Review

Plant-Mediated Zinc Oxide Nanoparticles: Advances in the New Millennium towards Understanding Their Therapeutic Role in Biomedical Applications

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Abstract: Zinc oxide nanoparticles have become one of the most popular metal oxide nanoparticles and recently emerged as a promising potential candidate in the fields of optical, electrical, food packaging, and biomedical applications due to their biocompatibility, low toxicity, and low cost. They have a role in cell apoptosis, as they trigger excessive reactive oxygen species (ROS) formation and release zinc ions ($Zn^{2+}$) that induce cell death. The zinc oxide nanoparticles synthesized using the plant extracts appear to be simple, safer, sustainable, and more environmentally friendly compared to the physical and chemical routes. These biosynthesized nanoparticles possess strong biological activities and are in use for various biological applications in several industries. Initially, the present review discusses the synthesis and recent advances of zinc oxide nanoparticles from plant sources (such as leaves, stems, bark, roots, rhizomes, fruits, flowers, and seeds) and their biomedical applications (such as antimicrobial, antioxidant, antidiabetic, anticancer, anti-inflammatory, photocatalytic, wound healing, and drug delivery), followed by their mechanisms of action involved in detail. This review also covers the drug delivery application of plant-mediated zinc oxide nanoparticles, focusing on the drug-loading mechanism, stimuli-responsive controlled release, and therapeutic effect. Finally, the future direction of these synthesized zinc oxide nanoparticles’ research and applications are discussed.

Keywords: antimicrobial; antioxidant; antidiabetic; anticancer; anti-inflammatory; drug delivery; photocatalytic
1. Introduction

Nanotechnology is a branch of science concerned with the processing and modification of materials at the nanometer scale. It is a product of nature that influences a material through physiochemical processes, and it has a wide range of applications in research [1–4]. At Caltech, Richard Feynman, the greatest theoretical physicist, was the first to communicate the idea of nanotechnology in 1959. Nanomaterials are microscopic materials with nanometer dimensions that are in use in different fields. They have distinct properties, such as a large surface area and quantum size effects, and are regarded as a significant state of matter [5]. Metal and metal oxide nanoparticles have many promising applications in agriculture, catalysts, electronics, fiber optics, sensors, biolabeling, and biomedical fields [6–11]. In the synthesis of nanoparticles, chemical methods often result in dangerous byproducts, and the chemical reducing reagents (such as hydrazine, sodium borohydride, and sodium dodecyl sulfate) used are toxic to nature. Hence, in comparison to the chemical methods, the eco-friendly green synthesis method has gained significant attention in the past decade for the synthesis of nanoparticles [4,8,12].

The synthesis of nanoparticles through biogenic methods involves the use of a variety of natural resources that include all forms of plants and microorganisms. During the synthesis of nanoparticles by biological route, active enzymes/biomolecules (active metabolites/phytochemicals) of the biotic source act as reducing and capping agents, thereby allowing for the mass production of the particles [1,13,14]. The usage of biotic sources not only reduces the risk of toxicity of the obtained particles to the environment but can also be produced in a large scale with the required parameters (well-defined size and morphology) [2,15,16]. Among the various metal nanoparticles synthesized through the usage of various biotic sources, zinc oxide nanoparticles synthesized through plant extracts have gained considerable importance in the present millennium due to their unique properties and various biomedical applications.

2. Zinc Oxide Nanoparticles

Zinc oxide is a unique inorganic material with semiconducting behavior and piezoelectric, triboelectric, pyroelectric, optoelectronics, and catalysts properties [12,17–20]. Zinc oxide is an n-type semiconductor with a band gap of 3.4 eV and an excitation binding energy of 60 meV at room temperature. Zinc oxide is nontoxic and skin-friendly, and it is even used as a UV blocker in sunscreens. Among the metal oxide nanoparticles, zinc oxide nanoparticles have been extensively used in various biological applications due to their nontoxic nature, and they are also listed as “generally recognized as safe” (GRAS) by the U.S. FDA (21CFR182.8991). Various studies have established zinc oxide as the most effective antimicrobial agent, as evidenced by releasing reactive oxygen species (ROS) on its surface [17].

Meanwhile, zinc oxide is known to be biocompatible and safe, with various applications in biomedical and drug delivery systems. Among the metal oxide nanoparticles, zinc oxide nanoparticles have piqued the interest of researchers for the past two decades due to their unique and wide range of properties. Due to their biocompatible nature, they are widely used as a semiconductor nanomaterial in ethanol gas sensors, photocatalysis, electronic and optoelectronic devices, pharmaceutical and cosmetic products, and, particularly, in the biomedicine field [10,20,21]. It has been well-documented that zinc oxide nanoparticles can be synthesized by different methods using various types of biotic sources, but the present review mainly focuses on the biosynthesis of zinc oxide nanoparticles using plant sources that are termed to be eco-friendly, cost-effective, and, also, efficient in biomedical applications, along with advances made in the “new millennium” towards understanding their role/mechanism of action involved.

3. Synthesis of Zinc Oxide Nanoparticles from Plants

Green synthesis is an emerging area in which nontoxic chemicals are generated using environmentally friendly and bio-safe reagents and may also be considered as a viable
alternative to the physical and chemical methods. However, the main problems with green synthesis are nanoparticle stability and a lack of understanding of its mechanisms. Researchers are focusing their efforts on the green synthesis of metal and metal oxide nanoparticles from various biological sources such as plants, bacteria, fungi, yeast, algae, etc. [22–25]. Among the different sources, plants are considered to be vastly available and are known to possess phytoconstituents that are reported to be beneficial in various ways to humankind [26–29]. Plant parts such as leaves, stems, bark, roots, rhizomes, fruits, flowers, and seeds have been extensively used for the synthesis of zinc oxide nanoparticles in the recent past and are found to be stable, highly pure, cost-effective, and possess greater biomedical properties [30,31]. Plants are the most popular choice for nanoparticle synthesis, because they produce large quantities of stable, varied-sized nanoparticles for specific applications on a large scale [20,32,33]. Plant phytochemicals such as polysaccharides, proteins, amino acids, alkaloids, flavonoids, and terpenoids are used as stabilizing agents in green synthesis methods to biologically reduce metal oxides (or metal ions) to metal nanoparticles in an aqueous solution [5,25,34].

The green synthesis of zinc oxide nanoparticles from plant sources usually begins with the washing of plant parts using double-distilled water or Tween 20, accompanied by drying at room temperature and grinding into powder with a mortar and pestle. The plant extract is prepared by boiling the weighted powder with continuous stirring with a magnetic stirrer. The solution is then filtered through Whatman filter paper and used as a plant extract in the following steps. Zinc precursors such as zinc acetate \([\text{Zn(OAc)}_2]\), zinc chloride \([\text{ZnCl}_2]\), zinc nitrate \([\text{Zn(NO}_3\text{)}_2]\) and zinc sulphate \([\text{ZnSO}_4]\) solutions are individually used with a fixed amount of plant extract, and it serves as the source for preparing zinc oxide nanoparticles through the application of various methods that involve heating, centrifugation, etc. that finally results in the formation of the desired nanoparticles [35–40]. Further, UV–Vis spectroscopy was used to confirm the nanoparticles that were synthesized. The morphology of the nanoparticles was determined using electron microscopes such as the Scanning Electron Microscope (SEM), Transmission Electron Microscope (TEM), and Atomic Force Microscopy (AFM). The nanoparticles’ crystal structure and chemical composition were calculated using X-Ray Diffraction (XRD), Energy Dispersive X-Ray Spectroscopy (EDS or EDX) used for determination of the elements present, and Fourier-transform infrared (FTIR) spectroscopy used to describe the functional groups present on the surfaces of the nanoparticles. The Dynamic Light Scattering (DLS) and Zeta Potential (ZP) methods were used to determine the size and dispersion of the nanoparticles in a liquid suspension.

It is well-documented that the ability of any organism to reduce metal ions apart from stabilizing them into nanoparticles is the basis for green synthesis. Plants are considered to be the best candidates for the green synthesis of nanoparticles, as they produce stable forms of the same compared to microorganisms [41]. Plants are considered to possess a rich biodiversity of secondary metabolites that are worth investigating. In the recent past, researchers were interested in the phytoconstituents produced by plants to investigate their bio-reduction process of metal nanoparticles by combinations of phytoconstituents/secondary metabolites [42]. These molecules not only acted as reducing agents but also played a key role in the capping of nanoparticles, which was crucial for their stability and biocompatibility, and due to these molecules, no extra chemical reducing and capping agents were required [4]. In addition, these plant-based molecules not only operated as the growth terminator of zinc oxide nanoparticles but also acted as a linker molecule between two or more molecules of zinc oxide-formed ZnO NPs, making them self-assemble [43].

Although many reports are available on the bioactivities (such as antimicrobial, antioxidant, anticancer, photocatalytic, etc.) of zinc oxide nanoparticles synthesized from various plant species, a few studies have been conducted to compare the activities of nanoparticles from different plants [12,44–46]. In addition, it is also noted that the plant-mediated zinc oxide nanoparticles possessed better biological activities than the nanoparticles synthe-
sized through the chemical route [12,28,44,47,48]. Further, it has been noted that, due to the coating of various pharmacologically active biomolecules on their surface, zinc oxide nanoparticles allow multiple ligand-based conjugations of nanoparticles with their respective receptors, leading to better bioactivities [3,4,12,14,45–47,49,50]. These comparisons have suggested that zinc oxide nanoparticles possess better bioactivities when they are synthesized from the potential reducing agents present in the plants. Table 1 lists the different plant sources used in zinc oxide nanoparticles synthesis, along with their morphological characteristics and applications.

Table 1. Morphology of plant-mediated zinc oxide nanoparticles and their applications.

| Plant Name | Plant Part Used | Size (nm) | Shape/ Morphology | Applications | Reference |
|------------|----------------|----------|------------------|--------------|-----------|
| Zinc Nitrate |               |          |                  |              |           |
| Solanum nigrum | Leaf          | 29       | Quasi-spherical | Antibacterial | Ramesh et al. [51] |
| Borassus flabellifer | Fruit       | 55       | Rod like         | Drug delivery | Vimala et al. [52] |
| Phyllanthus niruri | Leaf       | 25       | Quasi-spherical | Photocatalytic | Anbuvannan et al. [53] |
| Anisochilus carnosus | Leaf     | 30–40    | Quasi-spherical | Antibacterial and Photocatalytic | Anbuvannan et al. [54] |
| Hibiscus subdariffa | Leaf    | 12–46    | Spherical        | Antibacterial and Anti-diabetic | Bala et al. [35] |
| Plectranthus amboinicus | Leaf | 20–50    | Spherical and hexagonal | Antibacterial, Antibiotfilm and Larvicidal | Vijayakumar et al. [55] |
| Carissa edulis | Fruit       | 50–55    | Flower shape     | Photocatalytic | Fowsiya et al. [56] |
| Rosa canina | Fruit       | <50      | Spherical        | Antibacterial, Antioxidant and Anticancer | Jafarirad et al. [57] |
| Nephelium lappaceum | Peel    | 25–40    | Spherical        | Photocatalytic | Karnan and Selvakumar [58] |
| Limonia acidissima | Leaf    | 12–53    | Spherical        | Antibacterial (TB) | Patil and Taranath [59] |
| Carica papaya | Milk latex | 11–26    | Hexagonal        | Photocatalytic and Antibacterial | Sharma [60] |
| Boswellia ovalifoliolata | Bark       | 20       | Spherical        | Antimicrobial | Supraja et al. [61] |
| Camellia sinensis | Leaf     | -        | Hexagonal        | Photocatalytic | Nava et al. [62] |
| Ceropogia candelabrum | Leaf | 12–35    | Hexagonal wurtzite | Antibacterial and Antioxidant | Murali et al. [5] |
| Ziziphus nummularia | Leaf | 12–26    | Spherical and irregular | Antifungal and Anticancer | Padalia and Chanda [7] |
| Vaccinium arctostaphylos | Fruit | 13       | Spherical        | Anti-diabetic | Bayrami et al. [63] |
| Citrus sinensis | Peel       | 12–24    | Hexagonal prisms and oval spheres; highly irregular sponge-like | Photocatalytic | Luque et al. [64] |
| Mangifera indica | Leaf       | 45–60    | Nearly spherical and hexagonal quartzite | Antioxidant and Anticancer | Rajeshkumar et al. [65] |
| Costus pictus | Leaf       | 40       | Hexagonal, rod-shaped and spherical | Antimicrobial and Anticancer | Suresh et al. [66] |
Table 1. Cont.

| Plant Name                  | Plant Part Used | Size (nm) | Shape/ Morphology        | Applications                                      | Reference                  |
|-----------------------------|-----------------|-----------|--------------------------|--------------------------------------------------|-----------------------------|
| Solanum torvum              | Leaf            | 28        | Spherical                | Toxicological effect in Wistar albino rats        | Ezealisiji et al. [67]      |
| Artabotrys hexapetalu       | Leaf            | 20–30     | Spherical and rod-like   | Antibacterial and Photocatalytic                  | Shanavas et al. [68]        |
| Bambusa vulgaris            | Leaf            | 20–50     | Hexagonal and quasi hexagonal plate like | Antibacterial and Anticancer                      | Ruddaraju et al. [69]      |
| Annona squamosa             | Leaf            | 20–50     | Hexagonal and quasi hexagonal plate like | Antibacterial and Anticancer                      | Tettey and Shin [70]        |
| Scutellaria baicalensis     | Root            | 33–99     | Spherical                | Antioxidant and Anticancer                        |                             |
| Albizia lebbek              | Bark            | 66        | Irregular spherical      | Antimicrobial, Antioxidant, Cytotoxic and Antiproliferative | Umar et al. [26]          |
| Citrus sinensis             | Peel            | 33        | Hexagonal                | Antibacterial, Antifungal and Anticancer          | Gao et al. [19]            |
| Beta vulgaris               | Plant           | 20        | Spherical                | Antibacterial and Antifungal                      | Pillai et al. [25]         |
| Cinnamomum tamala           | Plant           | 30        | Rod                      | Antibacterial and Antifungal                      |                             |
| Cinnamomum verum            | Plant           | 46        | Spherical                | antibacterial and Antifungal                      |                             |
| Brassica oleracea var. italic | Leaf           | 47        | Spherical                | Antibacterial and Anticancer                      |                             |
| Crotalaria verrucosa        | Leaf            | 16–38     | Hexagonal                | Anti-inflammatory                                 | Sana et al. [71]          |
| ZINC NITRATE HEXAHYDRATE    |                 |           |                          |                                                  |                             |
| Azadirachta indica          | Leaf            | 40        | Spherical                | Antimicrobial                                     | Elumalai and Velmurugan [13]|
| Vitex trifolia              | Leaf            | 30        | Nearly spherical and hexagonal | Antimicrobial and Photocatalytic                  | Elumalai et al. [72]       |
| Plectranthus amboinicus     | Leaf            | 88        | Rod shape                | Photocatalytic                                    | Fu and Fu [73]             |
| Polygala tenuifolia         | Root            | 33–73     | Spherical                | Antioxidant and Anti-inflammatory                 | Nagajyothi et al. [17]     |
| Allium sativum and A. cepa  | Bulbs           | 14–70     | Spherical                | Photocatalytic activity                           | Stan et al. [74]           |
| Petroserum crisum           | Leaf            | 100       | Spherical, nanorod and hexagonal | Antibacterial                                     | Sundrarajan et al. [75]   |
| Pongamia pinnata            | Leaf            | ~5–15     | Sponge like irregular    | Photocatalytic, Antioxidant and Antibacterial     | Suresh et al. [76]         |
| Cassia fistula              | Leaf            | 11.53     | Spherical                | Photocatalytic and Antioxidant                    | Suresh et al. [77]         |
| Artocarpus gomezianus       | Fruit           | 5         | Spherical                | Photocatalytic and Antioxidant                    |                             |
| Corynum citroidora          | Leaf            | 64        | Polyhedron               | Photocatalytic                                    | Zheng et al. [78]          |
| Plant Name                        | Plant Part Used | Size (nm) | Shape/Morphology          | Applications                             | Reference                  |
|----------------------------------|-----------------|-----------|---------------------------|------------------------------------------|----------------------------|
| *Azadirachta indica*             | Leaf            | 10–30     | Hexagonal                 | Antibacterial, Antioxidant and Photocatalytic | Madan et al. [36]          |
| *Terminalia chebula*             | Fruit           | 12        | Roughly spherical         | Photocatalytic                           | Rana et al. [79]           |
| *Citrus limon*                   | Leaf            | 10–20     | Spherical                 | Antioxidant                              | Madan et al. [36]          |
| *Citrullus colocynthis*          | Fruit           | 85–100    | Flower                    | Photocatalytic                           | Azizi et al. [80]          |
|                                  | Seed            | 20–35     | Hexagonal                 | Antimicrobial                            |                            |
|                                  | Pulp            | 30–80     | Irregular polygons        | Photocatalytic                           |                            |
| *Ocimum tenuiflorum*             | Leaf            | 10–20     | Spherical                 | Photocatalytic                           | Dayakar et al. [81]        |
| *Cochlospermum religiosum*       | Leaf            | ~76       | Hexagonal                 | Antimicrobial                            | Mahendra et al. [82]       |
| *Azadirachta indica*, *Hibiscus*| Leaf            | 27–54     | Spherical                 | Photocatalytic                           | Rehana et al. [22]         |
| *raosa-sinensis*, *Murraya koenigii*, *Moringa oleifera* and *Tamarindus indica* | Leaf | –         | Irregular                 | Antimicrobial                            |                            |
| *Eucalyptus globulus*            | Leaf            | 11.6      | Spherical                 | Antioxidant and Photocatalytic           | Siripireddy and Mandal [83]|
| *Acacia senegal*                 | Arabic gum      | 10        | Spherical                 | Photocatalytic                           | Taghavi Fardood et al. [84]|
| *Coryza canadensis*              | Leaf            | –         | Irregular                 | Antimicrobial                            | Ali et al. [85]            |
| *Garcinia mangostana*            | Fruit pericarp   | 21        | Spherical                 | Photocatalytic                           | Aminuzzaman et al. [86]    |
| *Andrographis paniculata*        | Leaf            | 57        | Spherical, oval and hexagonal | Antioxidant, Anti-diabetic and Anti-inflammatory | Rajakumar et al. [34]     |
| *Barleria gibsoni*               | Leaf            | 50        | Hexagonal (Wurtzite)      | Wound healing                            | Shao et al. [87]           |
| *Anacardium occidentale*         | Leaf            | 33        | Hexagonal                 | Anticancer                               | Zhao et al. [88]           |
| *Gracilaria edulis*              | Aqueous         | 20–50     | Hexagonal (Wurtzite) rod  | Anticancer                               | Asik et al. [89]           |
| *Populus ciliata*                | Leaf            | 60–70     | Sphere-like               | Antibacterial                            | Hafeez et al. [90]         |
| *Mentha pulegium*                | Leaf            | 40        | Quasi-spherical           | Antimicrobial                            | Rad et al. [91]            |
| *Laurus nobilis*                 | Leaf            | 20–30     | Spherical and hexagonal   | Antimicrobial                            | Chemingui et al. [92]     |
| *Justicia wynaadensis*           | Leaf            | ~39       | Hexagonal                 | Antimotic and DNA-binding activities     | Hemanth Kumar et al. [8]   |
| *Artocarpus heterophyllus*       | Leaf            | 12–24     | Spherical                 | Anticancer                               | Majeed et al. [93]         |
| *Eucalyptus globules*            | Leaf            | 25–70     | Spherical or globular     | Antifungal                               | Ahmad et al. [94]          |
| *Camellia sinensis*              | Leaf            | 11        | Sphere                    | Drug delivery                            | Akbarian et al. [95]       |
| *Cinnamomum verum*               | Bark            | ~45       | Hexagonal wurtzite        | Antibacterial                            | Ansari et al. [2]          |
| Plant Name             | Plant Part Used | Size (nm) | Shape/Morphology | Applications                                      | Reference                  |
|------------------------|-----------------|-----------|------------------|---------------------------------------------------|----------------------------|
| Ziziphus jujuba        | Fruit           | 29        | Spherical        | Photocatalytic                                    | Golmohammadi et al. [96]  |
| Mussaenda frondosa     | Leaf            | 8–15      | Hexagonal        | Antibacterial, Antioxidant, Antidiabetic, Anticancer, Anti-inflammatory | Jayappa et al. [97]       |
|                        | Stem            | 9–12      | Spherical        |                                                   |                            |
|                        | Leaf-derived callus | 5–7    |                  |                                                   |                            |
| Aegle marmelos         | Juice           | ~20       | Hexagonal        | Antibacterial, Antioxidant and Photocatalytic     | Mallikarjunaswamy et al. [98]|
| Zea mays               | Husk            | 300–550   | Flower-like      | Antibacterial and Antioxidant                     | Quek et al. [31]           |
| Artocarpus heterophyllus | Peel         | 380–900   | Cauliflower-like |                                                   |                            |
| Punica granatum        | Peel            | 260–500   |                  | Nanoflowers                                       |                            |
| Deverra tortuosa       | Plant           | 9–31      | Hexagonal        | Anticancer                                        | Selim et al. [99]          |
| ZINC ACETATE           |                 |           |                  |                                                   |                            |
| Passiflora caerulea    | Leaf            | 70        | Spherical        | Antibacterial                                     | Santhoshkumar et al. [100]|
| Cucumis melo inodorus  | Rough shell     | 25–40     | Crystals with pseudo spherical | Anticancer                                      | Mahdizadeh et al. [101]   |
| Hyssops officinalis    | Plant           | 20–40     | Pseudo spherical | Anti-angiogenesis, Anti-inflammatory and Anticancer | Rahimi Kalateh Shah Mohammad et al. [102]|
| Syzygium cumini        | Seed            | 50–60     | Spherical        | Larvicidal                                        | Roopan et al. [38]         |
| Lycopersicum esculentum| Leaf            | 10–50     | Hexagonal wurtzite| Antimicrobial and Anticancer                      | Vijayakumar et al. [103]  |
| Costus igneus          | Leaf            | 25–40     | Hexagonal        | Antibacterial, Antioxidant and Antidiabetic       | Vinotha et al. [33]        |
| Rehmanniae radix       | Plant           | 10–12     | Rod shape        | Anticancer                                        | Cheng et al. [104]         |
|                        | ~200            | Spherical |                  |                                                   |                            |
| Cratoxylum formosum    | Leaf            | ~500      | Nanosheets       | Antibacterial and Anticancer                      | Jevapatarakul et al. [105] |
| Syzygium cumini        | Leaf            | 64–78     | Spherical        | Photocatalytic                                    | Rafique et al. [106]       |
| Hyssopus officinalis   | Leaf            | 20–40     | Pseudo spherical | Anticancer activity                               | Rahimi Kalateh Shah Mohammad et al. [107]|
| Thlaspi arvense        | Plant           | 70–90     | Flower           | Antibacterial and Photocatalytic                  | Ullah et al. [108]         |
| Raphanus sativus       | Leaf            | 66        | Spherical        | Anticancer                                        | Umamaheshwari et al. [29]  |
| ZINC ACETATE DIHYDRATE |                 |           |                  |                                                   |                            |
| Anchusa italica        | Flower          | ~8–14     | Hexagonal        | Antimicrobial and Cytotoxicity                    | Azizi et al. [6]           |
| Lobelia leschenaultiana| Leaf            | 20–65     | Spherical and hexagonal | Acaricidal                                      | Banumathi et al. [109]     |
| Mimosa pudica          | Leaf            | 27        | Wurtzite and hexagonal | Photocatalytic                                | Fatimah et al. [110]       |
| Coffea arabicaca       | Seed            | 46        | Wurtzite and hexagonal | Photocatalytic                                |                            |
Table 1. Cont.

| Plant Name          | Plant Part Used | Size (nm) | Shape/Morphology       | Applications                        | Reference                  |
|---------------------|-----------------|-----------|------------------------|-------------------------------------|---------------------------|
| Pongamia pinnata    | Seed            | 30–40     | Spherical              | Anticancer and Antibiofilm          | Malaikozhundan et al. [111]|
| Couroupita guianensis | Leaf          | –         | Hexagonal              | Antibacterial                       | Sathishkumar et al. [112] |
| Catharanthus roseus | Leaf            | 50–92     | Hexagonal wurtzite      | Antibacterial                       | Gupta et al. [113]        |
| Nyctanthes arbor-tristis | Flower   | 12–32     | –                      | Antifungal                          | Jamdagni et al. [32]     |
| Coffea arabica      | Seeds           | 26        | Spherical              | Wound-healing                       | Khatami et al. [114]     |
| Ferulago angulata   | Boiss           | 32–36     | Spheroid               | Photocatalytic                      | Mehr et al. [115]        |
| Averrhoa bilimbi    | Fruit           | 37        | Spherical              | Photoelectrode                      | Ramanarayanan et al. [116]|
| Coccinia abyssinica | Tuber           | 10.4      | Hexagonal              | Antibacterial and Antioxidant       | Safawo et al. [117]      |
| Atalantia monophylla| Leaf            | 30        | Spherical and hexagonal| Antimicrobial                       | Vijayakumar et al. [103] |
| Kalanchoe pinnata   | Leaf            | 24        | Hexagonal and spherical| Antioxidant, Anticancer and Anti-inflammatory | Agarwal and Shanmugam [21]|
| Berberis aristata   | Leaf            | 20–40     | Needle like            | Antibacterial and Antioxidant       | Chandra et al. [118]     |
| Juglans regia       | Leaf            | 45–65     | Spherical              | Antibacterial and Anticancer        | Darvishi et al. [119]    |
| Cucurbita pepo      | Leaf            | 8         | Spherical              | Cytotoxicity                        | Hu et al. [120]          |
| Pandanus odorifer    | Leaf            | 90        | Spherical              | Antibacterial and Anticancer        | Hussain et al. [121]     |
| Dolichos lablab     | Leaf            | 29        | Hexagonal wurtzite      | Bactericidal and Photocatalytic     | Khsay et al. [122]       |
| Abelmoschus esculentus | Okra mucilage | 29–70     | Spherical, elongated, and rod-like | Photocatalytic | Prasad et al. [123] |
| Musa acuminata      | Peel            | 30–80     | Triangular-like        | Photocatalytic                      | Abdullah et al. [40]     |
| Mucuna pruriens     | Seed            | 60        | Flower and spherical   | Antibacterial                       | Agarwal et al. [27]      |
| Sambucus ebulus     | Leaf            | 25–30     | Spherical              | Antibacterial, Antioxidant and Photocatalytic | Alamdari et al. [124]  |
| Vernonia amygdalina | Leaf            | 20–40     | Cylindrical            | Anti-inflammatory                   | Liu et al. [125]         |
| Cassia fistula and Melia azadarach | Leaf          | 3–68      | Spherical              | Antibacterial                       | Naseer et al. [126]      |
| Aloe vera           | Leaf            | ~65       | Hexagonal              | Antibacterial and Photocatalytic    | Sharma et al. [127]      |
| Calliandra haematocepha | Leaf           | 60–180   | Spherical              | Photocatalytic                      | Vinayagam et al. [128]  |
| Euphorbia fischeriana | Root          | 30        | Spherical              | Anticancer                          | Zhang et al. [129]       |
Table 1. Cont.

| Plant Name               | Plant Part Used | Size (nm) | Shape/Morphology | Applications                                      | Reference          |
|--------------------------|-----------------|-----------|------------------|---------------------------------------------------|--------------------|
| *Myristica fragrans*     | Fruit           | 43–83     | Spherical or elliptical | Antibacterial, Antiparasitic, Antioxidant, Antidiabetic, Anticancer and Photocatalytic | Faisal et al. [11] |
| *Bridelia retusa*        | Leaf            | 11        | Flower-shape     | Photocatalytic                                   | Vinayagam et al. [130] |
| **ZINC SULPHATE**        |                 |           |                  |                                                   |                    |
| *Aloe barbadensis*       | Leaf            | 8–18      | Spherical, oval and hexagonal | Antibacterial | Ali et al. [131] |
| *Bauhinia tomentosa*     | Leaf            | 22–94     | Hexagonal        | Antibacterial                                    | Sharmila et al. [30] |
| *Trianthema portulacastrum* | Plant        | 25–90     | Spherical        | Antibacterial, Antifungal, Antioxidant, Anticancer and Photocatalytic | Khan et al. [39] |
| **OTHERS**               |                 |           |                  |                                                   |                    |
| *Tecoma castanifolia*    | Leaf            | 70–75     | Spherical        | Antibacterial, Antioxidant, and Anticancer        | Sharmila et al. [132] |
| *Trifolium pratense*     | Flower          | 60–70     | Agglomerated     | Antibacterial                                    | Dobrucka and Długaszewska [15] |
| *Jacaranda mimosifolia*  | Flower          | 2–4       | Spherical        | Antibacterial                                    | Sharma et al. [60] |
| *Heritiera fomes* and *Sonneratia apetala* | Bark and leaf | 40–50     | –                | Antibacterial, Antioxidant, Anti-diabetic and Anti-inflammatory | Thatoi et al. [16] |
| *Sedum alfredii*         | Shoots          | 100       | Columnar in shape | Photocatalytic                                   | Wang et al. [133] |
| *Juglans regia*          | Leaf            | –         | –                | Antifungal                                       | Saemi et al. [134] |
| Plants                   | –               | –         | –                | Antifungal                                       | Sun et al. [135] |

4. Biomedical Applications of Plant-Mediated Zinc Oxide Nanoparticles

4.1. Antibacterial Activity

Bacterial infections are a major threat to humanity’s health. Researchers have focused on metal and metal oxide nanoparticles as antibacterial agents due to the increased antibiotic resistance in bacteria and the emergence of new strains [2]. Zinc oxide nanoparticles have been studied extensively as antibacterial agents due to their unique physiochemical properties and increased surface areas [4]. Furthermore, zinc oxide nanoparticles are both safe and compatible with the human body. Numerous publications describe the possible antibacterial mechanisms of zinc oxide nanoparticles, which involves (1) the production of ROS (i.e., OH$^\bullet$ (hydroxyl radical) and O$_2^{−2}$ (peroxide)), which induces oxidative stress, cell membrane disruption, and DNA damage, resulting in the death of bacterial cells; (2) the dissolution of zinc oxide nanoparticles into the release of Zn$^{2+}$ ions, which interact with the bacterial cell, especially the cell membrane, cytoplasm, and nucleic acid, thus disintegrating the cellular integrity and resulting in bacterial cell death; and (3) direct interactions between zinc oxide nanoparticles and bacterial cell membranes through electrostatic forces.
that damage the plasma membrane and cause a leakage of intracellular components [30] (Figure 1).

Figure 1. Possible antibacterial mechanisms of plant-mediated zinc oxide nanoparticles.

In our previous study, zinc oxide nanoparticles synthesized from leaf extracts of *Ceropegia candelabrum* with zinc nitrate (as a precursor) by the hydrothermal process resulted in nanoparticles of high purity, a hexagonal wurtzite shape, and 12–35-nm sizes [5]. The biosynthesized zinc oxide nanoparticles significantly showed antibacterial potential against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Salmonella typhi* at 100 µg·mL⁻¹. One of our research groups also bio-fabricated zinc oxide nanoparticles from leaf extracts of *Cochlospermum religiosum* to study their antibacterial potentiality [82]. The bio-fabricated zinc oxide nanoparticles significantly exhibited the inhibition of Gram-positive (*B. subtilis* and *S. aureus*) and Gram-negative (*Pseudomonas aeruginosa* and *E. coli*) bacteria with minimum inhibitory concentrations (MIC) of 4.8–312.5 µg·mL⁻¹. The antibacterial potency of zinc oxide nanoparticles is probably due to their small size, which is more likely to damage the membrane, penetrate the cytoplasm, and produce numerous ROS that can damage the DNA and other cellular components of bacteria [31,80].

The difference in antibacterial activity can be associated with the structural and chemical compositions of the bacterial cell membranes [2]. Sharma et al. [127] studied the effect of the shape and size of zinc oxide nanoparticles synthesized by using *Aloe vera*
leaf extracts on their antibacterial activity and reported that cuboidal (40–45 nm)-shaped nanoparticles were shown to be more protuberant in antibacterial activity when compared to spherical (60–180 nm) and hexagonal (~65 nm)-shaped nanoparticles. Due to the small size of biosynthesized zinc oxide nanoparticles, they provide a high surface area, which leads to more interactions between nanoparticles and bacterial cells, which can be used as an antibacterial agent even at lower dosages. Biosynthesized zinc oxide nanoparticles initially interact with the bacterial plasma membrane, causing nanoparticles to enter the cytoplasm and release metal ions, thereby disrupting the membrane permeability and, finally, causing DNA damage, leading to the death of bacterial cells [71]. The antibacterial activity demonstrated by zinc oxide nanoparticles synthesized from leaf extracts of *Cassia fistula* and *Melia azadarach* have a substantial ability to suppress clinical pathogens (such as *E. coli* and *S. aureus*) compared to traditional drugs, and it was concluded that the synthesis of nanoparticles employing the extracts of medicinal plants could be effective in the treatment of various human infectious diseases [126]. Recently, Faisal et al. [11] showed that 1% zinc oxide nanoparticles (1 mg mL$^{-1}$) synthesized from aqueous fruit extracts of *Myristica fragrans* were found to display the maximum zone of inhibition against *Klebsiella pneumoniae*, *E. coli*, *P. aeruginosa*, and *S. aureus*. Further, the antibacterial efficacy of plant-mediated zinc oxide nanoparticles against various bacterial pathogens is listed in Table 2.
### Table 2. Antibacterial and antifungal activity of plant-mediated zinc oxide nanoparticles.

| Plant Name          | Plant Part Used | Pathogen Name                                    | Minimum Inhibitory Concentration (MIC) * (mg mL⁻¹) | Results                                                                 | Reference                           |
|---------------------|-----------------|--------------------------------------------------|--------------------------------------------------|-------------------------------------------------------------------------|--------------------------------------|
| **ANTIBACTERIAL ACTIVITY**                                                                                                 |
| Anisochilus carnosus | Leaf            | Salmonella paratyphi, Vibrio cholerae, Staphylococcus aureus and Escherichia coli | -                                                | Showed antibacterial activity towards various human pathogens           | Anbuvannan et al. [54]               |
| Hibiscus subdariffa  | Leaf            | Escherichia coli and Staphylococcus aureus       | 0.05                                             | Exerted better bactericidal property on S. aureus and E. coli           | Bala et al. [35]                    |
| Azadirachta indica  | Leaf            | Staphylococcus aureus, Pseudomonas aeruginosa, B. subtilis, Proteus mirabilis, E. coli | 0.006–0.05                                       | Showed significant inhibition against bacterial strains in a dose-dependent manner | Elumalai and Velmurugan [13]        |
| Vitex trifolia      | Leaf            | Staphylococcus aureus and Escherichia coli       | 0.006–0.05                                       | Superior antibacterial activity against Gram positive and Gram negative bacteria | Elumalai [72]                       |
| Pongamia pinnata    | Leaf            | Klebsiella aerogenes, Escherichia coli, Pseudomonas desmolyticum and Staphylococcus aureus | 0.5–0.1                                           | Showed an excellent bactericidal activity against pathogenic bacteria    | Sundaraj [73]                       |
| Cassia fistula      | Leaf            | Staphylococcus aureus                            | ≤0.01                                            | Controlled the growth of methicillin-resistant S. aureus biofilm         | Vijayakumar et al. [55]             |
| Plectranthus amboinicus | Leaf         | Staphylococcus aureus                           | 2.2–2.4                                          | Significant antibacterial activity against extended spectrum β-lactamases (ESBL) positive E. coli, P. aeruginosa, and methicillin resistant S. aureus (MRSA) clinical isolates | Ali et al. [131]                   |
| Anchozia italica    | Flower          | Bacillus megaterium, Staphylococcus aureus, Escherichia coli and Salmonella typhimurium | 0.016–0.032                                       | Showed antimicrobial activity against Gram positive and Gram negative bacteria decreased with increasing the heat treating temperature | Azizi et al. [6]                   |
| Trifolium pratense  | Flower          | Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus | –                                                | Exhibited high activity against standard and clinical strain of Gram-positive and Gram-negative bacteria | Dobrucka and Długaszewska [15]     |
| Rosa canina         | Fruit           | Listeria monocytogenes, Staphylococcus aureus and Escherichia coli | 0.5–1                                             | Relatively good antibacterial activity against Gram positive and Gram negative bacteria | Jafarirad et al. [57]               |
| Azadirachta indica  | Leaf            | Klebsiella aerogenes and Staphylococcus aureus   | 0.1–1                                             | Showed significant antibacterial activity against K. aerogenes and S. aureus | Madan et al. [36]                  |
| Limonia acidissima  | Leaf            | Mycobacterium tuberculosis                      | 0.0125                                            | Control the growth of M. tuberculosis                                   | Patil and Taranath [59]             |
| Carica papaya       | Milk            | Pseudomonas aeruginosa, Staphylococcus aureus, Klebsiella aerogenes and Pseudomonas desmolyticum | 0.2–0.4                                           | Showed significant antibacterial activity against bacterial stains      | Sharma [60]                        |
| Jacaranda mimosifolia | Flower        | Escherichia coli and Enterococcus faecium       | 0.1                                               | Enhanced antibacterial activity against pathogenic strains               | Sharma et al. [136]                |
| Plant Name                | Plant Part Used | Pathogen Name                                                                 | Minimum Inhibitory Concentration (MIC) * (mg mL⁻¹) | Results                                                                                           | Reference         |
|--------------------------|-----------------|-------------------------------------------------------------------------------|---------------------------------------------------|---------------------------------------------------------------------------------------------------|-------------------|
| Boswellia ovalifoliolata | Bark            | Sphingobacterium thalpophilum, Uncultured organism clone, Ochrobactrum sp., Uncultured Achromobacter sp., Uncultured bacterium clone, Sphingobacterium sp., Acinetobacter sp., Uncultured soil bacterium, Ochrobactrum sp., Uncultured bacterium | -                                                 | Showed good antibacterial activity at 170 ppm compared to 50 and 100 ppm                         | Supraj et al. [61] |
| Heritiera fomes          | Bark and Leaf   | Shigella flexneri                                                             | 0.1                                               | Displayed positive inhibition activity against S. flexneri                                        | Thatoi et al. [16] |
| Sonneratia apetala      | Bark            | Bacillus subtilis, Methicillin-resistant Staphylococcus aureus, Pseudomonas aeruginosa and Escherichia coli | 0.004–0.312                                       | Inhibited the growth of medically significant pathogenic Gram positive and Gram negative bacteria | Azizi et al. [80] |
| Cochlospermum religiosum | Leaf            | Bacillus subtilis, Staphylococcus aureus, Pseudomonas aeruginosa and Escherichia coli | 0.025                                             | Effectively inhibited Gram positive and Gram negative bacteria growth                             | Malaiakozhundan et al. [111] |
| Pongamia pinnata        | Seed            | Bacillus licheniformis, Pseudomonas aeruginosa, Vibrio para-haemolyticus       | 0.1                                               | Showed significant inhibition against Gram positive and Gram negative bacterial pathogens         | Murali et al. [5] |
| Ceropogia candelabrum    | Leaf            | Bacillus subtilis, Bacillus subtilis, Escherichia coli, Salmonella typhi       | 0.005                                             | Exhibited excellent dose dependent bactericidal effect against human pathogens                   | Sathishkumar et al. [112] |
| Passiflora caerulea     | Leaf            | Klebsiella sp., Streptococcus sp., Enterococcus sp., and Escherichia coli     | -                                                 | Showed very good inhibition of urinary tract infection causing microbes                           | Santhoshkumar et al. [100] |
| Couroupita guianensis   | Leaf            | Bacillus cereus, Klebsiella pneumonae, Escherichia coli, Micrococcus luteus, Salmonella typhi, and Vibrio cholera | 0.055–0.094                                       | Exhibited strong antibacterial activity                                                          | Ali et al. [85]   |
| Conjea canadensis       | Leaf            | Escherichia coli and Staphylococcus aureus                                   | 0.055–0.094                                       | Exhibited strong antibacterial activity                                                          | Ali et al. [85]   |
| Catharanthus roseus     | Leaf            | Staphylococcus aureus, Streptococcus pyogenes, Bacillus cereus, Pseudomonas aeruginosa, Proteus mirabilis and Escherichia coli | 1.5                                               | Exhibited effective growth inhibition activity against Gram positive and Gram negative bacteria | Gupta et al. [113] |
| Coccinia abyssinica     | Tubber          | Bacillus coagulans, Staphylococcus aureus, Shigella dysenteriae, Salmonella typhimurium and Sphingomonas paucimobilis | 0.001–0.005                                       | Showed effective growth inhibition activity against Gram negative and Gram positive bacteria     | Safawo et al. [117] |
| Bauhinia tomentosa      | Leaf            | Bacillus subtilis, Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosa | 0.001–0.005                                       | Exhibited better antibacterial activity against Gram negative bacteria than Gram positive bacteria | Sharmila et al. [30] |
| Costus pictus           | Leaf            | Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Salmonella paratyphi | 0.1                                               | Exhibited strong antimicrobial behavior against bacterial species                                | Suresh et al. [66] |
| Atalantia monophyllia   | Leaf            | Bacillus subtilis, Bacillus cereus, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa and Klebsiella pneumonae | 0.1                                               | Showed antimicrobial potential against pathogenic bacteria                                       | Vijayakumar et al. [103] |
| Berberis aristata       | Leaf            | Escherichia coli, Staphylococcus aureus, Klebsiella pneumonae, Bacillus subtilis, Bacillus cereus and Serratia marcescens | 0.064–0.256                                       | Displayed antibacterial activity against urinary tract infection causing pathogens                | Chandra et al. [118] |
| Plant Name         | Plant Part Used | Pathogen Name                          | Minimum Inhibitory Concentration (MIC) * (mg mL⁻¹) | Results                                                                 | Reference                      |
|-------------------|-----------------|----------------------------------------|---------------------------------------------------|-------------------------------------------------------------------------|--------------------------------|
| Laurus nobilis    | Leaf            | *Escherichia coli*                     | 1.2                                               | Proved as an effective antibacterial agent against *E. coli*             | Chemingui et al. [92]          |
| Juglans regia     | Leaf            | *Escherichia coli*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* | 0.2                                               | Exerted bactericidal property on resistant strains                       | Darvishi et al. [119]          |
| Populus ciliata   | Leaf            | *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Staphylococcus aureus* and *Streptococcus pyogenes* | –                                                 | Showed significant antibacterial potential on test pathogens             | Haifee et al. [90]             |
| Pandanus odorifer | Leaf            | *Bacillus subtilis*, *Escherichia coli* | 0.05                                              | Showed significant antibacterial potential on test pathogens             | Hussain et al. [121]           |
| Delichus lablab   | Leaf            | *Bacillus pumilus* and *Sphingomonas paucimobilis* | 5                                                 | Showed a bactericidal activity for pathogenic Gram positive and Gram negative bacteria | Kalsay et al. [122]           |
| Trianthema portulacastrum | Plant | *Staphylococcus aureus* and *Escherichia coli* | –                                                 | Showed significant antibacterial property                                | Khan et al. [39]               |
| Mentha pulegium   | Leaf            | *Staphylococcus aureus* and *Escherichia coli* | 0.2                                               | Exhibited significant antimicrobial potential on some food-borne pathogens | Rad et al. [91]                |
| Annona squamosa   | Leaf            | *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Enterococcus faecium* | 0.006–0.012                                      | Synergetic antibacterial potential against wound/burn infection causing bacteria | Rudderaj et al. [69]          |
| Artabotrys hexapetalu | Leaf            | *Streptococcus* and *Serratia*          | –                                                 | Showed better antibacterial performance against Gram positive and Gram negative bacteria | Shanavas et al. [68]          |
| Bambusa vulgaris  | Leaf            | *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* | 0.075–0.1                                        | Excellent antibacterial activity against Gram positive and Gram negative bacteria | Sharmila et al. [132]         |
| Tecoma castanifolia | Leaf            | *Bacillus cereus*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumonia*, and *Salmonella typhi* | 35.5                                              | Strong antibacterial potential against Gram-negative and Gram-positive bacterial pathogens | Umar et al. [26]              |
| Albizia lebbeck   | Bark            | *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumonia*, and *Salmonella typhi* | 0.008–0.01                                       | A notable reduction in bacterial growth was observed                     | Vijayakumar et al. [137]      |
| Lycopersicon esculentum | Leaf            | *Enterococcus faecalis* and *Proteus vulgaris* | 0.008–0.01                                       | Showed promising antibacterial activity against targeted pathogenic bacteria | Vinotha et al. [33]            |
| Costus igneus     | Leaf            | *Streptococcus mutans*, *Lysinibacillus fusiformis*, *Proteus vulgaris*, and *Vibrio parahaemolyticus* | 0.04–0.07                                        | Showed concentration dependent inhibition of the growth of *B. subtilis*  | Agarwal et al. [27]            |
| Mucuna pruriens  | Seed            | *Bacillus subtilis*                     | 0.02                                              | Showed stronger antibacterial activity                                   | Gao et al. [19]                |
| Sambucus ebulus   | Leaf            | *Bacillus cereus*, *Staphylococcus aureus*, *Escherichia coli* | 0.1                                               | Exhibited antibacterial activity over all three bacteria                 | Alamdari et al. [124]         |
| Cinnamonum verum  | Bark            | *Escherichia coli* and *Staphylococcus aureus* | 0.062–0.125                                      | Inhibited the growth of harmful pathogens                                | Ansari et al. [2]              |
| Citrus sinensis   | Fruit Peel      | *Escherichia coli* and *Staphylococcus aureus* | 0.020–0.040                                       | Showed inhibition against bacterial strains                               | Jayappa et al. [97]           |
| Mussaenda freonda | Leaf, Stem and Leaf-derived callus | *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Pseudomonas aeruginosa* | 0.019–0.185                                      | Showed inhibition against bacterial strains                               |                                |
| Plant Name                        | Plant Part Used | Pathogen Name                                                                 | Minimum Inhibitory Concentration (MIC) * (mg mL⁻¹) | Results                                                                                     | Reference                        |
|----------------------------------|----------------|-------------------------------------------------------------------------------|---------------------------------------------------|--------------------------------------------------------------------------------------------|----------------------------------|
| Cratoxylum formosum              | Leaf           | Bacillus subtilis, Staphylococcus epidermidis, Escherichia coli               | 5                                                 | Inhibited Gram positive and Gram negative bacterial growth                                  | Jevapatarakul et al. [105]       |
| Aegle marmelos                   | Juice          | Staphylococcus aureus, Bacillus cereus, Micrococcus luteus, Escherichia coli, Klebsiella pneumonia, Enterobacter aerogenes, Pseudomonas fluorescens, Pseudomonas aeruginosa and Salmonella enteritidis | 3.84–8.65                                        | Showed good bactericidal activity                                                          | Mallikarjunaswamy et al. [98]    |
| Cassia fistula and Melia azadarach | Leaf          | Escherichia coli and Staphylococcus aureus                                  | 0.05                                              | Showed strong antimicrobial activity against clinical pathogens                             | Naseer et al. [126]              |
| Beta vulgaris                    | Plant          | Escherichia coli and Staphylococcus aureus                                  | –                                                 | Shown antibacterial activity both Gram negative and Gram positive bacteria                  | Pillai et al. [25]               |
| Cinnamomum tamala                | Plant          | Escherichia coli and Staphylococcus aureus                                  | –                                                 | Excellent antibacterial activity against *E. faecalis* compared to zinc oxide synthesized without plant extract and commercial zinc oxide | Quek et al. [31]                 |
| Brassica oleracea                | Husk           | Enterococcus faecalis                                                        | –                                                 | Showed antibacterial activity against pathogenic bacteria                                  |                                 |
| Artocarpus heterophyllus         | Peel           | Escherichia coli, Staphylococcus aureus, Proteus vulgaris, and Klebsiella pneumonia | 0.1                                               | Exhibited significant antibacterial potentiality against Gram positive and Gram negative pathogenic bacteria | Sana et al. [71]                 |
| Punica granatum                  |                |                                                                              |                                                   |                                                                                             |                                  |
| Crotalaria verrucosa             | Leaf           | Escherichia coli, Staphylococcus aureus, Proteus vulgaris, and Klebsiella pneumonia | 0.195–3.125                                      | Showed antibacterial activity against pathogenic bacteria                                  | Sharma et al. [127]              |
| Aloe vera                        | Leaf           | Bacillus subtilis, Staphylococcus aureus and Escherichia coli               | 0.015                                             | Exhibited a significant antibacterial activity against Gram negative *E. coli*              | Ullah et al. [108]               |
| Thlaspi arvense                  | Plant          | Escherichia coli                                                            | 0.015                                             |                                 |                                  |
| Myristica fragrans               | Fruit          | Klebsiella pneumonia, Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus | 1                                                 | Showed successful capacity against bacterial strains                                       | Faisal et al. [11]               |

**ANTIFUNGAL ACTIVITY**

| Plant Name                        | Plant Part Used | Pathogen Name                                                                 | Minimum Inhibitory Concentration (MIC) * (mg mL⁻¹) | Results                                                                                     | Reference                        |
|----------------------------------|----------------|-------------------------------------------------------------------------------|---------------------------------------------------|--------------------------------------------------------------------------------------------|----------------------------------|
| Azadirachta indica               | Leaf           | Candida albicans and Candida tropicalis                                       | 0.006–0.05                                        | Showed significant inhibition against fungal strains in a dose-dependent manner              | Elumalai and Velmuruigan [13]   |
| Vitex trifolia                   | Leaf           | Candida albicans and Candida tropicalis                                       | 0.006–0.05                                        | Excellent antifungal activity against human pathogenic fungi                                | Elumalai et al. [72]             |
| Boswellia ovalifoliolata         | Bark           | Meyerozyma caribica, Aspergillus parvicoliformis, Meyerozyma guilliermondii, Rhizopus oryzae, Uncultured fungus clone, Aspergillus oryzae, Trichoderma asperellum | –                                                 | Showed good antifungal activity at 170 ppm compared to 50 and 100 ppm                      | Supraja et al. [61]              |
| Pongamia pinnata                 | Seed           | Candida albicans                                                            | 0.05                                              | Effectively inhibited the biofilm formation of *C. albicans*                                | Malaikozhundan et al. [11]       |
| Ziziphus nummularia              | Leaf           | Candida albicans, Candida glabrata and Cryptococcus neoformans                | 1.25–10                                           | Showed very good antifungal activity against clinical isolates                              | Padalia and Chanda [7]           |
Table 2. Cont.

| Plant Name          | Plant Part Used | Pathogen Name                                      | Minimum Inhibitory Concentration (MIC) * (mg mL⁻¹) | Results                                                                 | Reference                  |
|---------------------|-----------------|----------------------------------------------------|----------------------------------------------------|--------------------------------------------------------------------------|-----------------------------|
| Nyctanthes arbor-tristis | Flower          | Alternaria alternata, Aspergillus niger, Botrytis cinerea, Fusarium oxysporum and Penicillium expansum | 0.016                                              | Showed good antifungal potential against fungal phytopathogens           | Jamdagni et al. [32]        |
| Costus pictus       | Leaf            | Aspergillus niger and Candida albicans             | 0.1                                                | Exhibited strong antimicrobial behavior against fungal species           | Suresh et al. [66]          |
| Atalantia monophylla| Leaf            | Candida albicans and Aspergillus niger             | –                                                  | Showed antimicrobial potential against pathogenic fungi                 | Vijayakumar et al. [103]    |
| Trianthema portulacastrum | Plant         | Aspergillus niger, Aspergillus flavus and Aspergillus fumigatus | 0.1                                                | Showed significant antifungal potential                                | Khan et al. [39]            |
| Lycopersicon esculentum | Leaf          | Candida albicans                                   | 0.013                                              | A notable reduction in fungal growth was observed                        | Vijayakumar et al. [137]    |
| Eucalyptus globules  | Leaf            | Alternaria mali, Botryosphaeria dothidea and Diplodia seriata | –                                                  | Showed considerable fungicidal property against phytopathogenic fungi   | Ahmad et al. [84]           |
| Citrus sinensis     | Peel            | Botrytis cinerea                                   | 0.2                                                | Showed stronger antifungal activity against B. cinerea                  | Gao et al. [19]             |
| Beta vulgaris       |                 |                                                    |                                                    |                                                                          |                             |
| Cinnamomum tamala   | Plant           | Candida albicans and Aspergillus niger             | –                                                  | Shown activity against the fungal strains                                | Pillai et al. [25]          |
| Cinnamomum verum    |                 |                                                    |                                                    |                                                                          |                             |
| Brassica oleracea   |                 |                                                    |                                                    |                                                                          |                             |

* Range of MIC concentration depicts the changes in the concentrations between the test pathogens.
4.2. Antifungal Activity

In addition to antibacterial activity, zinc oxide nanoparticles also possess antifungal activity against many harmful fungi and yeasts, making them promising antifungal food additives [19,103]. The possible mechanisms of antifungal activity of zinc oxide nanoparticles are described for zinc oxide nanoparticles that can enter fungal (conidial) cells by diffusion and endocytosis; they interfere in the mitochondrial function and promote ROS production Zn$^{2+}$ ion release inside the cytoplasm. The excess production of ROS and Zn$^{2+}$ ions released from zinc oxide nanoparticles can penetrate the nuclear membrane and cause irreversible DNA damage, inducing cell death [134,135] (Figure 2). The role of the electronic band gap ($E_g$) property of zinc oxide nanoparticles with the redox potential (EH) of numerous ROS generation reactions have also been proposed [134]. Zinc oxide nanoparticles electrons ($e^-$), when excited with energy higher than $E_g$, are promoted across the band gap energy to the conduction band edge ($E_c$), which creates a hole ($h^+$) in the valence band ($E_v$). The $e^-$ in $E_c$ and holes in $E_v$ exhibit high reducing and oxidizing power, respectively. The $e^-$ reacts with molecular oxygen ($O_2$) to produce superoxide anion ($O_2^{•−}$) through sequential reduction reactions. The $h^+$ can extract $e^-$ from water ($H_2O$) and/or hydroxyl ions to generate hydroxyl radical ($OH^•$).

Figure 2. Possible antifungal mechanism of plant-mediated zinc oxide nanoparticles. (a) Hypothetical anticandidal mechanisms of zinc oxide nanoparticles, and (b) plausible mechanisms of action of zinc oxide nanoparticle-induced ROS generation for their anticandidal activity.
The zinc oxide nanoparticles synthesized from flower extracts of \textit{Nyctanthes arbor-tristis} demonstrated antifungal activity against fungal phytopathogens (such as \textit{Fusarium oxysporum}, \textit{Botrytis cinerea}, \textit{Penicillium expansum}, \textit{Alternaria alternata}, and \textit{Aspergillus niger}) with the lowest MIC value of 16 \(\mu\)g \(\text{mL}^{-1}\), suggesting that they could be used to develop antifungal agents for commercial use in agriculture [32]. Similarly, Khan et al. [39] suggested that zinc oxide nanoparticles synthesized using \textit{Trianthema portulacastrum} extracts were found to exhibit antifungal properties against \textit{Aspergillus niger}, \textit{A. flavus}, and \textit{A. fumigatus}. Additionally, zinc oxide nanoparticles synthesized from different plant extracts such as \textit{Beta vulgaris}, \textit{Cinnamomum tamala}, \textit{C. verum}, and \textit{Brassica oleracea} were found effective against \textit{Candida albicans} and \textit{A. niger} [25]. Furthermore, the plant-mediated zinc oxide nanoparticles that were effective antifungal agents against various fungal pathogens are provided in Table 2.

4.3. Antioxidant Activity

The antioxidant activity of zinc oxide nanoparticles is attributed to their smaller size, but another explanation may be a phenomenon in 2,2-diphenyl-1-picrylhydrazyl (DPPH) where the electron density is transferred from the oxygen atom to the odd electron located at the nitrogen atom, resulting in a decrease in the \(n \rightarrow \pi^*\) transition intensity at 517 nm. The antioxidant activity’s mechanism involves the unstable deep violet-colored methanolic solution of DPPH, which turns into stable pale-yellow color with the addition of zinc oxide nanoparticles due to their DPPH free radical scavenging activity through the transfer of an electron from the oxygen atom to the odd electron of a nitrogen atom, resulting in stable DPPH molecule formation (Figure 3) [83]. In other words, the antioxidant property of zinc oxide nanoparticles is determined by their ability to donate hydrogen. Furthermore, even in the absence of UV light, the formation of a large number of electron and hole pairs on the surfaces of zinc oxide nanoparticles results in a high redox potential that splits water (\(H_2O\)) molecules into hydroxyl (\(OH^*\)) and hydrogen (\(H^*\)) radicals, which are available for DPPH free radical reduction and DPPH molecule stability [17,83,124].

![Figure 3. Possible antioxidant mechanisms of plant-mediated zinc oxide nanoparticles.](image)

Our previous study reported that the antioxidant activity of biosynthesized zinc oxide nanoparticles from \textit{C. candelabrum} showed significantly DPPH free radical scavenging activity from 0\% to 55\%, with an IC\(_{50}\) value of 95.09 \(\mu\)g \(\text{mL}^{-1}\), compared with the 75\% inhibition offered by ascorbic acid (a positive control) at 50 \(\mu\)g \(\text{mL}^{-1}\) [5]. It is also reported that an increased antioxidant activity was observed with an increase in the zinc oxide nanoparticle concentration. According to the findings of Khan et al. [39], the green synthesized zinc oxide nanoparticles had a strong antioxidant activity due to their charge density and capping materials on their surface. Alamdari et al. [83] revealed that zinc oxide nanoparticles biosynthesized from leaf extracts of \textit{Sambucus ebulus} were found to exhibit \(H_2O_2\) free radical scavenging activity with an IC\(_{50}\) value of 43 \(\mu\)g \(\text{mL}^{-1}\) and concluded that
the presence of metal or Zn ions in the structure could enhance the antioxidant capabilities of the biosynthesized zinc oxide nanoparticles. Recently, Faisal et al. [11] revealed that zinc oxide nanoparticles synthesized from the aqueous fruit extracts of *M. fragrans* were found to show excellent free radical scavenging irrespective of the methods employed, viz., ABTS (82.12% TEAC), DPPH (66.3% FRSA), TAC (71.1 µg AAE·mg⁻¹), and TRP (63.41 µg AAE·mg⁻¹). In accordance with the above findings, the antioxidant efficacy of plant-mediated zinc oxide nanoparticles is represented in Table 3.
Table 3. Antioxidant activity of plant-mediated zinc oxide nanoparticles.

| Plant Name | Description | Concentration | Maximum Activity | Results | Reference |
|------------|-------------|---------------|------------------|---------|-----------|
| \( \text{Phytolacca americana} \) | Leaf | 1 mg mL\(^{-1} \) | 45.47\% | Moderate antioxidant activity by scavenging DPPH free radical | Nagapriyan et al. [17] |
| \( \text{Cassia fistula} \) | Leaf | 2853 \( \mu \)g mL\(^{-1} \) | 50\% | Inhibiting DPPH free radical scavenging activity | Suresh et al. [27] |
| \( \text{Artocarpus communis} \) | Fruit | 15.8 \( \mu \)g mL\(^{-1} \) | 50\% | Inhibiting DPPH free radical scavenging activity | Suresh et al. [27] |
| \( \text{Rose cossus} \) | Fruit | 0.2 \( \mu \)g mL\(^{-1} \) | <1\% | DPPH free radical scavenging activity | Jafarirad et al. [34] |
| \( \text{Azadirachta indica} \) | Leaf | 8295 \( \mu \)g mL\(^{-1} \) | 92\% | Inhibiting DPPH free radical scavenging activity | Madan et al. [39] |
| \( \text{Heritiera fomes} \) and \( \text{Senecio sp.} \) | Bark and leaf | 53.05 \( \mu \)g mL\(^{-1} \) | 50\% | Strong DPPH free radical scavenging potential | Dhote et al. [24] |
| \( \text{Citrus limon} \) | Fruit, seed and pulp | 0.22 mg mL\(^{-1} \) (fruit), 0.29 mg mL\(^{-1} \) (seed) and 0.26 mg mL\(^{-1} \) (pulp) | 50\% | Inhibiting DPPH free radical scavenging activity | Buy et al. [50] |
| \( \text{Corymbia candollei} \) | Leaf | 95.99 \( \mu \)g mL\(^{-1} \) | 55.43\% | DPPH free radical scavenging activity | Murthy et al. [72] |
| \( \text{Annona squamosa} \), \( \text{Heritiera fomes} \), \( \text{Morus alba} \), \( \text{Moringa oleifera} \) and \( \text{Artocarpus heterophyllus} \) | Leaf | 11.03–31.51 \( \mu \)g mL\(^{-1} \), 11.49–37.8 \( \mu \)g mL\(^{-1} \), 23.31–45.9 \( \mu \)g mL\(^{-1} \) (hydroxyl) and 24.4–53.2 \( \mu \)g mL\(^{-1} \) (superoxide) and 31.4–58.4 \( \mu \)g mL\(^{-1} \) (hydrogen peroxide) | 50\% | Moderate antioxidant activity by scavenging DPPH free radical | Jafarirad et al. [37] |
| \( \text{Jatropha curcas} \) | Leaf | 3.55 \( \mu \)g mL\(^{-1} \) | 50\% | DPPH free radical scavenging activity | Bhattacharya and Mandal [8] |
| \( \text{Trichosanthes pterocarpon} \) and \( \text{Trichosanthes cucumerina} \) | Plant | 500 \( \mu \)g mL\(^{-1} \) | 75\% | Efficient DPPH free radical inhibition | Khan et al. [44] |
| \( \text{Terminalia arjuna} \) | Leaf | 100 \( \mu \)g mL\(^{-1} \) | 67\% | DPPH free radical scavenging activity | Sharmila et al. [112] |
| \( \text{Salvia hispanica} \) | Root | 5000 \( \mu \)g mL\(^{-1} \) | 56.11\% | Scavenging DPPH free radicals | Tetlay and Shin [14] |
| \( \text{Allium cepa} \) | Stem bark | 45.5 \( \mu \)g mL\(^{-1} \) | 50\% | Showed the concentration-dependent effect in hydrogen peroxide (\( \text{H}_2\text{O}_2 \)) free radical scavenging activity | Umar et al. [29] |
| \( \text{Cotinus coggygria} \) | Leaf | 100 \( \mu \)g mL\(^{-1} \) | 75\% | DPPH free radical scavenging activity | Viretha et al. [115] |
| \( \text{Sambucus chinensis} \) | Leaf | 45 \( \mu \)g mL\(^{-1} \) | 50\% | Exhibited hydrogen peroxide (\( \text{H}_2\text{O}_2 \)) free radical scavenging activity | Alamdar et al. [124] |
| \( \text{Alstonia boonei} \) | Leaf, stem and leaf-derived culture | 82.4 \( \mu \)g mL\(^{-1} \) (leaf), 782 \( \mu \)g mL\(^{-1} \) (stem) and 887 \( \mu \)g mL\(^{-1} \) (callus) | 50\% | Quenching the DPPH free radical scavenging | Jayappa et al. [97] |
| \( \text{Angelica archangelica} \) | Juice | 5.75–6.78 mg mL\(^{-1} \) \( \text{(DPPH)} \), 4.45–5.05 mg mL\(^{-1} \) \( \text{(ARIS)} \) and 7.86–9.05 mg mL\(^{-1} \) \( \text{(Superoxide)} \) | 50\% | ARIS cation radical, DPPH free radical, and superoxide anion radical scavenging activities | Malik et al. [80] |
| \( \text{Ziziphus spina-christi} \) and \( \text{Paonia picta} \) | Husk (\( \text{Z. spina-christi} \)) and peel (\( \text{A. archangelica} \) and \( \text{P. picta} \)) | 385.2 \( \mu \)g mL\(^{-1} \) (\( \text{Z. spina-christi} \)) and 450 \( \mu \)g mL\(^{-1} \) (\( \text{P. picta} \)) | 50\% | Inhibitory of DPPH radical scavenger | Quark et al. [53] |

Note: ABTS=2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) diammonium salt, DPPH=2,2-diphenyl-1-picrylhydrazyl, TAC=total antioxidant capacity, TRP=total reduction power, and FRSA=free radical scavenging assay.
4.4. Antidiabetic Activity

Diabetes is a complex disease that requires an effective multifaceted treatment approach to care for patients. Antidiabetic medications are often used in conjunction with insulin or other drugs, resulting in higher medication costs overall. Zinc supplementation has been shown to improve glycemic regulation in diabetic humans and animals [33,66]. Furthermore, this metal can boost diabetic problems such as nephropathy and cardiomyopathy [35]. Due to their capacity to deliver Zn$^{2+}$ ions, zinc oxide nanoparticles are currently being studied to treat diabetes and diabetic complications. The antidiabetic properties of zinc oxide nanoparticles are an antihyperglycemic effect, i.e., improving the glucose tolerance, enhancement of pancreatic functions (through the regulation of main pancreatic hormones, namely insulin and glucagon), upregulation of glucose transporters and biosensors to regulate insulin secretion, weight maintenance, anti-dyslipidemic effect (i.e., improve dyslipidemia), anti-inflammatory, inhibition of α-amylase and α-glucosidase activities for lowering the post-prandial rise of blood glucose levels, and improving the insulin sensitivity and antioxidative system to eradicate ROS-induced oxidative stress [138] (Figure 4).

**Figure 4.** Possible antidiabetic mechanism of plant-mediated zinc oxide nanoparticles.

The inhibition of carbohydrate metabolizing enzymes (such as α-amylase and α-glucosidase) is a unique strategy for controlling blood sugar, and it requires a large number of compounds to be evaluated in order to rule out inactive molecules and save time and money. In vitro α-amylase and α-glucosidase inhibitory studies revealed that zinc oxide nanoparticles synthesized from *Tamarindus indica* extract had the highest inhibitory activity compared to the zinc oxide nanoparticles synthesized from other plant extracts [22]. Additionally, Rajakumar et al. [34] confirmed that the synthesized zinc oxide nanoparticles from *Andrographis paniculata* leaf extract displayed better antidiabetic potential in terms of α-amylase inhibition activity with an IC$_{50}$ value of 121.42 µg·mL$^{-1}$. Similarly, the zinc oxide nanoparticles synthesized from *Costus igneus* leaf extract were found to show more effective antidiabetic activity, wherein the percentage of inhibition ranged from 20% to 74% for α-amylase and 36% to 82% for α-glucosidase at concentration of 20–100 µg·mL$^{-1}$ of nanoparticles [33]. Recently, Faisal et al. [11] indicated that an excellent α-amylase (73.23%) and α-glucosidase (65.21%) inhibition activity at 400 µg·mL$^{-1}$ was offered by zinc oxide nanoparticles synthesized from aqueous fruit extracts of *M. fragrans* and revealed that the bio-based nanoparticles could have strong antidiabetic properties and are considered a useful therapeutic agent for the treatment of diabetes as a replacement for expensive and ineffective medicines. Additionally, other reports on the efficacy of antidiabetic activity by plant-mediated zinc oxide nanoparticles are listed in Table 4.
Table 4. Antidiabetic activity of plant-mediated zinc oxide nanoparticles.

| Plant Name                        | Description                        | Concentration       | Activity (IC$_{50}$ Value) * (mg mL$^{-1}$) | Results                                                                 | Reference |
|-----------------------------------|------------------------------------|---------------------|---------------------------------------------|------------------------------------------------------------------------|-----------|
| Hibiscus subdariffa               | Leaf                               | 8 mg kg$^{-1}$ of body weight | –                                           | Streptozotocin (STZ: 100 mg/kg of body weight) induced diabetes was cured by intraperitoneal injection of zinc oxide in mice | Bala et al. [35] |
| Heritiera fomes (HF) and Sonneratia apetala (SA) | Bark and leaf                      | 100 µL              | 0.33 (HF) and 0.39 (SA)                      | Exhibited better anti-diabetic activity in terms of α-amylase inhibition activity | Thatoi et al. [16] |
| Azadirachta indica, Hibiscus rosa-sinensis, Murraya koenigii, Moringa oleifera and Tamarindus indica | Leaf                               | 100–1.52 µg mL$^{-1}$ | α-amylase: 0.025–0.05 α-glucosidase: 0.012–0.05 | Exhibited higher α-amylase and α-glucosidase inhibition activity | Rehana et al. [22] |
| Vaccinium arctostaphylos          | Fruit                              | –                   | –                                           | Exhibited great treating efficacy on alloxan-diabetic rats compared to chemically synthesized zinc oxide | Bayrami et al. [63] |
| Andrographis paniculata           | Leaf                               | 100 µL              | 0.12                                        | Exhibited better anti-diabetic activity in terms of exhibiting moderate α-amylase inhibitory activity | Rajakumar et al. [34] |
| Costus igneus                     | Leaf                               | 100 µg mL$^{-1}$    | –                                           | Increased the percentage of α-amylase and α-glucosidase inhibition with increased concentration of nanoparticles | Vinotha et al. [33] |
| Mussaenda frondosa                | Leaf, stem and leaf-derived callus | 20 µL               | α-amylase: 0.014–0.055 α-glucosidase: 0.014–0.035 | Exhibited on par α-amylase inhibitory activity and α-glucosidase inhibitory activity | Jayappa et al. [97] |
| Myristica fragrans                | Fruit                              | 400 µg mL$^{-1}$    | –                                           | Excellent α-amylase and α-glucosidase inhibition activity               | Faisal et al. [11] |

* Range of the IC$_{50}$ value depicts the changes in between the methods employed.
4.5. Anticancer Activity

The therapeutic regimes cannot distinguish between cancerous and normal cells, resulting in systemic toxicity and side effects. As a result, new chemotherapeutic agents with high selectivity for cancer cells are needed. Zinc deficiency initiates and facilitates the development of cancerous cells, as it is an important mineral that maintains homeostasis by controlling the enzyme activities in our body [104]. Zinc is essential for the function of p-53 (a tumor suppressor gene) that controls apoptosis by activating the Caspase-6 (Casp6) enzyme. In addition, zinc oxide nanoparticles have a special electrostatic property that aids in the selective targeting of cancer cells. Anionic phospholipids are abundant on the surface of cancer cells, resulting in electrostatic attraction with zinc oxide nanoparticles, which encourages cancer cells to take up zinc oxide nanoparticles, resulting in cytotoxicity in cancer cells [70,129].

The small size of zinc oxide nanoparticles, on the other hand, aids in the permeation and retention of nanoparticles within tumorous cells, allowing them to act. The possible mechanisms behind zinc oxide nanoparticles’ selective pH-responsive cytotoxicity towards cancer cells are (1) the pH-dependent rapid dissolution of zinc oxide nanoparticles into the release of Zn\(^{2+}\) ions under an acidic intracellular environment, which causes oxidative stress (via ROS production) and subsequent cell damage within cancer cells, and (2) the production of a large amount of ROS in cancer cells relative to normal cells; the elevated ROS level then causes mitochondrial dysfunction and activates the intrinsic mitochondrial apoptotic pathway (Figure 5) (Sana et al. [71]). ROS can also mediate cell death via extrinsic necrosis and apoptosis. Further, the overproduction of ROS leads to induced oxidative DNA damage and mitotic death and can also trigger autophagic/mitophagic cell death [19,26].

The MTT assay has been effectively used to confirm the anticancer activity of zinc oxide nanoparticles prepared using the plant-mediated green synthesis method against a variety of cell lines, which are detailed in Table 5. In addition, zinc oxide nanoparticles have been used successfully as an effective carrier to deliver anticancer drugs to tumor cells.

![Figure 5](image_url). Possible anticancer mechanism of plant-mediated zinc oxide nanoparticles.
Table 5. Anticancer activity of plant-mediated zinc oxide nanoparticles.

| Plant Name            | Description                  | Cell Lines Used                          | Activity (IC₅₀ Value) | Results                                                                                           | Reference          |
|-----------------------|------------------------------|------------------------------------------|-----------------------|---------------------------------------------------------------------------------------------------|--------------------|
| *Anchusa italica*     | Flower                       | Vero cells                               | 142 µg·mL⁻¹           | Showed concentration-dependent cytotoxicity on the growth of Vero cells                           | Azizi et al. [6]   |
| *Rosa canina*         | Fruit                        | Alveolar adenocarcinoma (A549) cells     | >0.1 mg·mL⁻¹          | Exhibited dose-dependent toxicity to A549 cells                                                  | Jafarirad et al. [57]|
| *Citrullus colocynthis* | Fruit, seed and pulp         | 3T3 cells                                | 0.258 mg·mL⁻¹ (Fruit), 0.160 mg·mL⁻¹ (Seed) and 0.210 mg·mL⁻¹ (Pulp) | Showed a dose dependent toxicity on the growth of 3T3 cells with non-toxic effect of concentration below 0.26 mg/mL | Azizi et al. [80] |
| *Pongamia pinnata*    | Seed                         | Human MCF-7 breast cancer cell lines      | 50 µg·mL⁻¹            | More successful in control of human MCF-7 breast cancer cells compared to the seed extract and bulk zinc oxide (positive control) | Malaikozhundan et al. [111] |
| *Ziziphus nummularia* | Leaf                         | HeLa cancer cell lines                   | 50 and 200 µg·mL⁻¹    | Showed potent dose-dependent cytotoxic effect against HeLa cancer cell lines                     | Padalia and Chanda [7] |
| *Mangifera indica*    | Leaf                         | Lung cancer A549 cell lines              | 25 µg·mL⁻¹            | Significant cytotoxic effect against lung cancer A549 cell lines                                 | Rajeshkumar et al. [65] |
| *Costus pictus*       | Leaf                         | Daltons lymphoma ascites (DLA) cells     | 50 µg·mL⁻¹            | Exhibited strong anticancer behavior against DLA bearing mice cell lines                          | Suresh et al. [66] |
| *Anacardium occidentale* | Leaf                        | Human normal fibroblast cell line (Hu02) and human pancreatic cancer cell lines (Panc-1 and AsPC-1) | 40 µM (Panc-1) and 30 µM (AsPC-1) | Exhibited the concentration-dependent cytotoxicity against human pancreatic cancer cell lines | Zhao et al. [88] |
| *Kalanchoe pinnata*   | Leaf                         | Murine macrophage RAW 264.7 cells        | –                     | Exhibited no significant cytotoxicity up to 1 mg/mL in RAW 264.7 cells                          | Agarwal and Shanmugam [21] |
| *Gracilaria edulis*   | Aqueous extract              | Cervical carcinoma cells (SiHa cells)     | 35 µg·mL⁻¹            | Exhibited cytotoxic effect against SiHa cells in a dose dependent manner                          | Asik et al. [89]   |
### Table 5. Cont.

| Plant Name        | Description     | Cell Lines Used                                                                 | Activity (IC₅₀ Value) | Results                                                                                                                                  | Reference               |
|-------------------|-----------------|---------------------------------------------------------------------------------|-----------------------|-----------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| *Juglans regia*   | Leaf            | Human skin fibroblasts                                                          | 200 µg mL⁻¹           | Have less cytotoxicity than chemical zinc oxide nanoparticles                                                                           | Darvishi et al. [119]    |
| *Cucurbita pepo*  | Leaf            | Mammalian osteoblast-like MG63 cells                                            | 20 ppm                | Induced cytotoxicity that affected the proliferation of MG63 cells in the concentration dependent manner                                 | Hu et al. [120]          |
| *Pandanus odorifer* | Leaf          | Breast cancer (MCF-7), liver cancer (HepG2), and lung cancer (A-549) cells | 100 µg mL⁻¹           | Apoptotic and necrosis effect on MCF-7, HepG2, and A549 cancer cell lines                                                              | Hussain et al. [121]     |
| *Trianthema portulacastrum* | Plant     | Mouse pre-osteoblast cell line (MC3T3-E1)                                        | –                     | Showed no toxic effect and the cells were found viable                                                                               | Khan et al. [39]         |
| *Cucumis melo inodorus* | Rough shell | Human (Michigan Cancer Foundation-7 [MCF7]) and murine (TUBO) breast cancer cell lines | 40 µg mL⁻¹ (MCF7); 20 µg mL⁻¹ (TUBO) | Found as a powerful apoptosis inducer in breast cancer cells in human cell line (MCF7) and murine (TUBO cell line and cancer model) | Mahdizadeh et al. [101]  |
| *Artocarpus heterophyllus* | Leaf        | Human colon cancer HCT-116 cell lines                                           | 20 µg mL⁻¹            | Showed excellent cytotoxic effect against human colon cancer HCT-116 cell lines                                                         | Majeed et al. [93]       |
| *Hysops officinalis* | Plant       | MDA-MB231 breast cancer cell line                                               | 125 µg mL⁻¹           | Inhibitory effects on the growth of breast cancer cells and induction of cytotoxicity depending on nanoparticle concentration and time of exposure | Rahimi Kalateh Shah Mohammad et al. [102] |
| *Annona squamosa* | Leaf           | Cervical cancer cells (HeLa cell lines)                                         | 50 µg mL⁻¹            | Anticancer activity against HeLa cell lines in a dose dependent pattern with a defensive prospect towards mammalian (HEK-293) cells | Ruddaraju et al. [69]    |
| *Tecoma castanifolia* | Leaf         | Human lung carcinoma cells (A549)                                               | 65 µg mL⁻¹            | Conferred better cytotoxic effects on proliferation of A549 cell line                                                               | Sharmila et al. [132]    |
Table 5. Cont.

| Plant Name              | Description                  | Cell Lines Used                                      | Activity (IC₅₀ Value) | Results                                                                 | Reference                     |
|-------------------------|------------------------------|-----------------------------------------------------|-----------------------|-------------------------------------------------------------------------|--------------------------------|
| *Scutellaria baicalensis* | Root                         | HeLa cells (Human cervical cancer cell line) and RAW 264.7 murine macrophage cells | 1000 µg·mL⁻¹          | Showed dose-dependent antiproliferative activity against the growth of HeLa cells and no toxicity on RAW 264.7 macrophages (normal immune system cells) | Tettey and Shin [70] |
| *Albizia lebbeck*       | Stem bark                    | Human breast cancer cell lines (MDA-MB 231 and MCF-7) | Cytotoxicity: 100 µg·mL⁻¹ (MDA-MB 231) and 5 µg·mL⁻¹ (MCF-7); Proliferation: 100 µg·mL⁻¹ (MDA-MB 231 and MCF-7) | Inhibited the cell viability and cell number (proliferation) of MDA-MB 231 and MCF-7 cells in concentration dependent manner | Umar et al. [26] |
| *Lycopersicon esculentum* | Leaf                         | Murine macrophage cells (RAW 264.7) and Human cervical cancer (HeLa) cells | 100 µg·mL⁻¹          | Zinc oxide nanoparticles were non-toxic to macrophage cells, as no alterations in viability. Treatment of HeLa cells with zinc oxide nanoparticles induced cell growth retardation, cell clumping, cell bursting, and loss of membrane stability and they prevented the proliferation of HeLa cells | Vijayakumar et al. [137] |
| *Rehmanniae radix*      | Plant                        | Bone cancer cell line MG-63                        | 30 µg·mL⁻¹           | Exhibited strong anticancer activity and inducing apoptosis on MG-63 cells via stimulating increased generation of ROS | Cheng et al. [104] |
| *Citrus sinensis*       | Peel                         | Human umbilical vein endothelial cells (HUVECs)    | Below 25 mg·L⁻¹      | Cytotoxicity towards HUVECs exhibited when the concentration exceeded 12.5 mg·L⁻¹ | Gao et al. [19] |
| *Mussaenda frondosa*    | Leaf, stem and leaf-derived callus | Human lung adenocarcinoma cells (A549) | 67.75 µg·mL⁻¹ (Callus) and 85.66 µg·mL⁻¹ (Stem) | Exhibited on par cytotoxic activity on A549 cells in a dose-dependent action | Jayappa et al. [97] |
| *Hyssopus officinalis*  | Leaf                         | Human prostate cancer (PC3) cells                  | 8.07 µg·mL⁻¹ (24 h) and 5 µg·mL⁻¹ (48 h) | Demonstrated the dose-dependent cytotoxicity effect and induced apoptosis on PC3 cells | Rahimi Kalateh Shah Mohammad et al. [107] |
| Plant Name          | Description | Cell Lines Used                      | Activity (IC50 Value)                                                                 | Results                                                                                                                                                                                                 | Reference |
|--------------------|-------------|--------------------------------------|---------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Crotalaria verrucosa | Leaf        | HeLa and DU145 cell lines             | 7.07 µg·mL⁻¹ (HeLa); 6.30 µg·mL⁻¹ (DU145)                                               | Exhibited the dose-dependent inhibition curve with IC50 value of 7.07 µg/mL and 6.30 µg/mL in HeLa and DU145 cells, respectively                                        | Sana et al. [71] |
| Deverra tortuosa    | Plant       | Human colorectal epithelial adenocarcinoma (Caco-2), human lung epithelial carcinoma (A549) and normal human lung fibroblast cell line (WI38) | 83.47 µg·mL⁻¹ (A549), 50.81 µg·mL⁻¹ (Caco-2) and 434.60 µg·mL⁻¹ (WI38)       | Exhibited the profound selective concentration dependent cytotoxic effect on Caco-2 and A549 cancer cell lines with appreciable lower cytotoxic activity on normal WI38 cells                                      | Selim et al. [99] |
| Euphorbia fischeriana | Root        | Lung cancer (A549) cells              | 14.5 µg·mL⁻¹                                                                         | Induced cytotoxicity and also activated apoptosis during increased ROS formation, decreased mitochondrial membrane potential, inhibited cell migration, altered AO/EtBr staining and induced pro-apoptotic and inhibited anti-apoptotic protein | Zhang et al. [129] |
| Myristica fragrans  | Fruit       | 85E strain for protein kinase inhibition capability | 5 mg·mL⁻¹                                                                            | Clear zones were observed against 85E strain which used to elucidate the protein kinase inhibition capability                                                                                       | Faisal et al. [11] |
| Raphanus sativus    | Leaf        | Lung cancer cell line (A549)          | 40 µg·mL⁻¹                                                                            | Showed a better anticancer activity by reducing cell viability                                                                                                                                         | Umamaheswari et al. [29] |
Zinc oxide nanoparticles have a particle size, shape, surface charge, concentration, and time-dependent cytotoxicity in cancer cells, and photo-irradiation with ultraviolet (UV) or near-infrared (NIR) lasers enhance its anticancer activity through a synergistic chemo-photodynamic effect [29,71]. The majority of the researchers also demonstrated that zinc oxide nanoparticles are less or nontoxic compared to normal cells in vitro when used in the same concentration range as cancer cells. Zinc oxide nanoparticles can cause systemic toxicity in tumor-bearing mouse models. However, using antioxidants in combination with zinc oxide nanoparticles may minimize the toxic side effects and increase the antitumor potential [11]. Zinc oxide nanoparticles’ adverse toxic side effects can also be prevented or decreased by using cancer cell-specific ligands. While numerous reports on the anticancer properties of plant-mediated green synthesized zinc oxide nanoparticle in vitro systems are available, only a few studies in tumor-bearing mouse models have been performed [93]. In vivo tumor models can be used to conduct further research using plant-mediated green synthesized zinc oxide nanoparticles with active cancer cell-targeting strategies.

The semiconducting nature of biosynthesized zinc oxide nanoparticles has been reported to induce cytotoxicity in cancer cells by forming ROS on the particle’s surface; the released Zn$^{2+}$ ions are dissolved in culture media, indicating the direct interaction of nanoparticles with a cancer cell membrane, resulting in oxidative stress and, ultimately, cancer cell death [71]. Zinc oxide nanoparticles synthesized from the aqueous extract of D. tortuosa exhibited enticing selective cytotoxic efficacy against two cancer lines (Caco-2 and A549), providing appealing ‘safer and cheaper’ alternatives to traditional therapy regimens [99]. Faisal et al. [11] used the Streptomyces 85E strain to elucidate the protein kinase inhibition capability of zinc oxide nanoparticles synthesized from aqueous fruit extracts of M. fragrans and concluded that the plant extracts provide crucial capping and stabilizing agents to biogenic nanoparticles, which are responsible for their anticancer properties. Recently, Umamaheswari et al. [29] reported that the anticancer activity of zinc oxide nanoparticles biosynthesized from leaf extracts of R. sativus was higher after treating the A549 cell lines, indicating that cancer drugs can be prepared using this environmentally friendly method. The DNA damage pathways, paraptosis, autophagy, radio sensitizing, aberrant cellular metabolism, overcoming chemo resistance, oxidative stress modulation, induction of apoptosis, arresting of the cancer cell cycle, anti-invasion, and metastasis are some of the possible anticancer mechanisms that have been reported so far [139].

4.6. Anti-Inflammatory Activity

Nanoparticles have been widely exploited as a potential anti-inflammatory agent in recent years. The large surface area-to-volume ratio causes nanoparticles to have more surface reactive properties, resulting in more interactions with the cell membrane and easier transport within the membrane [34,97,125]. Zn is easily transported through the cell membrane because of the nanosizes of zinc oxide nanoparticles. The anti-inflammatory mechanisms adopted by zinc oxide nanoparticles involve the release of Zn$^{2+}$ ions from the dissolution of zinc oxide nanoparticles and subsequent block of the release of proinflammatory cytokines (like interleukin-1 (IL-1), interleukin-1β (IL-1β), interleukin-13 (IL-13), and tumor necrosis factor-α (TNF-α)) in mast cells; they suppress the expression of the lipopolysaccharide (LPS)-induced cyclooxygenase-2 (COX-2) gene in macrophages to prevent the release of prostaglandin-E2 (PG-E2), suppress the expression of inducible nitric oxide synthase (iNOS) to reduce nitric oxide (NO) production, inhibit myeloperoxidase (MPO) for the upregulation of inflammatory pathogenesis, inhibit the nuclear factor-kappa B (NF-κB) pathway and block the caspase-1 enzyme in activated mast cells, inhibit the proliferation of mast cells through the regulation of the p-53 protein level to prevent the release of High Mobility Group Protein-1 (HMG-1), and also, inhibit thymic stromal lymphopoietin (TSLP) production by primary epithelial cells [140] (Figure 6).
Figure 6. Possible anti-inflammatory mechanisms of plant-mediated zinc oxide nanoparticles.

The zinc oxide nanoparticles synthesized from *Polygala tenuifolia* root extract displayed excellent anti-inflammatory activity, even up to 1 mg·mL$^{-1}$, by suppressing the LPS-induced mRNA and protein expressions of iNOS; COX-2; and anti-inflammatory cytokines (IL-1β, IL-6, and TNF-α) in LPS-stimulated RAW 264.7 murine macrophage cells in a dose-dependent manner [17]. Agarwal and Shanmugam [21] also revealed that green synthesized zinc oxide nanoparticles from *Kalanchoe pinnata* leaf extract were found to be biocompatible up to 1 mg mL$^{-1}$ and to have an anti-inflammatory effect by inhibiting the production and release of proinflammatory mediators such as IL-1β, IL-6, TNF-α, and COX-2. Likewise, Liu et al. [125] proved the anti-inflammatory effects of synthesized zinc oxide nanoparticles from *Vernonia amygdalina* leaf extract against different pain and inflammation-induced mice. Moreover, the synthesized zinc oxide nanoparticles were found to exhibit potent anti-inflammatory effects via reducing the inflammatory response and proinflammatory cytokines level in mice. Other reports on the anti-inflammatory properties of plant-mediated zinc oxide nanoparticles are summarized in Table 6.
### Table 6. Anti-inflammatory activity of plant-mediated green synthesized zinc oxide nanoparticles.

| Plant Name | Description | Assay/Model | Activity (IC_{50} Value) | Results | Reference |
|------------|-------------|-------------|--------------------------|---------|-----------|
| *Polygala tenuifolia* | Root | LPS-stimulated RAW 264.7 murine macrophage cells | 1 mg·mL⁻¹ | Showed anti-inflammatory activity by suppressing the LPS-induced mRNA and protein expressions of iNOS, COX-2, and anti-inflammatory cytokines in LPS-stimulated RAW 264.7 murine macrophage cells | Nagajyothi et al. [17] |
| *Heritiera fomes* (HF) and *Sonneratia apetala* (SA) | Bark and leaf | Inhibition of protein denaturation in vitro assay | 72.35 µg·mL⁻¹ (HF) and 63.29 µg·mL⁻¹ (SA) | Anti-inflammation activity inhibiting protein (heat induced albumin) denaturation | Thatoi et al. [16] |
| *Andrographis paniculata* | Leaf | Inhibition of protein denaturation in vitro assay | 66.78 µg·mL⁻¹ | Anti-inflammatory activity by inhibiting protein denaturation | Rajakumar et al. [34] |
| *Kalanchoe pinnata* | Leaf | LPS-induced Murine Raw 264.7 cell lines; Detection of the mRNA expressions of TNF-α, IL-1β, IL-6, and COX-2 | – | Reduced the expression of pro-inflammatory cytokines, attenuated the release of IL-1β, IL-6, and TNF-α by inhibiting mRNA expression, inhibited the gene expression of COX-2 enzyme and suppressed NO production | Agarwal and Shanmugam [21] |
| *Hysops officinalis* | Plant | Reduction of mouse paw edema | 5 mg·kg⁻¹ | Reduction of inflammation by significantly reducing the thickness of mouse paw edema | Mohammad et al. [102] |
| *Mussaenda frondosa* | Leaf, stem & leaf-derived callus | Human red blood cells membrane stabilization method | 500 µg·mL⁻¹ | Exhibited varying degrees of human RBCs membrane and lysosomal membrane stabilizing activity in a dose-dependent manner | Jayappa et al. [97] |
| *Vernonia amygdalina* | Leaf | Swiss Albino male mice | 2.5, 5, and 7.5 mg·kg⁻¹ | Exhibited the potent anti-inflammatory activity against carrageenan induced-inflammation in mice | Liu et al. [125] |
4.7. Photocatalytic Activity

To prevent water pollution, various semiconductors, including zinc oxide, have been evaluated as photocatalysts and have proposed a viable solution. Zinc oxide nanoparticles synthesized from biological origin have shown a remarkable photocatalytic degradation of several dyes, including methylene blue, methyl orange, etc., due to their intrinsic ability to absorb UV irradiation and optical transparency. Since methylene blue is a major water pollutant emitted by industries such as textiles and is widely recognized as a traditional organic pollutant, these zinc oxide nanoparticles have gained much publicity due to environmental concerns [92,110,130]. Furthermore, the toxic effluents discharged by the textile industry have harmed marine life and the ecosystem, resulting in a serious environmental crisis. The bio-fabricated zinc oxide nanoparticles were utilized as a photocatalyst to degrade carcinogen organic dyes where the structure, particle size, crystallinity, photocatalyst band gap, surface area, and other factors were considered [40,96].

The mechanism of photodegradation is that, when semiconductors (catalysts) consume energy (photons) greater than their bandgap energy, charge separation occurs due to an electron jumping from the valence band to the conduction band of the catalyst, resulting in the creation of a hole in the valence band [64,70,108,122]. The created electron-hole pairs diffuse onto the photocatalyst’s surface and participate in the chemical reaction with the electron donor and acceptor when illuminated by light stronger than the band gap energy. With super strongoxidization, certain free electrons and holes convert the surrounding oxygen or water molecules into highly reactive unstable \( \text{OH}^\bullet \) free radicals. When zinc oxide nanoparticles absorb photons with energies greater than their band gap energy from illumination, photocatalytic reactions begin to degrade the dyes [83] (Figure 7). Therefore, among the other zinc species in aqueous dye solutions under the experimental conditions, \( \text{Zn}^{2+} \) ions must be the most abundant, followed by \( \text{Zn(OH)}^+ \), \( \text{Zn(OH)}_3^- \), and \( \text{Zn(OH)}_4^{2-} \).

![Figure 7. Possible photocatalytic mechanism of plant-mediated zinc oxide nanoparticles.](image-url)
In the presence of solar light as a catalyst, the biosynthesized zinc oxide nanoparticles showed a strong degradation capability for Synozol navy blue K-BF, and the hypothesized degradation mechanism yielded the formation of hydroxyl radical and dye degradation into smaller fragments [39]. Alamdari et al. [124] indicated that zinc oxide nanoparticles biosynthesized from the leaf extract of S. ebulus showed the maximum degradation of methylene blue dye noticeably around 80% after 200 min of UV radiation. Recently, Faisal et al. [11] reported that zinc oxide nanoparticles biosynthesized from aqueous fruit extracts of M. fragrans were used as photocatalytic agents, resulting in 88% of methylene blue dye degradation in 140 min of UV light illumination. In addition, Vinayagam et al. [130] reported that zinc oxide nanoparticles synthesized from Bridelia retusa leaf extract promoted the photocatalytic degradation of Rhodamine B dye by up to 94.74% within 165 min of solar irradiation. The crystalline and mesoporous natures, high surface area, and good electron acquiring features of the zinc oxide nanoparticles might be attributed to the accelerated degradation. Furthermore, the improved photocatalytic activity could be attributed to the stabilizing phytocompounds. Likewise, the photocatalytic activity of the plant-mediated zinc oxide nanoparticles is represented in Table 7.
Table 7. Photocatalytic activity of the plant-mediated zinc oxide nanoparticles.

| Plant Name                        | Dye Degraded                  | Solar Irradiation Time | pH Range | Degradation Efficiency (%) | Reference                                |
|-----------------------------------|-------------------------------|------------------------|----------|----------------------------|------------------------------------------|
| Phyllanthus niruri                | Methylene blue (MB)           | 30 min                 | –        | 99%                        | Anbuvannan et al. [53]                   |
| Anisochilus carnosus             | Methylene blue (MB)           | 90 min                 | –        | 100%                       | Anbuvannan et al. [54]                   |
| Vitex trifolia                   | Methylene blue (MB)           | 90 min                 | –        | 92.13%                     | Elumalai et al. [72]                     |
| Plectranthus ambotonicus         | Methyl red (MR)               | 180 min                | –        | 92.45%                     | Fu and Fu [73]                           |
| Allium sativum, Allium cepa and Petroselinum crispum | Methylene blue | 180 min | – | >90% | Stan et al. [74] |
| Cassia fistula                   | Methylene blue                | 120 min                | 7        | 90% (for 5 ppm)            | Suresh et al. [76]                       |
| Artocarpus gomezianus            | Methylene blue (MB)           | 120 min                | 10       | 100% (for 5 ppm, sun light); 65% (for 5 ppm, UV light) | Suresh et al. [77]                       |
| Corymbia citriodora              | Methylene blue                | 90 min                 | –        | 83.45%                     | Zheng et al. [78]                        |
| Mimosa pudica                   | Methylene blue                | 120 min                | –        | 90%                        | Fatimah et al. [110]                     |
| Coffea arabica                  | Methylene blue                | 120 min                | –        | 98%                        |                                         |
| Carissa edulis                  | Congo red                     | 130 min                | –        | 97%                        | Fowsiya et al. [56]                      |
| Nephelium lappacecum            | Methyl orange (MO)            | 120 min                | 7.01     | 83.99%                     | Kannan and Selvakumar [58]               |
| Azadirachta indica              | Methylene blue (MB)           | 120 min                | –        | >80%                       | Madan et al. [36]                        |
| Terminalia chebula              | Rhodamine B (RhB)             | 5 h                    | –        | 70% (for 5 ppm)            | Rana et al. [79]                         |
| Carica papaya                   | Alizarin Red-S                | 120 min                | –        | 99%                        | Sharma [60]                              |
| Sedum alfredii                  | 2-chlorophenol (2-CP)         | 120 min                | 6.3      | 96.93%                     | Wang et al. [133]                        |
| Camellia sinensis              | Methylene blue (MB)           | 240 min                | –        | 100%                       | Nava et al. [62]                         |
| Eucalyptus globulus              | Methylene blue (MB) and Methyl orange (MO) | 50 min (MB) and 1 h (MO) | – | 98.2% (MB) and 96.6% (MO) | Siripireddy and Mandal [83] |
| Acacia senegal                  | Direct blue 129 (DB129)       | 105 min                | –        | 95%                        | Taghavi Fardood et al. [84]              |
| Conyza canadensis              | Methylene blue (MB) and Methyl orange (MO) | 45 min (MO) and 20 min (MB) | – | 94.5% (MO) and 85.3% (MB) | Ali et al. [85] |
| Garcinia mangostana              | Malachite green               | 180 min                | –        | 99%                        | Aminuzzaman et al. [86]                  |
| Citrus sinensis                 | Methylene blue (MB)           | 120 min                | –        | 83%                        | Luque et al. [64]                        |
| Ferulago angulata               | Rhodamine B (RhB)             | 150 min                | –        | 93%                        | Mehr et al. [115]                        |
Table 7. Cont.

| Plant Name                  | Dye Degraded                          | Solar Irradiation Time | pH Range      | Degradation Efficiency (%) | Reference            |
|-----------------------------|---------------------------------------|------------------------|---------------|----------------------------|----------------------|
| *Laurus nobilis*            | Remazol Brilliant Red F3B             | 45 min                 | Around 6.8    | 99%                        | Chemingui et al. [92]|
| *Dolichos lablab*           | Methylene blue (MB), Rhodamine B (RhB) and Orange II (OII) | 210 min                | 11 (MB), 9 (RhB) and 5 (OII) | 80% (MB), 95% (RhB), and 66% (OII) | Kahsay et al. [122] |
| *Trianthema portulacastrum* | Synozol navy blue K-BF                | 150 min                | –             | 91%                        | Khan et al. [39]     |
| *Abelmoschus esculentus*    | Methylene blue (MB) and Rhodamine B (RhB) | 60 min (MB) and 50 min (RhB) | ~7            | 100%                       | Prasad et al. [123]  |
| *Artabotrys hexapetalu* (AH) and *Bambusa vulgaris* (BV) | Rhodamine B (RhB)                  | 180 min                | Neutral       | 92% (AH) and 88% (BV)      | Shanavas et al. [68] |
| *Musa acuminata*            | Methylene blue (MB)                   | 7 h                    | 12            | 98.13%                     | Abdullah et al. [40] |
| *Sambucus ebulus*           | Methylene blue                        | 200 min                | –             | 80%                        | Alamdari et al. [124]|
| *Ziziphus jujuba*           | Methylene blue (MB) and Eriochrome black-T (ECBT) | 5 h                    | –             | 92% (MB) and 86% (ECBT)    | Golmohammadi et al. [96]|
| *Mussaenda frondosa*        | Methylene blue                        | 100 min (Leaf), 100 min (Stem), and 120 min (Callus) | 7            | 30% (Leaf), 30% (Stem) and 90% (Callus) | Jayappa et al. [97] |
| *Aegle marmelos*            | Methylene blue (MB)                   | 35 min                 | –             | 96%                        | Mallikarjunaswamy et al. [98]|
| *Quince*                    | Methylene blue                        | 2 h                    | Normal        | 80%                        | Moghaddas et al. [141]|
| *Syzygium cumini*           | Rhodamine B (RhB)                     | 100 min                | 9             | 98%                        | Rafique et al. [106] |
| *Aloe vera*                 | Methyl orange (MO)                    | 140–160 min            | –             | 95%                        | Sharma et al. [127] |
| *Thlaspi arvense*           | Methylene blue                        | 2 h                    | –             | 100%                       | Ullah et al. [108]  |
| *Calliandra haematocephala* | Methylene blue (MB)                   | 270 min                | –             | 88%                        | Vinayagam et al. [128]|
| *Myristica fragrans*        | Methylene blue                        | 140 min                | –             | 88%                        | Faisal et al. [11]   |
| *Bridelia retusa*           | Rhodamine B                           | 165 min                | –             | Upto 94.74%                | Vinayagam et al. [130]|
4.8. Wound-Healing Activity

Since our skin is our body’s largest organ, it protects us from external attack, and any damage to it results in a wound. The healing of a wound takes time and can be slowed by microbial infection (P. aeruginosa and S. aureus). Nanoparticles have antibacterial properties and produce hydrogen peroxide, which causes cell damage [87]. Metal oxide nanoparticles can be utilized to destroy the pathogenic species and thereby improve wound healing [67]. Zinc oxide nanoparticles synthesized biologically from plant sources can be tremendously used as a wound-healing agent for treating general wounds and wounds caused due to burning [67,87,114]. Khatami et al. [114] indicated that zinc oxide nanoparticles (about 26 nm in size) synthesized from Prosopis fracta and coffee were found to impregnate on cotton wound bandages, conferring patches with a strong antimicrobial effect. Hence, they can potentially be used for treating and covering infection-sensitive wounds, namely diabetic or burns wounds. Shao et al. [87] biosynthesized zinc oxide nanoparticles from a Barleria gibsoni leaf extract, which acted as efficient and superior tropical antimicrobial formulations for the healing of burn infections by exhibiting a remarkable wound-healing potential in rats. Kiran Kumar et al. [142] studied zinc oxide nanoparticles synthesized from a Raphanus sativus root extract and showed their antimicrobial property against Escherichia fergusonii and E. coli strains that can be further explored for wound-healing potential. Apart from these, many reports have also indicated that the application of zinc oxide nanoparticles/or their biocomposites, irrespective of their application, possessed potential wound-healing ability and help in wound healing [143–146].

4.9. Targetted Drug Delivery System

Zinc oxide nanoparticles have been considered as a potential candidate for targeted drug delivery because of their ease of synthesis from low-cost metal precursors, biocompatibility, and successful cellular internalization via endocytosis. Nanoparticles’ smaller particle sizes and larger surface areas make it easier for them to penetrate cell membranes and be absorbed into cells, resulting in better distribution. As a result, nanoparticles are commonly used in drug delivery systems, where they are loaded with drugs that reach their targets in appropriate quantities and then guide the drug release from the nanoparticles [51]. The effect of zinc oxide nanoparticles on drug delivery revealed that these nanoparticles aid in the rapid release of the drug at first and then transition to regulate the release over the treatment period [95]. The mechanisms underlying the enhanced cytotoxic potential of anticancer drug-loaded zinc oxide nanoparticles involve the pH-dependent release of targeted drug and zinc oxide nanoparticles in the cytoplasm once the drug-loaded zinc oxide nanoparticles enter through receptor-mediated endocytosis. The release of targeted anticancer drugs act upon cancer cells and cause cell death. Additionally, zinc oxide nanoparticles release Zn^{2+} ions and produce excessive ROS (oxidative stress) and, subsequently, lead to cancer cell death (Figure 8).
Figure 8. Possible mechanisms of plant-mediated zinc oxide nanoparticles in a targeted drug delivery system.

Vimala et al. [52] used green synthesized doxorubicin (DOX)-loaded zinc oxide nanoparticles with *Borassus flabellifer* fruit extract in a drug delivery system for anticancer therapy. The synthesized DOX–zinc oxide nanoparticles showed dose-dependent cytotoxicity against the human breast cancer MCF-7 and colon cancer HT-29 cell lines, with an inhibitory concentration (IC$_{50}$) of 0.125 µg·mL$^{-1}$. Additionally, the toxicity assessment in vivo showed that these DOX–zinc oxide nanoparticles had low systemic toxicity in the murine model system. The low toxicity and high anticancer therapy efficacy of DOX–zinc oxide nanoparticles were found to provide strong evidence for plant-mediated green synthesized zinc oxide nanoparticles as promising candidates in drug delivery systems. Akbarian et al. [95] successfully loaded an important anticancer drug (Paclitaxel, PTX) on chitosan-coated zinc oxide nanoparticles, which were synthesized from the ethanolic leaf extract of *Camellia sinensis* and evaluated their biological activity as a drug delivery system on breast cancer cell lines (MCF-7). The PTX loaded on the chitosan-coated zinc oxide nanoparticles were found to show acytotoxic (anticancer) effect on cancerous MCF-7 cell lines and reduced the cytotoxic effect on normal fibroblast cell lines. Despite the reports on the use of zinc oxide nanoparticles in targeted drug delivery systems, further research is required to develop zinc oxide nanoparticles synthesized from plant sources as a flexible drug delivery system for targeted delivery. Passive targeting administered nanoparticles preferentially accumulate in solid tumors with discontinuous endothelium based on the enhanced permeability and retention (EPR) phenomenon, which is directly
dependent on the size of the particles, which is smaller than the tumor inter-endothelial gap cut-off size. Apart from this, the two fundamental characteristics of neoplastic tissues, such as leaky vasculature and impaired lymphatic drainage, may also facilitate nanoparticle targeting [147].

4.10. Tissue Engineering and Regenerative Medicine

Zinc oxide nanoparticles have emerged as promising materials for tissue engineering and regenerative medicine applications, which can help to promote tissue regeneration while reducing immune responses and preventing infections because of their antineoplastic, angiogenic, ultraviolet scattering, and wound-healing properties [148]. The osteogenesis and angiogenesis effects of zinc oxide nanoparticles have been effectively proven in several investigations due to their extraordinary antibacterial activity, and inexpensive cost [149,150]. Zinc oxide nanoparticles are also found to promote cell growth, proliferation, differentiation, and metabolic activity in a variety of cell lines for tissue engineering and regenerative medicine applications [151]. As a result, the use of plant-mediated zinc oxide nanoparticles in tissue engineering and regenerative medicine has become even more specialized and utilizing the innovative concept that zinc oxide nanoparticles’ proangiogenic properties might be tremendously advantageous in increasing the integration of advanced scaffolds into host tissue, as evidenced by in vitro and in vivo experiments.

Shubha et al. [152] synthesized zinc oxide nanoparticles using Gallic acid isolated from the aqueous extract of *Phyllanthus emblica* and reported that the smaller-sized plant-mediated zinc oxide nanoparticles were found to cause noticeably lesser toxicity than clinically advocated zinc oxide nanoparticles. Since they employed 3T3 fibroblasts from Balb mice, which are important connective tissue cells that aid in tissue repair and regeneration, and because these zinc oxide nanoparticles are benign to the cells, they can be used close to connective tissue cells. Shafique et al. [153] reported that biosynthesized zinc oxide nanoparticles from a *Cymbopogon citratus* leaf extract were found, showing a promising calllogenesis and regeneration frequency at their optimum concentrations (20 mg L\(^{-1}\) and 30 mg L\(^{-1}\) in the internodes and seeds, respectively) in *Panicum virgatum*, and it was confidently believed that this finding would open new doors in tissue culture technology by increasing the frequency of plant in vitro regeneration in different plant groupings.

5. Future Perspective and Conclusion

Zinc oxide nanoparticles have superior properties in contrast to bulk materials due to their small size and large surface area-to-volume ratio, which makes them explored in various fields, viz., biomedical, biosensor, cosmetic, food industries, etc. Among the different types of zinc oxide nanoparticle synthesis, the nanoparticles synthesized by the green route using plant extract have gained considerable importance in the new millennium due to their eco-friendly, nontoxic, cost-effective nature that can also be reproduced under a large scale. The phytoconstituents/secondary metabolites of plant extracts readily reduce the metal ions and stabilize them into nanoparticles. These phytofabricated zinc oxide nanoparticles offer better antimicrobial, anticancer, anti-inflammatory, and antidiabetic, along with other biomedical, applications due to the coating of various pharmacologically active biomolecules on their surfaces. This review elucidated the eco-friendly nature of green synthesized zinc oxide nanoparticles and their potential application in various biomedical fields, including drug delivery systems, along with their mechanism of action involved at the cellular level. From this review, it may be noted that plant-mediated zinc oxide nanoparticles possess better biological properties that are of human importance and can also be used in drug delivery systems due to their biocompatibility. Inconclusively, this review discussed the possible mechanisms behind plant-mediated green synthesized zinc oxide nanoparticles and advances made towards their role in therapeutic applications in the new millennium.
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