

Progress in Green Synthesis of Zinc oxide Nanoparticles and their utilization as Antidiabetic: An overview

Sakshi Patil¹, Shubhangi Sutar^{2*}, Rachana Bhimanwar³, Animesh Sanap⁴

¹Student, Ashokrao Mane College of Pharmacy, Pethvadgaon-416112, India

^{2*}HOD, Pharmaceutical Quality Assurance Department, Ashokrao Mane College of Pharmacy, Pethvadgaon-416112, India

³Professor, Dr. D. Y. Patil Unitech Society's, Dr. D. Y. Patil Institute of Pharmaceutical Sciences and Research, Pimpri, Pune-411018, India

⁴Student, Dnyaan Prasad Global University, School of Pharmacy and Research, Pimpri, Pune-411018, India

*Corresponding author: Shubhangi Sutar, HOD, Pharmaceutical Quality Assurance Department, Ashokrao Mane College of Pharmacy, Pethvadgaon-416112, India

ABSTRACT

This comprehensive review explored synthesis, evaluation, and potential uses of plant extract-based zinc oxide nanoparticles (ZnO NPs), with a particular focus on their potential role in diabetes management. Plant extract-based green synthesis offered an eco-friendly alternative, addressing the environmental concerns associated with traditional chemical methods. With an emphasis on a variety of plant sources, synthesis of ZnO NPs was described with its unique characteristics, including structure, size and shape influencing their potential applications in diabetes management. The anti-diabetic properties of these NPs were highlighted, showcasing their efficacy in improving insulin levels, reducing fasting blood sugar levels, and impacting glucose metabolism. A thorough exploration of characterization techniques, including morphological, structural, optical, and thermal analyses, was presented. The article emphasized the importance of these techniques in understanding NPs properties for diverse applications. Although ZnO NPs may have harmful effects on a variety of organs and tissues, their toxicity was acknowledged and discussed. The toxicity studies underscored the need for a comprehensive understanding of potential risks when considering the therapeutic applications of these nanoparticles. The gathered insights aimed to guide researchers in harnessing the potential of ZnO NPs for diabetes management while addressing safety concerns associated with their usage.

KEYWORDS: Plant extracts, Green synthesis, Antidiabetic applications, Zinc oxide nanoparticles, Toxicity, characterization.

How to cite this article: Patil S, Sutar S, Bhimanwar R, Sanap A. Progress in Green Synthesis of Zinc oxide Nanoparticles and their utilization as Antidiabetic: An overview. *Int J Drug Deliv Technol.* 2026;16(57s): 1173-1188. DOI: 10.25258/ijddt.16.57s.117

Source of support: Nil.

Conflict of interest: None.

1. INTRODUCTION

Advancements in global nanotechnology research have been rapid, with a specific emphasis on nanoparticles (NPs) due to their wide-ranging applications in diagnostics, biomarkers, delivery of drugs, and cancer treatment [1]. The rapidly progressing field of material sciences delves into the unique characteristics of NPs, considering factors such as their shape, size, and structure [2]. It is recognized that the size ranges from 1 to 100 nm is particularly beneficial for creating effective NPs [3]. NPs classified into two categories: inorganic, covering semiconductor NPs (such as Zinc Oxide, Zinc Sulfide, and Cadmium sulfide), metallic NPs (like Gold, Silver, and Copper), and magnetic NPs (like Cobalt, Nickel, and Iron); and organic, predominantly consisting of carbon-related NPs [4].

NPs (NPs) can be synthesized using two distinct approaches, each of which uses a particular technique (Fig. 1) [5]. The Top-Down method involves using a variety of size reduction techniques, such as ball milling, pulse laser ablation, and evaporation-condensation, to break up

selected bulk materials into fine particles [6]. This process involves breaking down the material into smaller components to achieve the desired NPs size [7]. Conversely, Bottom-Up strategy entails methodical synthesis of NPs using chemical and biological techniques like atomic condensation, sol-gel, and co-precipitation [8-10]. In this, atoms undergo self-assembly, forming new nuclei that subsequently grow into NPs at the nanoscale [11]. This complex bottom-up approach enables precise manipulation of the characteristics of the produced NPs. These two approaches provide researchers with the flexibility to select the most suitable technique according to the particular needs of their nanoparticle synthesis, empowering them to regulate particle size, structure, and characteristics of resulting NPs [11].

While the latter method is unpredictable, the former results in NPs that can be transferred chemically, physically, and with a green approach, causing atomic-sized particles to self-assemble [12].

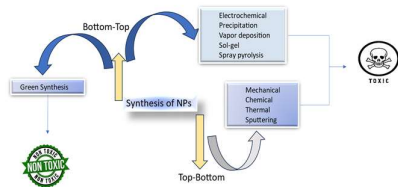


Fig. (1). Diverse strategies for synthesizing NPs

2. SYNTHESIS OF NANOPARTICLES

The synthesis of NPs includes various techniques, including chemical, physical, and biological methods [13]. The Chemical methods include precipitation, co-precipitation, colloidal, sol-gel, microemulsion, hydrothermal techniques, that depends on various parameters like temperature, time, and concentration of reactants. Changes in these parameters have an impact on the size and shape of NPs [14-16]. The use of hazardous reducing agents and solvents that endanger the environment is a drawback of this technique [17]. The physical methods for NPs synthesis includes various techniques such as ultrasonic treatment, melt mixing, and physical vapour deposition and ion implantation. However, these techniques are having poor efficiency, significant energy use, and environmental contamination [18, 19].

To tackle these challenges, the adoption of green chemistry approaches for NP production has become widespread. Green synthesis produces stable NP production, is widely used, and is economical [20-22].

Table 1 outlines the benefits and drawbacks of the techniques for NP synthesis.

Table 1: Overview of NPs Synthesis Methods

Method	Benefits	Drawbacks
Chemical synthesis	Controlled size High purity and quality NPs are considerably stable	Use of hazardous chemicals
Physical synthesis	Absence of harmful components Rapid technique High production rates High quality and purity	Costly High energy Stability is low
Green synthesis	Safe and toxicity-free Simple and cost-effective Biocompatible Eco-friendly	Difficulty in controlling physical properties

2.1. GREEN SYNTHESIS OF NANOPARTICLES

The green synthesis approach provides a more straightforward, convenient, less energy-demanding and environmentally friendly option, minimizing the reliance on harmful substances while optimizing operational effectiveness. Three primary categories of green synthesis exist: (i) use of yeast, fungi, actinomycetes and bacteria; (ii) utilizing templates such as membranes, viral DNA, and diatoms; and (iii) harnessing plants and their extracts (Fig. 2) [23].

The production of NPs, particularly from plant extracts or organic sources, has attracted significant attention because it is highly capable and has a large variety of bioactive-reducing metabolites. Plants, known for their resistance to metal toxicity compared to bacteria and algae, offer a more environmentally friendly alternative for synthesizing NPs [24, 25]. Different components of plants, including, fruit, leaves, latex, seeds, stems, and roots are utilized for synthesizing NPs [26]. The green methodology that utilizes plant extracts for nanoparticle manufacturing is a biological approach that minimizes hazardous by-products and eliminates the need for chemical agents or toxic solvents that are employed in Conventional methods (Chemical and Physical methods) [27].

The Plant extracts are high in bioactive substances such polyphenols, flavonoids, alkaloids, terpenoids, saponins, proteins, and carbohydrates. By acting as stabilizing and reducing agents, these compounds improve biocompatibility, inhibit agglomeration and are used in the environmentally friendly manufacturing of NPs [28]. Alkaloids and terpenoids promote nucleation and surface functionalization [29], whereas polyphenols and flavonoids help with metal ion reduction and capping [30]. Proteins and saponins increase stability and dispersion [31], while carbohydrate increases solubility [32]. By reducing harmful by products [33, 34], this environmentally friendly method provides a viable substitute for traditional chemical synthesis.

By using extracts, several kinds of metallic NPs were synthesized, like Copper oxide (CuO) NPs [35], Cerium oxide (CeO₂) NPs [36], Palladium (Pd) NPs [37], Silver (Ag) NPs [38], Zinc oxide (ZnO) NPs [39], and Gold(Au) NPs [40]. ZnO NPs are unique among other metal oxides because of their abundance, stability, electric conductivity, and optical transparency [41].

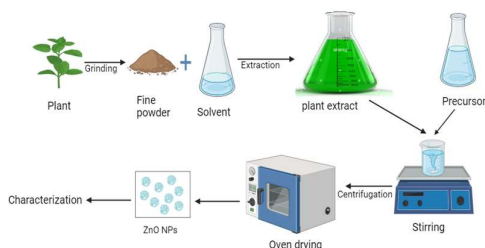


Fig. (2). Synthesizing Plant extract loaded ZnO NPs

3. CHARACTERIZATION OF NANOPARTICLES

Characterizing NPs is a pivotal process in comprehending their characteristics, guaranteeing their excellence, and establishing their appropriateness for diverse applications. Various analytical methods are utilized for this purpose. The following are some techniques [42].

- Assessing morphology and topography involves the use of Scanning Electron Microscopy (SEM) as well as Transmission Electron Microscopy (TEM) to evaluate dimensions, configuration, distribution, and grouping of NPs. SEM is especially beneficial for thorough surface analysis, offering high-resolution visuals of nano as well as micro-sized structures by utilizing electron beams. Its capability to penetrate deeper into surfaces and offer high magnification renders SEM images beneficial for evaluating surface topology of NPs based on their electron density. Dynamic Light Scattering (DLS) is employed for examining dimensions and dispersion of NPs. Additionally, the surface area of NPs is analysed by Brunauer Emmett Teller (BET), while Barrett Joyner Halenda (BJH) model determines particle pore size.
- Structural & Chemical characterization- Crystallinity of particles determined by X-ray diffraction (XRD). The Debye-Scherrer equation is employed to approximate the size of NPs.

$$D = \frac{k\lambda}{\beta \cos \theta}$$

In this context, wavelength of the x-ray is represented by λ , β denotes full width at half maximum of diffraction peak, Bragg angle is denoted by θ , and d indicates the size of NPs in nanometer (nm). Scherrer constant (0.9) is represented by k in this equation.

- Fourier-transform infrared (FTIR) spectroscopy- Examining the relationship between zinc precursors and plant extracts can assist in identifying functional groups in charge of reduction process. According

to FTIR analysis, extracts that contain functional groups including C=C, C-N, C-H, C=O, and N-H function as effective in the synthesis of NPs.

- Optical characterization- The absorption, reflectance, and band gap of NPs is determined by UV-Vis spectroscopy. Synthesized NPs are subjected to scanning within the ultraviolet (UV) range of the electromagnetic spectrum, usually covering a wavelength range from 200 to 700 nm. Moreover, diffuse reflectance spectroscopy (DRS) is utilized to evaluate the photo activity and electrical conductivity of NPs.

4. APPLICATIONS OF PLANT EXTRACT-BASED ZnO NPs

As previously discussed various metallic NPs synthesized using plant extract ZnO NPs, silver NPs, CuO NPs, and cerium oxide NPs offer a more promising approach to managing diabetes with fewer side effects. ZnO NPs exhibit diverse biological properties, including antimicrobial, antitumor, antioxidant, antifungal, antiviral, anti-inflammatory, wound healing, and anti-diabetic properties [43].

4.1. AN OVERVIEW OF ZnO NPs AS ANTIDIABETIC

Over 300 enzymes in the body are activated by zinc, a vital metal that is involved in many metabolic processes, including the metabolism of glucose [44]. Zinc enhances glucose consumption by stimulating hepatic glycogenesis via the insulin pathways [45]. Supplementing with zinc helps diabetic humans and animals maintain glycaemia control [45, 46].

ZnO NPs are promising delivery vehicles for zinc that may be used to treat diabetic mellitus (DM). Because of their small size, they can be absorbed by cells, interacting with biomolecules and triggering specific biological reactions [47]. In numerous studies ZnO NPs have been shown to decrease blood glucose level in diabetic animals [48-51]. One study elaborated the decrease in blood glucose level in a concentration- and time-dependent manner. When ZnO NPs (1-10 mg/kg/day) were given orally to diabetic rats for 56 days [52].

Pancreatic dysfunction and damage play a crucial role in the onset and progression of diabetes mellitus (DM), as the pancreas are responsible for regulation of glucose levels by production of insulin [53]. Pancreatic β cells contain several zinc transporters, including zinc transporter 8, which is important for insulin secretion [54]. Apart from its function in the production, preservation, and release of insulin it is also recognized for its role in

preserving of structural integrity of insulin [55]. Some study demonstrates the decreased histological alterations in diabetic rat pancreas, after administration of oral ZnO NPs (10 mg/kg/day) for 4 weeks, either by itself or in combination with vildagliptin (10 mg/kg/day) for 7 weeks [56, 57]. Furthermore, it was found that ZnO NPs (1–10 µg/ml) increased the proliferation of insulin-secreting RIN-5F cells in a dose-dependent manner after 24-hour incubation [58].

Another mechanism for ZnO NPs to lower blood glucose level is to improve insulin regulation in diabetes models [59]. Glucose transporter 2 (GLUT2) functions as glucose sensor in pancreatic β-cells and control the release of insulin [60]. According to studies conducted, a 24-hour treatment with ZnO NPs (1–10 µg/ml), which is comparable to 0.1 IU/ml insulin, increased GLUT4 translocation and glucose uptake in rat L6 myoblasts and mouse 3T3-L1 adipocytes [61].

Enzymes are essential for the management of diabetes as they control the metabolism of carbohydrates and the absorption of glucose. Postprandial blood glucose levels can be managed by inhibiting important enzymes such as α-amylase and α-glucosidase. ZnO-NPs successfully inhibited α-amylase from human saliva and the pig pancreas, according to research on enzyme inhibition [62, 63]. Furthermore, ZnO-NPs decreased α-glucosidase activity in the colon (98% suppression) and pancreas (21% inhibition) of mice. Interestingly, they had a marginally stronger inhibitory impact on intestinal glucosidase than the common antidiabetic medication acarbose [64].

Protein tyrosine phosphatase 1B (PTP1B) as a key negative regulators of the insulin signalling pathway, plays a crucial role in management of type 2 diabetes mellitus (T2DM) [65]. It was found that Inhibition of PTP1B enhances glucose metabolism and insulin sensitivity by prolonging and insulin signalling. One study revealed a 1.5-fold enhancement in PTP1B phosphorylation by deactivating it in HepG2 cells by administration of ZnO NPs at 10 µg/ml [61]. Thus, by above specific mechanisms ZnO NPs can demonstrate potential role in improving insulin sensitivity and glucose utilization, addressing diabetes-related complication (Fig. 3).

The increasing focus on environmentally friendly methods for synthesizing ZnO NPs, alongside their prospective uses in diabetes management through diverse mechanisms, underscores their attractiveness for review. Thus, this review seeks to offer detailed insights into plant extract-based green synthesis of ZnO NPs, specifically exploring their anti-diabetic properties as reported in recent literature. The article presents a thorough examination of ZnO NPs synthesis utilizing various plant extracts, their

characterization, and their application in diabetes management through various approaches.

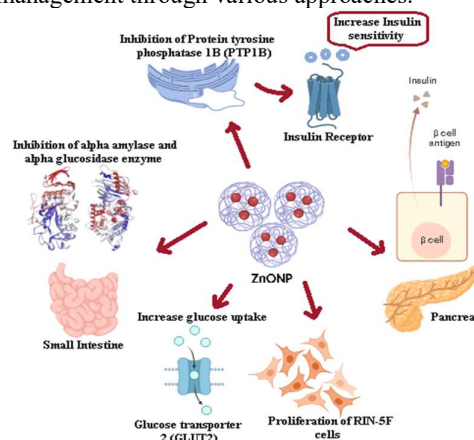


Fig. (3). Schematic Representation of ZnO NP's role in Diabetes Management

4.1.1. *Helichrysum cymosum* shoots extracts ZnO nanoparticles

Nkemzi et al. carried out synthesis of ZnO NPs using aqueous extract of *Helichrysum cymosum*. Zinc nitrate hydrate was used as a precursor for the synthesis. Different analytical methods, such as UV–Vis spectroscopy, SEM-EDX, XRD, TEM, and zeta potential were utilised to characterise the NPs. The TEM and XRD analysis revealed a spherical structure of nanoparticle, with an average dimension of 28–58.3 nm. The zeta potential evaluation indicated the stability of ZnO NPs. The toxicity studies revealed the cytotoxic effect at higher concentration range. There was a significant increase in the inhibitions of alpha-glucosidase enzyme indicating beneficial antidiabetic effects [66].

4.1.2. Propolis extract ZnO nanoparticles

The propolis methanolic extract was used to synthesize ZnO NPs in the research conducted Da et al. using zinc nitrate hexahydrate as a precursor. The synthesized ZnO NPs was characterised to have a hexagonal wurtzite shape with a particle size ranging from 30–50 nm and zeta potential of -60.567 mV. The FTIR analyses also confirmed the role of phytoconstituents in propolis methanolic extract for stabilizing NPs. Obtained Pro-ZnO NPs were proven as NPs with. The in vitro assays confirmed the α-amylase and α-glucosidase inhibitory activity with IC₅₀ of 43.57 mg/mL and 40.69 mg/mL respectively, significant as compared to standard Metformin [67].

4.1.3. *Silybum marianum* L. seed extracts ZnO nanoparticles

Mohammadi et al. employed a microwave-assisted method to synthesize ZnO NPs, utilizing an aqueous extract of *S. marianum* L. Seeds using zinc nitrate.

Methods were utilized to examine the shape, crystalline structure, chemical makeup, surface features, thermal behaviour, and optical

characteristics of the produced NPs. These techniques encompassed XRD, SEM, TEM, EDX, FT-IR, TGA, and UV-Vis spectroscopy. NPs exhibited diffraction peaks indicative of a hexagonal crystalline structure known as wurtzite, with a size of 40 nm. EDX detected the presence of elements such as zinc (Zn) and oxygen (O), suggesting robust bonding between ZnO NPs and organic molecules. The possible anti-diabetic properties of ZnO NPs synthesized using *S. marianum* extract in diabetic rats were evidenced by reductions in fasting blood sugar (FBS) levels, enhancements in insulin levels as well as improved lipid profiles. These findings suggest promising therapeutic uses for managing hyperlipidemia [68].

4.1.4. *Vaccinium arctostaphylos* L. leaf extracts ZnO nanoparticles

Bayrami and colleagues outlined a method for producing ZnO NPs utilizing zinc nitrate sourced from an aqueous extract of *Vaccinium arctostaphylos* L. leaves, facilitated by ultrasonication. SEM and TEM analysis showed that NPs had a hexagonal wurtzite structure with a particle size of 40 nm. Additionally, Bayrami et al. illustrated the potential uses of these NPs in diabetes management. Their findings indicated improvements in diabetic rats, including reduced fasting blood sugar (FBS) levels, enhanced insulin levels, enhanced glucose transport, and beneficial alterations in lipid profiles, such as elevated HDL and reduced triglyceride levels [69].

4.1.5. *Momordica charantia* fruit extracts ZnO nanoparticles

In the conducted study by Kalakotla et al. ZnO NPs were synthesized using zinc nitrate and aqueous extract of *Momordica charantia*. The characteristics of these NPs such as crystalline structure, particle size, and functional groups, were thoroughly examined using various techniques such as SEM, XRD, particle size analysis, and FTIR spectroscopy. XRD affirmed hexagonal structure of NPs. SEM images depicted uniform and symmetrical morphological shapes with a size of 55.8 nm. Moreover, these NPs exhibited notable anti-diabetic properties, restoring insulin levels to baseline in rats treated with ZnO NPs compared to control ($p < 0.001$) [70].

4.1.6. *Quercus infectoria* galls extracts ZnO nanoparticles

An aqueous extract of *Quercus infectoria* was utilized by Jawahar and group for synthesizing ZnO NPs with zinc acetate as the precursor and sodium hydroxide to regulate pH. Furthermore, the NPs underwent characterization through XRD, SEM, TEM, and FT-IR analysis. XRD patterns revealed presence of a hexagonal wurtzite in synthesized ZnO NPs. The authors also demonstrated a dose-dependent increase in inhibitory activity of ZnO NPs from *Quercus infectoria*, against the α -amylase enzyme. The NPs

exhibited potent inhibitory effects on starch absorption, suggesting their potential as starch blockers compared to standard drugs like acarbose [71].

4.1.7. *Wattakaka volubilis* leaf extracts ZnO nanoparticles

Jeyabharathi et al. devised a method for producing ZnO NPs using *Wattakaka volubilis* leaf extract treated with zinc acetate, followed by centrifugation and sonication. In the present study, characterization via XRD, EDX analysis, FTIR, UV-Vis spectroscopy, and SEM confirmed ZnO NPs, showing a 16.79 nm crystallite size, peak at wavelength 291nm in UV spectroscopy and at 414.70 cm^{-1} in FTIR analysis. Evaluation of ZnO NPs on alloxan-induced zebrafish demonstrated significant reductions in glucose levels, with variations dependent on dosage and duration, indicating potential antihyperglycemic effects [72].

4.1.8. *Vaccinium arctostaphylos* L. fruit extracts ZnO nanoparticles

Bayrami et al. investigated hypoglycemic impact of ZnO NPs, produced by combining ethanolic extract of *Vaccinium arctostaphylos* L. and zinc nitrate. The characterization of synthesized NPs was conducted with the help of multiple techniques. Examination through XRD and SEM revealed a hexagonal crystalline structure with a particle size of 20nm. FT-IR analysis revealed bands for Zn-O and O-H stretching vibrations. At last, the authors concluded that significant decrease in fasting blood sugar levels, attributing it to ZnO NPs' insulin-like function, zinc's influence on glucose metabolism, and synergistic effects [73].

4.1.9. *Areca catechu* leaf extracts ZnO nanoparticles

The use of *Areca catechu* leaf extract in creating ZnO NPs by employing zinc nitrate as an oxidizing agent was investigated by Shwetha et al [74]. This resulted in the creation of milky white ZnO NPs. The authors verified that synthesized ZnO NPs demonstrated a hexagonal wurtzite arrangement, with crystallite size 29nm. Moreover, analysis using EDX verified elemental composition of NPs, revealed existence of zinc (Zn) and oxygen (O). Furthermore, the study investigated the influence of ZnO NPs on glucose uptake in yeast cells, indicating a potential antidiabetic effect within concentration range of 50-250 $\mu\text{g/mL}$.

4.1.10. *Myristica fragrans* fruit extracts ZnO nanoparticles

Faisal and group detailed production of ZnO NPs using extract derived from fruits of *Myristica fragrans* and zinc acetate. Different techniques for characterization, including TEM, FTIR spectroscopy, and SEM, were applied to analyze NPs. The TEM and SEM examinations verified that synthesized NPs exhibited an elliptical form, with crystallite size of 66nm. Additionally, FTIR analysis

was employed to confirm functional groups accountable for stabilizing and coating ZnO NPs. The study assessed inhibition of α -amylase as well as α -glucosidase enzymes by NP samples, demonstrating significant activity, with a maximum inhibition of 65.21 ± 0.49 for α -glucosidase enzyme and 73.23 ± 0.42 for α -amylase enzyme at the concentration $400\mu\text{g/mL}$ [75].

4.1.11. *Withania somnifera* leaf extracts ZnO nanoparticles

The utilization of *Ashwagandha*, also known as *Withania somnifera*, a versatile medicinal plant, for producing ZnO NPs, was investigated by Malaikozhundan et al. An aqueous solution was extracted and NPs were synthesized through a heat-induced reaction with zinc acetate. Several characterization techniques, such as HR-TEM, UV-vis spectroscopy, zeta analysis, EDX analysis, XRD, and SAED pattern were utilized. The successful synthesis of NPs was confirmed by UV-vis absorption peaks, which exhibited a prominent peak at 384 nm. XRD analysis identified a hexagonal structure in NPs, with a particle size of 15.6 nm. An elemental zinc composition of 88.06% was validated by EDX analysis. Zeta analysis revealed a zeta value of -12.14 mV. Significant anti-diabetic effects were demonstrated, with inhibition of α -glucosidase and α -amylase enzymes to 95% and 90% at a concentration $100\mu\text{g/mL}$ respectively, surpassing the positive control acarbose. The potential therapeutic implications of ZnO NPs derived from *Ashwagandha* were underscored by the study [76].

4.1.12. *Bambusa arundinacea* leaf extracts ZnO nanoparticles.

The synthesis of ZnO NPs utilizing ethanolic extract of *Bambusa arundinacea* was detailed by Jayarambabu et al. [77] employing a green approach involving the interaction of tannins, flavonoids, phenols, glycosides, and alkaloids with zinc acetate. SEM analysis confirmed agglomerated spherical ZnO NPs, while TEM analysis revealed spherical particles ranging from 7-20 nm. EDX analysis confirmed existence of zinc (Zn) as well as oxygen (O) elements, as well as atmospheric absorbed carbon (C), ensuring the purity of ZnO. XRD indicated a crystalline structure, and the zeta potential distribution of -27.4 mV suggested long-term stability. The NPs exhibited hepatoprotective effects against streptozotocin (STZ)-induced cell damage in liver segments and potential hypoglycemic effects by enhancing insulin secretion in islet β -cells, indicating anti-hyperglycemic activity through improved pancreatic insulin production.

4.1.12. *Elsholtzia blanda*. C leaf extracts ZnO nanoparticles

Maheo et al. elaborated on the chitosan-assisted synthesis of ZnO NPs utilizing *E. blanda* leaf extract and zinc nitrate. The NPs were

characterized with the help of multiple tools including FTIR spectroscopy, UV-vis spectroscopy, X-ray diffraction, SEM, EDX, and TEM, which revealed rod-shaped NPs with a particle size of 43nm. *In vitro* evaluation of anti-diabetic activity, particularly through the α -amylase enzyme inhibition assay, revealed significant inhibition (74%) by ZPCB at the maximum inhibitory concentration, with IC_{50} value of $14.46\mu\text{g/mL}$. The enhanced inhibitory potential of ZnO NPs was attributed to synergistic effect of chitosan as well as biomolecules extracted from leaves, emphasizing its promising role in diabetes management [78].

4.1.13. *Tridax procumbens* L. leaf extracts ZnO nanoparticles

The antidiabetic investigations of ZnO NPs significantly reductions in glucose levels in diabetic rats in a dose-dependent manner, surpassing effects of reference drug glibenclamide. Ahmed et al produced ZnO NPs using *Tridax procumbens* L. Leaf extract, employing double-distilled water and a magnetic stirrer. The extract, combined with zinc sulfate solution as a precursor, underwent characterization through UV-Vis spectroscopy, SEM imaging, FTIR analysis, zeta potential measurement, and DLS-based PSD (Particle size distribution). The results confirmed of ZnO NP synthesis with a peak absorbance at 380 nm and identified functional groups in the FTIR spectrum. A zeta potential of -26.5 mV indicated uniform distribution and potential long-term stability. SEM revealed spherical NPs with size of $75.8 \pm \text{nm}$. DLS showed uniformity with low polydispersity index (PDI) of 0.56 [79].

4.1.14. *Amygdalus scoparia* stem extracts nanoparticles

The extraction and synthesis of ZnO NPs using an aqueous extract of *Amygdalus scoparia* stem, zinc acetate, and a magnetic stirrer were outlined by Norouzi et al. Characterization methods, including UV-visible spectroscopy, SEM, TEM, EDX, and XRD, validated successful synthesis and provided insights into the shape, composition, and structure of NPs. UV-vis spectroscopy confirmed ZnO NP formation, showing peak absorption at 368 nm. SEM analysis unveiled primarily spherical ZnO NPs with a diameter of 29 nm, which was supported by TEM observations ranging from 10 to 60 nm. Presence of zinc and oxygen was indicated by EDX, accounting for 68.7% and 31.3% of the weight, respectively. XRD analysis verified a hexagonal wurtzite structure with a crystallite size of 19.14 nm. Both *A. scoparia* stem extract as well as synthesized zinc oxide NPs reduced blood glucose levels in diabetic rats, indicating potential anti-diabetic effects alongside increased insulin and beneficial gene expression [80].

Andrographis paniculata leaf extracts nanoparticles

Rajakumar investigated the extraction, synthesis, characterization, and antidiabetic uses of ZnO NPs obtained from *Andrographis paniculata* leaves [81]. The aqueous leaf extract facilitated ZnO NPs biosynthesis with a magnetic stirrer and zinc nitrate. TEM, SEM, EDX analysis, and XRD were utilized for characterization, confirmed hexagonal wurtzite structure of ZnO NPs, with a particle size of 13.8 nm. SEM showed spherical and hexagonal NPs with agglomeration, while TEM displayed oval, spherical, and hexagonal shapes sized around 57nm, confirming their nanocrystalline nature. ZnO NPs exhibited moderate α -amylase inhibition (IC₅₀: 121.42 μ g/mL), suggesting their potential in diabetes management by impacting glycogenolysis, gluconeogenesis, and glucagon secretion.

4.1.15. *Mussaenda frondosa* L. stem extracts nanoparticles

The study by Jayappa et al. 2020 presented a method for synthesizing ZnO NPs (ZnONPs) via solution combustion synthesis (SCS) with zinc nitrate and aqueous extract of *Mussaenda frondosa* L. By using XRD, EDX, SEM, DLS UV-Vis spectroscopy, and FTIR, NPs were characterized, confirming the hexagonal wurtzite crystal structure, with UV-Vis absorption spectra revealing a peak absorbance at 370 nm. SEM showed flat hexagonal formations with a particle size of 12nm, while presence of zinc and oxygen was affirmed by EDX spectra. FTIR spectra indicated bioreduction and stabilization roles of functional groups, with metallic ZnO stretching vibrations at 486 cm⁻¹. The synthesized NPs exhibited high stability (zeta potential: -25.4), suggesting potential for stable colloidal formation. Green-synthesized ZnO NPs showed promising antidiabetic properties by inhibiting key enzymes involved in carbohydrate hydrolysis, with an IC₅₀ value of 47.66 μ g/mL, indicating potential for managing postprandial hyperglycaemia [82].

4.1.16. *Urtica dioica* leaf extracts nanoparticles

An aqueous extract of *Urtica dioica* leaves was used for synthesis of ZnO NPs using a magnetic stirrer [83]. To form a complex with the extract, zinc nitrate was used, along with sodium hydroxide to maintain pH. The authors utilized a range of characterization techniques to assess the NPs, including XRD, FTIR, TEM, TGA, SEM, EDX, and UV-Vis DRS. XRD analysis of ZnO samples confirmed their wurtzite hexagonal crystalline structure. SEM and TEM analyses revealed a spherical nature of particles with a size of 60 nm. EDX analysis detected oxygen and zinc as common elements. FTIR analysis revealed a ZnO absorption peak at 555 cm⁻¹, confirming its presence. TGA analysis illustrated the thermal resilience of the ZnO extract, sustaining stability up to 600°C, characterized by two stages of weight loss: initial water evaporation and combustion of *Urtica dioica*

leaf extract. The study revealed that ZnO NPs exhibited insulin-mimicking effects and significantly lowered fasting blood sugar levels in diabetes-induced rats.

Table 2. Plant-Derived Zinc Oxide NPs: Eco-Friendly Synthesis and Applications

Plant & part used	Solvent used in extraction	Pre cursor	Method of ZnO NPs synthesis	Particle size & shape	Mechanism	Reference
<i>Helic hrysom cymosum</i> (shoot)	Water	Zinc Nitrate	Precipitation	28–58.3 nm	Inhibition of α -amylase and α -glucosidase enzyme	66
Propolis	Methanol	Zinc Nitrate	Magnetic stirring	30–50 nm	Inhibition of α -amylase and glucosidase enzyme	67
<i>Silybum marianum</i> (Seed)	Deionized water	Zinc Nitrate	Microwave-assisted	40nm & spherical	Improves insulin levels, decreases (FBS) fasting blood sugar levels	68

<i>Vaccinium arctostaphylos</i> (Leaf)	Double distilled water	Zinc Nitrate	Ultrasonic	40nm & spherical	Improves insulin levels, decreases FBS levels	73
<i>Momordica charantia</i> (Fruit)	Water	Zinc Nitrate	Microwave-assisted	55.8 nm & spherical	Improves insulin levels	70
<i>Quercus infectoria</i> (Galls)	Double distilled water	Zinc Acetate	Magnetic stirring	100 nm-200 nm & spherical	In-vitro (α -amylase inhibition)	71
<i>Wattakaka Volubilis</i> (Leaf)	Deionized water	Zinc Acetate	Precipitation	100 nm-200 nm & spherical	Reduces glucose levels	72
<i>Vaccinium arctostaphylos</i> (Fruit)	96% Ethanol	Zinc Nitrate	Microwave-assisted	20nm & spherical	Reduces FBS levels	73
<i>Areca catechu</i> (Leaf)	Water	Zinc Nitrate	Solution-combustion synthesis	29nm & spherical	increase in % inhibition of glucose uptake	74
<i>Myristica fragrans</i> (Fruit)	Distilled water	Zinc Acetate	Magnetic stirring	66nm & spherical	In vitro analysis of α -glucosidase and α -	75

					amylase inhibition	
<i>Withania somnifera</i> (Leaf)	Distilled water	Zinc Acetate	Stirrer-heater	15.6 nm & hexagonal	In vitro analysis of α -glucosidase and α -amylase inhibition	76
<i>Bambusa arundinacea</i> (Leaf)	60% Ethanol	Zinc Acetate	Magnetic stirring	20nm & spherical	Enhancing insulin secretion in islet β -cells	77
<i>Elsholtzia blanda</i> (Leaf)	Double distilled water	Zinc Nitrate	Magnetic stirring	43nm & Rod like	In-vitro (α -amylase inhibition)	78
<i>Tridax procumbens</i> (Leaf)	Double distilled water	Zinc sulfate	Magnetic stirring	75.8 nm & spherical	Reduces glucose levels	79
<i>Amygdalus scoparia</i> (Stem)	Distilled water	Zinc Acetate	Magnetic stirring	29nm & spherical	Improves insulin levels, decreases FBS level	80

					s	
<i>Andrographis paniculata</i> (Leaf)	Double distilled water	Zinc Nitrate	Magnetic stirring	57nm & spherical, hexagonal	In-vitro (α -amylase inhibition)	81
<i>Mussaenda Frondosa</i> (Stem)	Distilled water	Zinc Nitrate	Solution-combustion synthesis	12nm & hexagonal	In-vitro (α -glucosidase & α -amylase inhibition)	82
<i>Urtica dioica</i> (Leaf)	Distilled water	Zinc Nitrate	Magnetic stirring	60nm & spherical	Improves insulin levels, decreases FBS levels	83

5. TOXICITY ASSESSMENT OF ZINC OXIDE NANOPARTICLES: CHALLENGES AND PERSPECTIVES

Despite the use of ZnO NPs in a variety of commercial products, human exposure is growing. Several investigations have examined toxic effects of ZnO NPs in mammals through In-vitro and In-vivo studies. Within cells, NPs dissolve in lysosomes, resulting in cytotoxicity, oxidative stress, lipid peroxidation, and changes in mitochondrial membrane potential, destabilization of lysosomes, the release of inflammatory cytokines, DNA damage, and cell death [81]. The cytotoxicity of ZnO NPs was found to fluctuate depending on variables such as nanoparticle concentration, type of cells, and duration of exposure involved [84, 85].

Furthermore, Yousef et al. confirmed that ZnO NPs caused liver and kidney toxicity in male Wistar rats [86]. In another study, ZnO NPs and

their bulk counterpart in suspensions was assessed the impact of their acute oral toxicity at doses of 300 and 2000 mg/kg in healthy female Wistar rats. ZnO NPs produced more toxicological effect as compared to their bulk particles [87]. ZnO NPs were found to have low sub-chronic toxicity via inhalation in mice, with minimal pulmonary inflammation and cytotoxicity observed [88]. Even the ZnO NPs were also found to induce acute lung injury in rats that characterized by increased airway resistance, excessive inflammatory response and lung histological damage [89].

It was also reported that the inspiration of ZnO NPs leads to their entry in lungs, causing hazardous effects and inducing inflammatory responses due to their acidic nature [88]. The neurotoxicity study of the ZnO NPs showed interactions with neuronal cells, inducing mitochondrial impairment, cell death, and apoptosis in various neural cell types [89]. It has been noted that the NPs enter the brain via a variety of pathways, leading to oxidative stress, memory and learning impairment, and release of inflammatory cytokines [90]. Furthermore, Streit and team illustrated glial cell toxicity due to ZnO NPs' interaction with glial cells, which are essential for brain homeostasis and immune function [91].

However, oral administration in rats revealed more significant toxicological effects compared to bulk particles, including alterations in hematological and biochemical parameters and histopathological lesions in liver and kidney tissues [92, 93]. Intravenous and intraperitoneal administration in rats showed potential hepatotoxicity, with some anomalies in liver histology, ion content, and antioxidant systems [94]. Ecotoxicology assessments using *Artemia salina* and zebrafish demonstrated physical malformations and bioaccumulation, particularly in the gastrointestinal tract of zebrafish [95]. These studies highlight the importance of considering exposure route, dose, and model organism when assessing ZnO NP toxicity.

6. CHALLENGES IN THE COMMERCIALIZATION OF ZnO NPs.

The commercialization of ZnO NPs from laboratory to market faces various challenges. Green syntheses counter issues like batch-to-batch variability and specific synthesis conditions. The process involves extreme temperatures, prolonged reaction times, and inert atmospheres, making it complex and challenging to scale up. The heterogeneous size and irregular shapes of NPs synthesized from different plants further complicate matters [96]. Before using ZnO NPs, their safety needs to be thoroughly investigated, as they have been associated with hepatic, renal, neuronal, pulmonary, and reproductive toxicity [97]. Their entry into biological systems through dermal,

inhalation, and ingestion routes raises concerns, with factors like dose, size, physicochemical properties, and exposure duration influencing toxicity [98, 99]. It takes a lot of effort and time to get regulatory approval for novel NPs due to stringent safety, efficacy, and quality requirements. Transitioning from laboratory to large-scale production poses challenges in maintaining efficiency, cost-effectiveness, and product integrity. NPs may change over time, like aggregation or degradation, necessitating efforts to ensure their long-term stability as well as shelf-life for commercial [100]. The translation and commercialization of ZnO NPs necessitate a collaborative approach that involves scientists, regulators, and manufacturers, as well as comprehensive research, rigorous safety assessments, adherence to regulations, and efficient manufacturing protocols.

7. CONCLUSION

This review provides a comprehensive examination of ZnO NPs as potential agents to manage diabetes, focusing particularly on their eco-friendly synthesis utilizing plant extracts. Zinc, being an essential metal, plays crucial role in different physiological processes, like glucose metabolism, insulin regulation, and enzyme activation.

The environment friendly synthesis of ZnO NPs using plant extracts is a key highlight of this review. This approach not only promotes sustainability but also offers potential therapeutic benefits. Various plants have been used for green synthesis of ZnO NPs, and the review discusses their synthesis processes in detail. Additionally, emphasis is placed on characterizing these NPs and evaluating their therapeutic effects. Studies involving diverse plant extracts have shown promising outcomes, including enhanced insulin levels, lowered fasting blood sugar levels, and beneficial changes in lipid profiles, suggesting the potential of NPs in diabetes management.

However, despite promising results, translation of laboratory findings into practical applications faces several challenges. Regulatory approval, safety concerns, and scalability issues are among the hurdles that need to be addressed to bring ZnO NPs based anti-diabetic therapies to the market. Furthermore, the review explores the toxicological aspects of ZnO NPs, shedding light on their potential adverse effects on various organs like liver, lungs, and kidneys. Understanding toxicological profile of ZnO NPs is essential for ensuring their safety in therapeutic applications. In conclusion, the review emphasizes the need for a multidisciplinary approach to overcome challenges associated with translation of ZnO NPs into practical anti-diabetic therapies. Collaboration between researchers, clinicians, regulatory agencies, and manufacturers is crucial for

addressing safety concerns, obtaining regulatory approval, and scaling up production. By addressing these challenges collectively, ZnO NPs have potential to emerge as effective and sustainable therapies for managing diabetes.

AUTHOR CONTRIBUTION STATEMENT

RB: Conceived and designed the experiments, analyzed the data, wrote the paper, AS: wrote the paper; SC: provided facilities for experiments, Analysis tools or data.

COMPETING INTEREST STATEMENT

The authors declare no conflict of interest.

FUNDING

None

ACKNOWLEDGMENT

The authors are thankful to the Chairman and Principal, Dr. D.Y. Patil Institute of Pharmaceutical Science and Research, Pimpri, Pune, for providing excellent infrastructural facilities for undertaking this research work.

REFERENCES

- [1] Yadi, M.; Mostafavi, E.; Saleh, B.; Davaran, S.; Aliyeva, I.; Khalilov, R.; et al. Current developments in green synthesis of metallic nanoparticles using plant extracts: A review. *Artif. Cells Nanomed. Biotechnol.* 2018; 46 (3): 336–343. <https://doi.org/10.1080/21691401.2018.1427843>.
- [2] Li, Y.; Wu, T. Y.; Chen, S. M.; et al. Green synthesis and electrochemical characterizations of gold nanoparticles using leaf extract of *Magnolia kobus*. *Int. J. Sci. Res.* 2016; 5: 1073–12751.
- [3] Varadavenkatesan, T.; Vinayagam, R.; Selvaraj, R. Structural characterization of silver nanoparticles phyto-mediated by a plant waste, seed hull of *Vigna mungo* and their biological applications. *J. Mol. Struct.* 2017; 1147: 629–635.
- [4] Vadlapudi, V.; Kaladhar, D. Review: Green synthesis of silver and gold nanoparticles. *Middle East J. Sci. Res.* 2014; 19: 834–842.
- [5] Rafique, M.; Sadaf, I.; Rafique, M. S.; Tahir, M. B. A review on green synthesis of silver nanoparticles and their applications. *Artif. Cells Nanomed. Biotechnol.* 2017; 45 (7): 1272–1291. <https://doi.org/10.1080/21691401.2016.1256635>.
- [6] Daniel, M. C.; Astruc, D. Gold nanoparticles: Assembly, supramolecular chemistry, quantum-size-related properties, and applications toward biology, catalysis, and nanotechnology.

- Chem. Rev. 2004; 104: 293–346. <https://doi.org/10.1021/cr030698+>.
- [7] Ahmed, S.; Ahmad, M.; Swami, B. L.; et al. A review on plants extract mediated synthesis of silver nanoparticles for antimicrobial applications: A green expertise. *J. Adv. Res.* 2016; 7: 17–28. <https://doi.org/10.1016/j.jare.2015.10.008>.
- [8] Ataie, A.; Mali, A. Characteristics of barium hexaferrite nanocrystalline powders prepared by a sol-gel combustion method using inorganic agent. *J. Electroceram.* 2008; 21: 357–360.
- [9] Mostafavi, E.; Babaei, A.; Ataie, A. Synthesis of nano-structured $\text{La}_{0.6}\text{Sr}_{0.4}\text{Co}_{0.2}\text{Fe}_{0.8}\text{O}_3$ perovskite by co-precipitation method. *J. Ultrafine Grained Nanostruct. Mater.* 2015; 48: 45–52.
- [10] Lesani, P.; Babaei, A.; Ataie, A.; et al. Nanostructured MnCo_2O_4 synthesized via co-precipitation method for SOFC interconnect application. *Int. J. Hydrogen Energy* 2016; 41: 20640–20649. <https://doi.org/10.1016/j.ijhydene.2016.08.017>.
- [11] Ahmed, S.; Chaudhry, S. A.; Ikram, S. A review on biogenic synthesis of ZnO nanoparticles using plant extracts and microbes: A prospect towards green chemistry. *J. Photochem. Photobiol. B Biol.* 2017; 166: 272–284. <https://doi.org/10.1016/j.jphotobiol.2016.10.027>.
- [12] Thakkar, K. N.; Mhatre, S. S.; Parikh, R. Y. Biological synthesis of metallic nanoparticles. *Nanomedicine* 2016; 6: 257–262. <https://doi.org/10.1016/j.nano.2016.02.003>.
- [13] Smitha, S. L.; Nissamudeen, K. M.; Philip, D.; et al. Studies on surface plasmon resonance and photoluminescence of silver nanoparticles. *Spectrochim. Acta A Mol. Biomol. Spectrosc.* 2008; 71: 186–190. <https://doi.org/10.1016/j.saa.2008.03.048>.
- [14] Yu, D. G. Formation of colloidal silver nanoparticles stabilized by Na^+ -poly(γ -glutamic acid)-silver nitrate complex via chemical reduction process. *Colloids Surf. B Biointerfaces* 2007; 59:171–178. <https://doi.org/10.1016/j.colsurfb.2007.06.005>.
- [15] Ahmadi Shadmehri, A.; Namvar, F. A review on green synthesis, cytotoxicity mechanism and antibacterial activity of ZnO-NPs. *J. Res. Appl. Basic Med. Sci.* 2020; 6: 23–31.
- [16] Ul Haq, A. N.; Nadhman, A.; Ullah, I.; Mustafa, G.; Yasinzai, M.; Khan, I. Synthesis approaches of zinc oxide nanoparticles: The dilemma of ecotoxicity. *J. Nanomater.* 2017; 2017: 1–14.
- [17] Naraginti, S.; Li, Y. Preliminary investigation of catalytic, antioxidant, anticancer, and bactericidal activity of green synthesized silver and gold nanoparticles using *Actinidia deliciosa*. *J. Photochem. Photobiol. B Biol.* 2017; 170 :225–234. <https://doi.org/10.1016/j.jphotobiol.2017.03.009>.
- [18] Dhandapani, P.; Siddarth, A. S.; Kamalasekaran, S.; et al. Bio-approach: Ureolytic bacteria mediated synthesis of ZnO nanocrystals on cotton fabric and evaluation of their antibacterial properties. *Carbohydr. Polym.* 2014; 103: 448–455. <https://doi.org/10.1016/j.carbpol.2013.12.007>.
- [19] Harish, V.; et al. Cutting-edge advances in tailoring size, shape, and functionality of nanoparticles and nanostructures: A review. *J. Taiwan Inst. Chem. Eng.* 2023; 149: 105010.
- [20] DeSimone, J. M. Practical approaches to green solvents. *Science* 2002; 297: 799–803. <https://doi.org/10.1126/science.1073722>.
- [21] Gross, R. A.; Kalra, B. Biodegradable polymers for the environment. *Science* 2002; 297: 803–807. <https://doi.org/10.1126/science.1076192>.
- [22] Raveendran, P.; Fu, J.; Wallen, S. L. Completely "green" synthesis and stabilization of metal nanoparticles. *J. Am. Chem. Soc.* 2003; 125: 13940–13941. <https://doi.org/10.1021/ja0359839>.
- [23] Kumari, S.; Raturi, S.; Kulshrestha, S.; Chauhan, K.; Dhingra, S.; Andras, K.; et al. A comprehensive review on various techniques used for synthesizing nanoparticles. *J. Mater. Res. Technol.* 2023; 27: 1739–1763.
- [24] Rasheed, T.; Bilal, M.; Iqbal, H. M. N.; et al. Green biosynthesis of silver nanoparticles using leaves extract of *Artemisia vulgaris* and their potential biomedical applications. *Colloids Surf. B Biointerfaces* 2017; 158: 408–415. <https://doi.org/10.1016/j.colsurfb.2017.06.063>.
- [25] Pandey, S.; Mewada, A.; Thakur, M.; et al. Biogenic gold nanoparticles as flotillas to fire berberine hydrochloride using folic acid as molecular road map. *Mater. Sci. Eng. C* 2013; 33: 3716–3722. <https://doi.org/10.1016/j.msec.2013.01.050>.

- [26] Kharissova, O. V.; Dias, H. R.; Kharisov, B. I.; Perez, B. O.; Perez, V. M. J. The greener synthesis of nanoparticles. *Trends Biotechnol.* 2013; 31: 240–248.
- [27] Agarwal, H.; Kumar, S. V.; Rajeshkumar, S. A review on green synthesis of zinc oxide nanoparticles—An eco-friendly approach. *Resour. Technol.* 2017; 3 (4): 406–413. <https://doi.org/10.1016/j.reffit.2017.06.002>.
- [28] Kazemi, S.; Hosseingholian, A.; Gohari, S. D.; Feirahi, F.; Moammeri, F.; Mesbahian, G.; et al. Recent advances in green synthesized nanoparticles: From production to application. *Mater. Today Sustain.* 2023; 24: 100500. <https://doi.org/10.1016/j.mtsust.2023.100500>.
- [29] Ghosh, S.; Patil, S.; Ahire, M.; Kitture, R.; Gurav, D. D.; Jabgunde, A. M.; et al. *Gnidia glauca* flower extract mediated synthesis of gold nanoparticles and evaluation of its chemocatalytic potential. *J. Nanobiotechnol.* 2012; 10: 1–9. <https://doi.org/10.1186/1477-3155-10-17>.
- [30] Mittal, A. K.; Chisti, Y.; Banerjee, U. C. Synthesis of metallic nanoparticles using plant extracts. *Biotechnol. Adv.* 2013; 31 (2): 346–356. <https://doi.org/10.1016/j.biotechadv.2013.01.003>.
- [31] Kaviya, S.; Prasad, E. Sequential detection of Fe³⁺ and As³⁺ ions by naked eye through aggregation and disaggregation of biogenic gold nanoparticles. *Anal. Methods* 2015; 7 (1): 168–174. <https://doi.org/10.1039/C4AY01972A>.
- [32] Gholipour, B.; Shojaei, S.; Rostamnia, S.; Naimi-Jamal, M. R.; Kim, D.; Kavetsky, T.; et al. Metal-free nanostructured catalysts: Sustainable driving forces for organic transformations. *Green Chem.* 2021; 23 (17): 6223–6272. <https://doi.org/10.1039/D1GC02013A>.
- [33] Marstin, G.; Siram, K.; Maqbool, Q.; et al. Secondary metabolites in the green synthesis of metallic nanoparticles. *Materials* 2018; 11 (6): 940. <https://doi.org/10.3390/ma11060940>.
- [34] Zong, Y.; Li, Z.; Wang, X.; Ma, J.; Men, Y. Synthesis and high photocatalytic activity of Eu-doped ZnO nanoparticles. *Ceram. Int.* 2014; 40 (7): 10375–10382. <https://doi.org/10.1016/j.ceramint.2013.12.118>.
- [35] Reddy, K. R. Green synthesis, morphological and optical studies of CuO nanoparticles. *J. Mol. Struct.* 2017; 1150: 553–557. <https://doi.org/10.1016/j.molstruc.2017.06.065>.
- [36] Darroudi, M.; Hoseini, S. J.; Kazemi Oskuee, R.; et al. Food-directed synthesis of cerium oxide nanoparticles and their neurotoxicity effects. *Ceram. Int.* 2014; 40: 7425–7430. <https://doi.org/10.1016/j.ceramint.2014.02.105>.
- [37] Joudeh, N.; Saragliadis, A.; Koster, G.; Mikheenko, P.; Linke, D. Synthesis methods and applications of palladium nanoparticles: A review. *Front. Nanotechnol.* 2022; 4: 1–18.
- [38] Velmurugan, P.; Anbalagan, K.; Manosathyadevan, M.; et al. Green synthesis of silver and gold nanoparticles using *Zingiber officinale* root extract and antibacterial activity of silver nanoparticles against food pathogens. *Bioprocess Biosyst. Eng.* 2014; 37: 1935–1943. <https://doi.org/10.1007/s00449-014-1309-2>.
- [39] Dhanemozhi, A. C.; Rajeswari, V.; Sathyajothi, S. Green synthesis of zinc oxide nanoparticles using *Parthenium hysterophorus* leaf extract and evaluation of their antibacterial properties. *J. Biotechnol. Biomater.* 2017; 7 (3): 271–276. <https://doi.org/10.4172/2155-952X.1000319>.
- [40] Balalakshmi, C.; Gopinath, K.; Govindarajan, M.; et al. Green synthesis of gold nanoparticles using a cheap *Sphaeranthus indicus* extract: Impact on plant cells and the aquatic crustacean *Artemia nauplii*. *J. Photochem. Photobiol. B* 2017; 173: 598–605. <https://doi.org/10.1016/j.jphotobiol.2017.06.029>.
- [41] Tari, O.; Aronne, A.; Addonizio, M. L.; et al. Sol-gel synthesis of ZnO transparent and conductive films: A critical approach. *Sol. Energy Mater. Sol. Cells* 2012; 105: 179–186. <https://doi.org/10.1016/j.solmat.2012.04.017>.
- [42] Joudeh, N.; Linke, D. Nanoparticle classification, physicochemical properties, characterization, and applications: A comprehensive review for biologists. *J. Nanobiotechnol.* 2022; 20: 262. <https://doi.org/10.1186/s12951-022-01851-1>.
- [43] Hamed, R.; Obeid, R.; Abu-Huwaj, R. Plant-mediated green synthesis of zinc oxide nanoparticles: An insight into biomedical applications. *Nanotechnol. Rev.* 2023; 12 (1): 20230112. <https://doi.org/10.1515/ntrev-2023-0112>.

- [44] Haase, H.; Overbeck, S.; Rink, L. Zinc supplementation for the treatment or prevention of disease: Current status and future perspectives. *Exp. Gerontol.* 2008; 43 (5): 394–408. <https://doi.org/10.1016/j.exger.2008.01.004>.
- [45] De Carvalho, G. B.; Brandao-Lima, P. N.; Maia, C. S.; Barbosa, K. B.; Pires, L. V. Zinc's role in the glycemic control of patients with type 2 diabetes: A systematic review. *Biometals* 2017; 30: 151–162. <https://doi.org/10.1007/s10534-017-0009-7>.
- [46] Simon, S. F.; Taylor, C. G. Dietary zinc supplementation attenuates hyperglycemia in db/db mice. *Exp. Biol. Med.* 2001; 226 (1): 43–51.
- [47] Mosquera, J.; García, I.; Liz-Marzán, L. M. Cellular uptake of nanoparticles versus small molecules: A matter of size. *Acc. Chem. Res.* 2018; 51 (9): 2305–2313. <https://doi.org/10.1021/acs.accounts.8b00292>.
- [48] Alkaladi, A.; Abdelazim, A. M.; Afifi, M. Antidiabetic activity of zinc oxide and silver nanoparticles on streptozotocin-induced diabetic rats. *Int. J. Mol. Sci.* 2014; 15 (2): 2015–2023. <https://doi.org/10.3390/ijms15022015>.
- [49] Umrani, R. D.; Paknikar, K. M. Zinc oxide nanoparticles show antidiabetic activity in streptozotocin-induced type 1 and 2 diabetic rats. *Nanomedicine* 2014; 9 (1): 89–104. <https://doi.org/10.2217/nmm.13.191>.
- [50] Amiri Dehkordi, R. A. F.; Heidarnejad, M. S.; Dehkordi, M. J. Effect of the zinc oxide nanoparticles and thiamine for the management of diabetes in alloxan-induced mice: A stereological and biochemical study. *Biol. Trace Elem. Res.* 2018; 181 (2): 258–264. <https://doi.org/10.1007/s12011-017-1045-3>.
- [51] Bayrami, A.; Parvinroo, S.; Habibi-Yangjeh, A.; Pouran, S. R. Bio-extract-mediated ZnO nanoparticles: Microwave-assisted synthesis, characterization and antidiabetic activity evaluation. *Artif. Cells Nanomed. Biotechnol.* 2018; 46 (5): 730–739. <https://doi.org/10.1080/21691401.2017.1345936>.
- [52] Nazarizadeh, A.; Asri-Rezaie, S. Comparative study of antidiabetic activity and oxidative stress induced by zinc oxide nanoparticles and zinc sulfate in diabetic rats. *AAPS PharmSciTech* 2016; 17 (4): 834–843. <https://doi.org/10.1208/s12249-015-0414-2>.
- [53] Gerber, P. A.; Rutter, G. A. The role of oxidative stress and hypoxia in pancreatic beta cell dysfunction in diabetes mellitus. *Antioxid. Redox Signal.* 2017; 26 (10): 501–518. <https://doi.org/10.1089/ars.2016.6755>.
- [54] Rungby, J. Zinc, zinc transporters and diabetes. *Diabetologia* 2010; 53 (8): 1549–1551. <https://doi.org/10.1007/s00125-010-1765-7>.
- [55] Sun, Q.; van Dam, R. M.; Willett, W. C.; Hu, F. B. Prospective study of zinc intake and risk of type 2 diabetes in women. *Diabetes Care* 2009; 32 (4): 629–634. <https://doi.org/10.2337/dc08-1825>.
- [56] Wahba, N. S.; Shaban, S. F.; Kattaia, A. A.; Kandeel, S. A. Efficacy of zinc oxide nanoparticles in attenuating pancreatic damage in a rat model of streptozotocin-induced diabetes. *Ultrastruct. Pathol.* 2016; 40 (6): 358–373. <https://doi.org/10.1080/01913123.2016.1216752>.
- [57] El-Gharbawy, R. M.; Emara, A. M.; Abu-Risha, S. E. Zinc oxide nanoparticles and a standard antidiabetic drug restore the function and structure of beta cells in type 2 diabetes. *Biomed. Pharmacother.* 2016; 84: 810–820. <https://doi.org/10.1016/j.biopha.2016.10.006>.
- [58] Asani, S. C.; Umrani, R. D.; Paknikar, K. M. In vitro studies on the pleotropic antidiabetic effects of zinc oxide nanoparticles. *Nanomedicine* 2016; 11 (14): 1671–1687. <https://doi.org/10.2217/nmm-2016-0010>.
- [59] Röder, P. V.; Wu, B.; Liu, Y.; Han, W. Pancreatic regulation of glucose homeostasis. *Exp. Mol. Med.* 2016; 48 (3): e219. <https://doi.org/10.1038/emm.2016.6>.
- [60] Thorens, B. GLUT2, glucose sensing and glucose homeostasis. *Diabetologia* 2015; 58 (2): 221–232. <https://doi.org/10.1007/s00125-014-3451-1>.
- [61] Asani, S. C.; Umrani, R. D.; Paknikar, K. M. In vitro studies on the pleotropic antidiabetic effects of zinc oxide nanoparticles. *Nanomedicine* 2016; 11 (14): 1671–1687. <https://doi.org/10.2217/nmm-2016-0010>.
- [62] Daniel, J. A.; Devi, S. A. Inhibition of key digestive enzymes involved in glucose metabolism by biosynthesized zinc oxide nanoparticles from *Syzygium cumini* (L.): An in vitro and in silico approach.

- Pharmacogn. Mag. 2019; 15 (3): S502–S509.
https://doi.org/10.4103/pm.pm_350_18.
- [63] Shaik, F.; Kumar, A. ZnO nanoparticles and their acarbose-capped nanohybrids as inhibitors for human salivary amylase. *IET Nanobiotechnol.* 2017; 11 (3): 329–335. <https://doi.org/10.1049/iet-nbt.2016.0121>.
- [64] Kitture, R.; Chordiya, K.; Gaware, S.; Ghosh, S.; More, P. A.; Kulkarni, P.; Chopade, B. A.; Kale, S. N. ZnO nanoparticles-red sandalwood conjugate: A promising anti-diabetic agent. *Life Sci.* 2019; 239: 117011. <https://doi.org/10.1016/j.lfs.2019.117011>.
- [65] Teimouri, M.; Hosseini, H.; ArabSadeghabadi, Z.; Babaei-Khorzoughi, R.; Gorgani-Firuzjaee, S.; Meshkani, R. The role of protein tyrosine phosphatase 1B (PTP1B) in the pathogenesis of type 2 diabetes mellitus and its complications. *J. Physiol. Biochem.* 2022; 78 (2): 307–322. <https://doi.org/10.1007/s13105-021-00860-7>.
- [66] Nkemzi, A. Q.; Okaiyeto, K.; Oyenih, O.; et al. Antidiabetic, anti-inflammatory, antioxidant, and cytotoxicity potentials of green-synthesized zinc oxide nanoparticles using the aqueous extract of *Helichrysum cymosum*. *3 Biotech* 2024; 14: 291. <https://doi.org/10.1007/s13205-024-04125-0>.
- [67] DA, P. D.; Plashintania, D. R.; Putri, R. M.; Wibowo, I.; Ramli, Y.; Herdianto, S.; et al. Synthesis of zinc oxide nanoparticles using methanol propolis extract (Pro-ZnO NPs) as antidiabetic and antioxidant. *PLoS One* 2023; 18 (7): e0289125. <https://doi.org/10.1371/journal.pone.0289125>.
- [68] Mohammadi Arvanag, F.; Bayrami, A.; Habibi-Yangjeh, A.; Rahim Pouran, S. A comprehensive study on antidiabetic and antibacterial activities of ZnO nanoparticles biosynthesized using *Silybum marianum* L. seed extract. *Mater. Sci. Eng. C* 2019; 97: 397–405. <https://doi.org/10.1016/j.msec.2018.12.016>.
- [69] Bayrami, A.; Parvinroo, S.; Habibi-Yangjeh, A.; Rahim Pouran, S. Bio-extract-mediated ZnO nanoparticles: Microwave-assisted synthesis, characterization and antidiabetic activity evaluation. *Artif. Cells Nanomed. Biotechnol.* 2018; 46 (4): 730–739. <https://doi.org/10.1080/21691401.2018.1473759>.
- [70] Kalakotla, S.; Jayarambabu, N.; Mohan, G.; et al. A sub-acute oral toxicity analysis and comparative in vivo anti-diabetic activity of zinc oxide, cerium oxide, silver nanoparticles, and *Momordica charantia* in streptozotocin-induced diabetic Wistar rats. *RSC Adv.* 2017; 7: 37158–37167. <https://doi.org/10.1039/c7ra05927a>.
- [71] Jawahar, B.; Rajendran, A. Antidiabetic activity of green synthesized zinc oxide nanoparticles using *Quercus infectoria*. *Int. J. Zool. Investig.* 2021; 7 (2): 1009–1021. <https://doi.org/10.3390/ijzi7020032>.
- [72] Jeyabharathi, S.; Naveenkumar, S.; Chandramohan, S.; et al. Biological synthesis of zinc oxide nanoparticles from the plant extract, *Wattakaka volubilis* showed antimicrobial and antihyperglycemic effects. *J. King Saud Univ. Sci.* 2022; 34 (3): 1017–1024. <https://doi.org/10.1016/j.jksus.2021.05.012>.
- [73] Bayrami, A.; Alioghli, S.; Rahim Pouran, S.; et al. A facile ultrasonic-aided biosynthesis of ZnO nanoparticles using *Vaccinium arctostaphylos* L. leaf extract and its antidiabetic, antibacterial, and oxidative activity evaluation. *Ultrason. Sonochem.* 2019; 55: 57–66. <https://doi.org/10.1016/j.ultsonch.2019.03.019>.
- [74] Shwetha, U. R.; Latha, M. S.; Rajith Kumar, C. R.; et al. Facile synthesis of zinc oxide nanoparticles using novel *Areca catechu* leaves extract and their in vitro antidiabetic and anticancer studies. *J. Inorg. Organomet. Polym. Mater.* 2020; 30: 4876–4883. <https://doi.org/10.1007/s10904-020-01458-2>.
- [75] Faisal, S.; Jan, H.; Shah, S. A.; et al. Green synthesis of zinc oxide (ZnO) nanoparticles using aqueous fruit extracts of *Myristica fragrans*: Their characterizations and biological and environmental applications. *ACS Omega* 2021; 6 (14): 9709–9722. <https://doi.org/10.1021/acsomega.1c00793>.
- [76] Malaikozhundan, B.; Vinodhini, J.; Kalanjiam, M. A. R.; et al. High synergistic antibacterial, antibiofilm, antidiabetic, and antimetabolic activity of *Withania somnifera* leaf extract-assisted zinc oxide nanoparticles. *Bioprocess Biosyst. Eng.* 2020; 43 (9): 1533–1547. <https://doi.org/10.1007/s00449-020-02477-7>.
- [77] Jayarambabu, N.; Rao, T. V.; Kumar, R. R.; et al. Anti-hyperglycemic, pathogenic,

- and anticancer activities of Bambusa arundinacea-mediated zinc oxide nanoparticles. *Mater. Today Commun.* 2021; 26: 101772. <https://doi.org/10.1016/j.mtcomm.2021.101772>.
- [78] Maheo, A.; Vithiya, B. S.; Arul Prasad, T. A.; et al. Cytotoxic, antidiabetic, and antioxidant study of biogenically improvised *Elsholtzia blanda* and chitosan-assisted zinc oxide nanoparticles. *ACS Omega* 2022; 8: 3467–3478. <https://doi.org/10.1021/acsomega.2c07375>.
- [79] Ahmed, S. S.; Alqahtani, A. M.; Alqahtani, T.; et al. Green synthesis, characterizations of zinc oxide nanoparticles from aqueous leaf extract of *Tridax procumbens* Linn. and assessment of their anti-hyperglycemic activity in streptozotocin-induced diabetic rats. *Materials (Basel)* 2022; 15 (22): 8202. <https://doi.org/10.3390/ma15228202>.
- [80] Norouzi Jobie, F.; Ranjbar, M.; Hajizadeh Moghaddam, A.; Kiani, M. Green synthesis of zinc oxide nanoparticles using *Amygdalus scoparia* Spach stem bark extract and their applications as an alternative antimicrobial, anticancer, and antidiabetic agent. *Adv. Powder Technol.* 2021; 32 (6): 2043–2052. <https://doi.org/10.1016/j.apt.2021.04.009>.
- [81] Rajakumar, G.; Thiruvengadam, M.; Mydhili, G.; Gomathi, T.; Chung, I. M. Green approach for synthesis of zinc oxide nanoparticles from *Andrographis paniculata* leaf extract and evaluation of their antioxidant, anti-diabetic, and anti-inflammatory activities. *Bioprocess Biosyst. Eng.* 2018; 41 (1): 21–30. <https://doi.org/10.1007/s00449-017-1916-1>.
- [82] Jayappa, M. D.; Ramaiah, C. K.; Kumar, M. A. P.; et al. Green synthesis of zinc oxide nanoparticles from the leaf, stem, and in vitro grown callus of *Mussaenda frondosa* L.: Characterization and their applications. *Appl. Nanosci.* 2020; 10 (8): 3057–3074. <https://doi.org/10.1007/s13204-020-01353-2>.
- [83] Bayrami, A.; Haghgooeie, S.; Rahim Pouran, S.; Mohammadi Arvanag, F.; Habibi-Yangjeh, A. Synergistic antidiabetic activity of ZnO nanoparticles encompassed by *Urtica dioica* extract. *Adv. Powder Technol.* 2020; 31 (5): 2110–2118. <https://doi.org/10.1016/j.apt.2020.04.017>.
- [84] Saranya, S.; Vijayanarai, K.; Pavithra, S.; Raihana, N.; Kumanan, K. In vitro cytotoxicity of zinc oxide, iron oxide, and copper nanoparticles prepared by green synthesis. *Toxicol. Rep.* 2017; 4: 427–430. <https://doi.org/10.1016/j.toxrep.2017.06.007>.
- [85] Fernández-Bertólez, N.; Alba-González, A.; Touzani, A.; Ramos-Pan, L.; Méndez, J.; Reis, A. T.; Quelle-Regaldie, A.; Sánchez, L.; Folgueira, M.; Laffon, B.; Valdíglesias, V. Toxicity of zinc oxide nanoparticles: Cellular and behavioural effects. *Chemosphere* 2024; 363: 142993. <https://doi.org/10.1016/j.chemosphere.2024.142993>.
- [86] Yousef, M. I.; Mutar, T. F.; Kamel, M. A. E.-N. Hepato-renal toxicity of oral sub-chronic exposure to aluminum oxide and/or zinc oxide nanoparticles in rats. *Toxicol. Rep.* 2019; 6: 336–346. <https://doi.org/10.1016/j.toxrep.2019.06.006>.
- [87] Srivastav, A. K.; Kumar, M.; Ansari, N. G.; Jain, A. K.; Shankar, J.; Arjaria, N.; et al. A comprehensive toxicity study of zinc oxide nanoparticles versus their bulk in Wistar rats: Toxicity study of zinc oxide nanoparticles. *Hum. Exp. Toxicol.* 2016; 35 (12): 1286–1304. <https://doi.org/10.1177/0960327116663901>.
- [88] Adamcakova-Dodd, A.; Stebounova, L. V.; Kim, J. S.; Vorrink, S. U.; Ault, A. P.; O'Shaughnessy, P. T.; et al. Toxicity assessment of zinc oxide nanoparticles using sub-acute and sub-chronic murine inhalation models. *Part. Fibre Toxicol.* 2014; 11: 1–15. <https://doi.org/10.1186/s12989-014-0004-4>.
- [89] Zhuo, L. B.; Liu, Y. M.; Jiang, Y.; Yan, Z. Zinc oxide nanoparticles induce acute lung injury via oxidative stress-mediated mitochondrial damage and NLRP3 inflammasome activation: In vitro and in vivo studies. *Environ. Pollut.* 2024; 341: 122950. <https://doi.org/10.1016/j.envpol.2023.122950>.
- [90] Kao, Y. Y.; Cheng, T. J.; Yang, D. M.; Liang, Y. C.; Wang, C. S.; Chang, L. W. Demonstration of an olfactory bulb-brain translocation pathway for ZnO nanoparticles in rodent cells in vitro and in vivo. *J. Mol. Neurosci.* 2012; 48: 464–471. <https://doi.org/10.1007/s12031-012-9905-7>.
- [91] Tian, L.; Lin, B.; Wu, L.; Zheng, Y.; Peng, P.; Wang, J.; et al. Neurotoxicity induced

- by zinc oxide nanoparticles: Age-related differences and interaction. *Sci. Rep.* 2015; 5: 16117. <https://doi.org/10.1038/srep16117>.
- [92] Streit, W. J.; Xue, Q.-S. Life and death of microglia. *J. Neuroimmune Pharmacol.* 2009; 4: 371–379. <https://doi.org/10.1007/s11481-009-9180-2>.
- [93] Boamah, B.; Siciliano, S.; Hogan, N.; Hecker, M.; Hanson, M.; Campbell, P.; et al. Target organ toxicity in Sprague Dawley rats following oral exposure to complex groundwater mixture: Assessment of dose-response relationships using histopathological and biochemical alterations. *Regul. Toxicol. Pharmacol.* 2024; 154: 105744. <https://doi.org/10.1016/j.yrtph.2024.105744>.
- [94] Abouzeinab, N. S.; Kahil, N.; Fakhruddin, N.; Awad, R.; Khalil, M. I. Intraperitoneal hepato-renal toxicity of zinc oxide and nickel oxide nanoparticles in male rats: Biochemical, hematological and histopathological studies. *EXCLI J.* 2023; 22: 619–644. <https://doi.org/10.17179/excli2023-6237>.
- [95] Casiano-Muñiz, I. M.; Ortiz-Román, M. I.; Lorenzana-Vázquez, G.; Román-Velázquez, F. R. Synthesis, characterization, and ecotoxicology assessment of zinc oxide nanoparticles by in vivo models. *Nanomaterials (Basel)* 2024; 14 (3): 255. <https://doi.org/10.3390/nano14030255>.
- [96] Guan, Z.; Ying, S.; Ofoegbu, P. C.; Lin, W.; Wang, C.; Zhou, J. Green synthesis of nanoparticles: Current developments and limitations. *Environ. Technol. Innov.* 2022; 26: 102336. <https://doi.org/10.1016/j.eti.2022.102336>.
- [97] Singh, T. A.; Das, J.; Sil, P. C. Zinc oxide nanoparticles: A comprehensive review on its synthesis, anticancer and drug delivery applications as well as health risks. *Adv. Colloid Interface Sci.* 2020; 286: 102317. <https://doi.org/10.1016/j.cis.2020.102317>.
- [98] Verma, R.; Pathak, S.; Srivastava, A. K.; Singh, P.; Singh, J.; Singh, P.; et al. ZnO nanomaterials: Green synthesis, toxicity evaluation and new insights in biomedical applications. *J. Alloys Compd.* 2021; 876: 160175. <https://doi.org/10.1016/j.jallcom.2020.160175>.
- [99] Cheng, T. M.; Chu, H. Y.; Huang, H. M.; Lin, W. H.; Tsai, M. J.; Wang, C. C. Toxicologic concerns with current medical nanoparticles. *Int. J. Mol. Sci.* 2022; 23 (14): 7597. <https://doi.org/10.3390/ijms23147597>.
- [100] Martínez, R.; Poupard, M. F. N.; Álvarez, A.; Rodríguez-Pérez, M. A.; Jiménez, A. R.; Marquina, M.; et al. Nanoparticle behaviour and stability in biological environments. In *Nanoparticles for Biomedical Applications*; Elsevier: 2020; pp 5–18. <https://doi.org/10.1016/B978-0-12-819503-0.00002-0>.
- [101]