytosol, cytochrome C binds to Apaf-1 and procaspase-9 to form apoptosome, activating caspase-9 and the terminal executioner caspase-3. However, this is quite an efficient pathway when fighting tumors with abnormal apoptotic resistance signals [144]. The capacity of ZnO-NPs to cause mitochondrial impairment promotes cancer cell death and qualifies them as candidate drugs for tumors possessing high levels of anti-apoptotic proteins. Moreover, the direct accumulation of the ZnO-NPs to mitochondria could effectively induce apoptosis depending on the cancer cells without affecting the normal healthy cells as much as compared to traditional chemo drugs.

7.1.3. Activation of Apoptotic Proteins

ZnO-NP's impact on apoptotic signal transduction also relates to the regulatory effects on pro-apoptotic and anti-apoptotic proteins. It has shown that ZnO-NPs can down-regulate the pro-apoptotic proteins such as Bax in cancer cells while up-regulating anti-apoptotic proteins such as Bcl-2 [145]. This ratio plays a pivotal role as it alters the membrane permeability of mitochondria and releases cytochrome C, which triggers the apoptotic signaling pathway. The highest cytotoxicity of ZnO-NPs in cancer cells relative to healthy cells is due to the higher affinity of ZnO-NPs to the tumor cells [146]. This specificity could be attributed to differences in cell membrane charge and permeability; thus, ZnO-NPs have optimal effects in the carcinogenic milieu. This mechanism also highlights the possibility of ZnO-NPs being used as targeted treatment strategies that have improved temporal duration and minimal toxicities like those observed with conventional chemotherapy drugs.

7.2. Inhibition of Cell Proliferation

In addition to inducing apoptosis in cancer cells, ZnO-NPs modify cell division through cell cycle disruption and DNA fragmentation. Awareness of such processes can help recognize numerous facets of ZnO-NPs' antitumor activity.

7.2.1. Cell Cycle Arrest

The ZnO-NPs, which bind to the cell membrane and get internalized by cells, affect cell cycle phases, which regulate growth and divisions, given the synthesis and degradation of proteins necessary for cyclin/CDK complexes formation. These complexes are checkpoints that are important in the cell cycle because they allow only the correct progression of each cycle phase. Cell cycle arrest caused by ZnO-NPs is mainly during the G1 and G2/M phases, where DNA synthesis and mitosis occur [147]. Cancer cells are especially vulnerable to the alterations of these phases because of their rapid division and are easily influenced by the stress signals that limit cell division. Among the major anti-proliferative effects of ZnO-NPs, the most significant seems to be their ability to generate ROS, which is signaling particles that bring about oxidative stress in the cell. This results in activating other proteins [42]. One of them is the p53 protein, a specialized tumor suppressor critical in stopping cell division in the event of cellular stress or DNA damage. When the damage is massive, activation of the p53 protein can result in apoptosis, where the damaged cell does not survive**.** This aspect is most helpful in treating highly proliferative malignancies since the cycle is augmented to increase cytotoxicity in malignant tissues where cycling is prevalent [143]. These findings reveal that ZnO-NPs increased ROS production to boost p53-mediated cell death at the tumor site. This increased ROS level is also instrumental in the degradation of cyclin proteins, including cyclin D, cyclin E, and cyclin B, which are essential in the phase transition of the cell cycle. Thus, CDK inhibitors prevent the formation of functional complexes of the CDKs and, therefore, inhibit the process of cell progression. This bimodal action, altering cyclins and CDKs, makes ZnO-NPs worthwhile in controlling rapidly growing tumors since they both halt cell cycling and induce cell death. Moreover, this mechanism successfully addressed the cancer types characterized by mutations in the CDK and cyclin proteins that result in the growth of cancer cells. Through ROS generation, ZnO-NPs are selective for these proteins. They may effectively diminish the malignancy of such tumors, which remains a significant approach when conventional treatments remain inefficient. **Table 5** examines how ZnO-NPs interact with specific cyclin-CDK complexes, impacting different cell cycle phases in cancer cells.

Table 5: Cyclin-CDK Complexes and Their Role in the Cell Cycle Affected by ZnO-NPs

Cyclin-CDK Complex	Cell Cycle Phase	Effect of ZnO-NP Interaction	Cancer Type Impacted	Reference
Cyclin D-CDK4/6	G1 Phase	Causes cell cycle arrest	Breast, Lung Cancer	[147]
Cyclin E-CDK2	S Phase	Inhibits DNA replication	Liver Cancer	[148]
Cyclin B-CDK1	M Phase	Reduces mitotic activity	Prostate Cancer	[147]

7.2.2. DNA Damage and Repair Inhibition

ZnO-NPs also damage Deoxyribonucleic Acid. (DNA) through ROS production, which causes strand breaks and oxidative alteration and prevents replication. The potential of ZnO-NPs to cause DNA damage is notable in rapidly dividing cancer cells, in which high rates of cell division increase the likelihood of oxidative lesions occurring [149]. The base excision repair and the p53-dependent signaling for DNA damage response are initiated whenever the cellular DNA is damaged. These pathways lead to apoptosis when the DNA damage cannot be repaired, hence the connection between DNA damage and cell death. This aspect of selectively causing DNA damage to the cancer cells while overloading the repair mechanisms is a robust anticancer advantage that can be harnessed by exploiting the resistance-free growth characteristic of cancer cells [150, 151].

7.2.3. Epigenetic Effects

Recent investigations have also demonstrated that ZnO-NPs may alter one of the epigenetic mechanisms that regulate gene expression, for example., DNA methylation and Histone modification. Thereby, ZnO-NPs can remove oncogenes and activate tumor suppressor genes, hence controlling cancer cell growth and proliferation [101]. Such epigenetic changes are pivotal for developing cancer therapies based on ZnO-NPs since other traditional therapies are often met with some resistance in patients. Given these epigenetic roads for regulation opponents, ZnO-NPs could amplify the tumor suppressor effects of current treatments and mitigate the issue of tumor heterogeneity and plasticity. These complex processes by which ZnO-NPs employ their anticancer effects propose the material as a novel therapeutic approach for treating cancer [152]. Further research on these mechanisms may also open new possibilities for employing ZnO-NPs in clinical oncological practice and expanding a list of practical strategies for various cancer types.

8. Current Research and Applications

The central area where ZnO-NPs are increasingly studied and used is in antibacterial and anticancer treatments, with numerous research efforts devoted to the compound's use in clinical approaches, drug delivery, and companion therapies. This section will further discuss the current studies and developed applications of ZnO-NPs, focusing on their medical aspect and new role today. **Fig. 7** shows the distribution of research focus across clinical applications, including antibacterial coatings, cancer therapy, drug delivery, and wound healing.

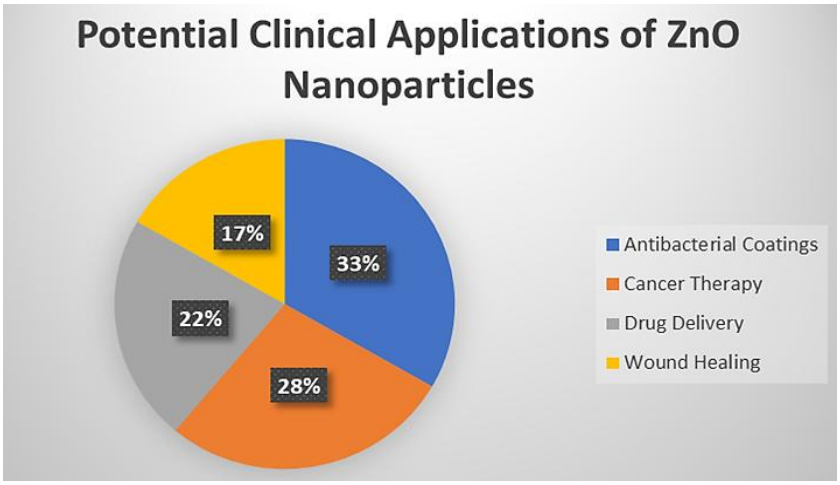

Figure 7: Potential Clinical Applications of ZnO-NPs

8.1. Clinical Trials and Therapeutic Development

ZnO-NPs are currently under investigation in phase I trials to determine their efficacy and side effects for cancer therapy. ZnO-NPs are being examined as complementary to standard chemotherapeutic treatments. The premise for the above strategy lies in the fact that ZnO-NPs might potentially increase the therapeutic-to-toxicity ratio of cytotoxic agents [153]. Decreasing the necessary doses of these drugs to use within the presence of ZnO-NPs may also reduce the side effects of the mentioned medication and increase the perceived quality of life in patients with a disease that requires the current medication [154]. Furthermore, it is also essential to consider that the ZnO-NPs are being explored for their antibacterial activities, apart from their potential uses in oncology. More trials are being conducted on their application in wound treatment and as a surface coating for medical appliances to prevent hospital-acquired infections. The use of ZnO-NPs in such applications is most advantageous due to the bio-compatibility and the localized antibacterial characteristics, which are paramount for post-operative care and overall patient outcomes [116].

8.2. ZnO-NPs as Drug Carriers

As for nanocarriers, ZnO-NPs are being utilized to enhance the delivery of antineoplastic compounds. Researchers have conjugated anticancer drugs to ZnO-NPs to improve drug stability and its intracellular delivery system and reduce the impacts on neighboring healthy tissues [51]. Such a targeted delivery system is sound, especially for toxic agents, where toxicity directly translates to dosing frequency. Applying ZnO-NPs in drug delivery systems makes it achievable to formulate novel nanoscale systems that can cross biological barriers, thus improving drug bioavailability [36]. Moreover, it is accepted that ZnO-NPs can protect delicate drugs from degradation by biological systems to enhance efficacy. It also improves the outcomes of the therapy and puts the foundation for creating personalized drugs connected with the characteristics of the tumor [148].

8.3. Photodynamic and Photothermal Applications

ZnO-NPs are anticipated for photodynamic therapy (PDT) and photothermal therapy (PTT) as different methods for tumor cell eradication using light. The data collected using PDT indicated that ZnO-NPs could produce ROS in any spot to which focused light is applied to enhance tumor cells' treatments with minimal damage to healthy tissues. Such selective action helps avoid side effects, and this is typically an issue in conventional oncology therapies. In Partial Thromboplastin Time (PTT), ZnO-NPs emit light and then convert it to heat energy for localized hyperthermia, leading to cell death in the cancer cells [5]. Thus, as photocatalysts enable efficient photothermal conversion, ZnO-NPs can also be used as agents in thermal ablation strategies. PDT and PTT are calculated as new-wave cancer treatments, and ZnO-NPs can be considered to possess a multidimensional structure to enhance the potential of treatment [44, 100, 155].

8.4. Emerging Trends in Combination Therapies

Consequently, studies are transitioning towards coprocessing ZnO-NPs with other nanoparticles, such as gold and silver, to boost their antibacterial and anticancer efficacy. Further studies suggested that these hybrid nanoparticles possess more in vitro ROS-generating capacity, better cellular uptake, and stability than the isolated nanoparticles [100]. These outcomes propose that combined consolidation of ZnO-NPs with other NP types could offer improved treatment options, particularly in complex ailments such as malignancy and chronic diseases. Moreover, ZnO-NPs have been used against multidrug-resistant cancer cells. Data suggests these nanoparticles may escape the resistance by accumulating oxidative stress and DNA damage. This capability should effectively address stem cell-maintained resistant cancer phenotypes that limit the activity of dominant chemotherapeutic agents [145, 153]. Studies on the possible interaction of ZnO-NPs with other antitumor agents increase the effectiveness of combined treatments and the assessment of an emerging problem of mutative drug resistance. Table 6 highlights ZnO-NPs' synergistic potential when combined with other treatments and emphasizes improved outcomes in cancer therapies.

Table 6: ZnO-NPs in Combination Therapies for Cancer

Combination Agent	Mechanism with ZnO-NP	Improved Outcome	Reference
Chemotherapeutics	Enhanced drug delivery	Increased cancer cell targeting	[37, 114]
Photodynamic Therapy	Improved ROS production	Enhanced localized cytotoxicity	[42, 44]
Antibiotics	Reduced resistance	Effective against resistant strains	[156, 157]

9. Conclusions

ZnO-NPs show significant promise in many biomedical applications, primarily as an effective bactericide and anticancer agent derived from plant origin. Their effectiveness in treating bacterial infections and various cancers stems from their action mechanisms, for instance, generating reactive oxygen species (ROS), destabilizing cell membranes, and prompting apoptosis. However, the practice of these materials makes it impossible to enhance the synthesis of these techniques, biocompatibility, and the level of toxicity, especially in vivo. Such problems are crucial in developing and using ZnO-NPs in clinical studies.

Further studies are therefore required for better optimization of the physical and chemical nature of ZnO-NPs to enhance their selection ratio and minimize the detrimental consequences of their usage. This may require some size, morphology, and surface charge alteration because these features play critical roles in how nanoparticles integrate with biological systems. Besides, expanding clinical trials to explore the utility of ZnO-NPs in treating real cases of cancer and antibacterial properties and improving the eligibility criteria of corresponding trials is vital. Such trials help ascertain the correct doses of the ZnO-NPs and their impact on the patient's health. These are important in putting ZnO-NPs in standard treatment, as the case with other NP formulations in medicine has been practiced.

To enhance the clinical potential of ZnO nanoparticles, researchers could focus on combining them with other agents and incorporating them into drug delivery systems. Gaining a deeper understanding of how ZnO nanoparticles interact with different drugs may lead to improved treatment outcomes by preventing infections caused by multidrug-resistant organisms and tackling complex cancers. Advanced delivery methods can localize ZnO nanoparticles to the infection site or tumor while minimizing exposure to the rest of the body. Further exploration of applications beyond antibacterial and anticancer therapies could position these valuable nanoparticles as a cornerstone of innovative therapeutic strategies, revolutionizing the patient journey in nanomedicine.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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