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NEEM-MEDIATED GREEN SYNTHESIS OF ZINC OXIDE NANOPARTICLES: THERAPEUTIC MECHANISMS, ENVIRONMENTAL UTILITY, AND CRITICAL RESEARCH FRONTIERS

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Abstract *Zinc oxide nanoparticles (ZnO NPs) have emerged at the forefront of nanomaterials chemistry, biomedicine, environmental engineering, and agricultural technology owing to their exceptional physicochemical and biological properties. Among the various synthetic approaches, biogenic fabrication using botanical extracts has gained significant momentum, with Azadirachta indica (neem) emerging as a particularly powerful phytochemical platform. This review critically synthesises five years of primary literature on neem-mediated ZnO NP synthesis and evaluates their applications in antimicrobial, anticancer, antidiabetic, antioxidant, wound healing, and photocatalytic contexts, demonstrating that neem-derived ZnO NPs exhibit a superior biological activity profile compared to chemically synthesised counterparts. Five high-priority knowledge gaps are identified and interrogated with actionable research recommendations to guide responsible scientific translation.*

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Introduction

Zinc oxide nanoparticles (ZnO NPs) are among the most extensively studied nanomaterials, with applications ranging from precision oncology to solar-driven wastewater treatment. This breadth stems from a convergence of favourable physicochemical properties: a direct bandgap of 3.37 eV enabling UV-range photocatalysis, an exciton binding energy of 60 meV permitting room-temperature excitonic emission, near-zero toxicity at physiological zinc concentrations, and exceptional amenability to morphological and surface engineering (Dey et al., 2025; Ansari et al., 2024).

Recent years have witnessed a significant expansion of ZnO NP applications into high-value biomedical domains — including antimicrobial activity against multidrug-resistant (MDR) bacteria, cancer immunotherapy, antidiabetic nanomedicine, and photodynamic oncology — in addition to established environmental applications. Phytochemical surface functionalisation through green synthesis has been demonstrated to confer biological performance superior to that of chemically synthesised counterparts (Jiang et al., 2023; Gupta et al., 2023; Chawla et al., 2024).

In this green synthesis context, Azadirachta indica (neem) has proven to be an exceptionally powerful botanical resource. The therapeutic legacy of neem derives from a chemically diverse phytome encompassing flavones, organic acids, limonoids (azadirachtin, nimbin), terpenoids, tannins, and phenolic acids. These phytochemicals not only mediate nanoparticle formation but also functionalise particle surfaces with bioactive molecules that synergistically amplify the intrinsic activity of ZnO, yielding nanomaterials with greater efficacy than either botanical extract or bare ZnO NPs alone (Choudhary et al., 2023; El-Beltagi et al., 2024). This review addresses the science of ZnO NPs with neem-mediated synthesis as its thematic centrepiece. Sections 2–3 explore physicochemical properties and synthetic approaches; Section 4 covers neem-ZnO NP synthesis, characterisation, and applications; Section 5 surveys the broader applications landscape; Section 6 addresses nanotoxicology; and Section 7 identifies five critical research gaps with actionable recommendations.

Physicochemical Architecture of ZnO Nanoparticles

Under standard thermodynamic conditions, ZnO crystallises in the non-centrosymmetric hexagonal wurtzite lattice, characterised by alternating planes of tetrahedrally coordinated Zn^{2+} and O^{2-} ions along the polar c-axis. This structural polarity is the origin of ZnO's piezoelectric behaviour, and the surface defect chemistry — encompassing oxygen vacancies, zinc interstitials, and antisite defects — governs the density of photocatalytic active sites and the photoluminescence characteristics.

Decreasing particle size elevates the surface-to-volume ratio and enhances surface reactivity. The bandgap of 3.37 eV restricts intrinsic photoexcitation to UV wavelengths; however, ZnO NPs self-assemble into diverse architectures — nanorods, nanowires, nanospheres, nanoflowers, nanocages, and nanobelts — each exposing distinct crystal facets with characteristic surface energies and catalytic

selectivities. Neem-mediated synthesis consistently yields spherical-to-hexagonal nanoparticles in the 15–70 nm range, with morphology sensitive to extract concentration, pH, reaction temperature, and calcination temperature (Ahmad et al., 2023; Ansari et al., 2024).

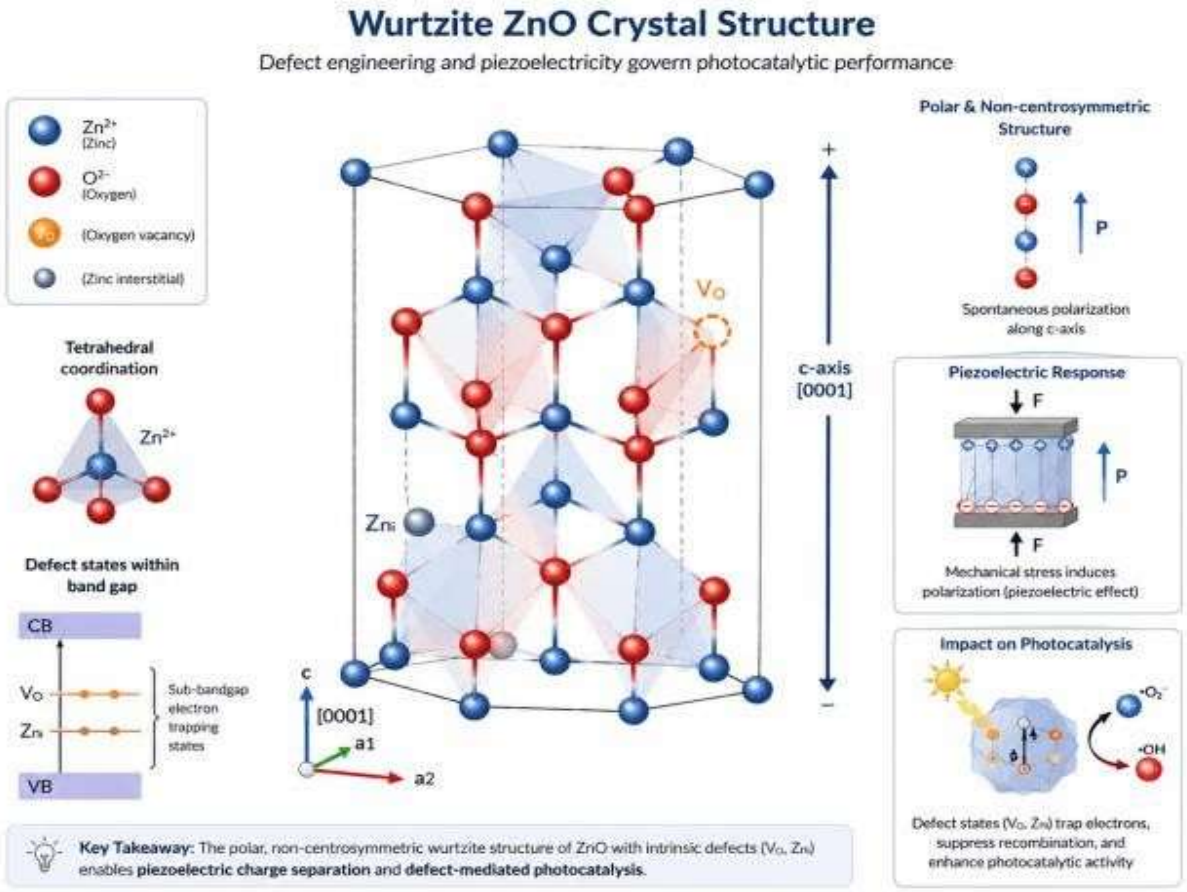

Figure 1. ZnO wurtzite crystal structure schematic. Zn^{2+} (blue) and O^{2-} (red) ions in tetrahedral coordination along the polar c-axis. Oxygen vacancies (Vo, orange) and zinc interstitials function as sub-bandgap electron trapping sites that modulate photocatalytic activity. The non-centrosymmetric structure drives piezoelectric behaviour (Original diagram)

Standard characterisation parameters include: XRD (phase identification, crystallite size via Scherrer equation), FTIR (surface phytochemical functional groups), SEM/FE-SEM/EDX (morphology and elemental composition), TEM/HRTEM (size and lattice fringe imaging), UV-Vis spectrophotometry (optical bandgap via Tauc plot), DLS (hydrodynamic diameter and zeta potential), XPS (surface oxidation states), and TGA (thermal stability). Multi-technique characterisation is now considered essential for high-impact publications in this field (Ahmad et al., 2023; Dey et al., 2025).

Synthetic Strategies for ZnO Nanoparticles

Chemical and Physical Routes

Principal chemical synthesis methods include co-precipitation, hydrothermal crystallisation, sol-gel processing, and chemical vapour deposition (CVD). Co-precipitation is low-cost and scalable; hydrothermal methods afford morphological control; sol-gel is well-suited to thin-film production; CVD and atomic layer deposition (ALD) deliver device-grade compositional precision. Common limitations include the use of hazardous reagents, generation of toxic by-products, and substantial energy consumption. Physical top-down techniques (ball milling, laser ablation, sputtering) yield high-purity nanoparticles but with poor morphological control and limited scalability (Dey et al., 2025; Jha et al., 2023).

Table 1. Comparative summary of common ZnO nanoparticle synthesis methods. Data consolidated from recent reports on chemical, physical, and biogenic routes

Method	Size (nm)	Scalability	Process Toxicity	Morphology Control	Cost	Key Refs.
Co-precipitation	50–140	High	Moderate	Low	Low	(Dey et al., 2025; Jha et al., 2023)
Hydrothermal	20–100	Moderate	Moderate	High	Moderate	(Dey et al., 2025; Vagena et al., 2024)

Sol–gel	10–80	Moderate	Moderate–High	Moderate	Moderate	(Choudhary et al., 2023)
Ball milling	50–500	High	Low	Very Low	Low	(Gulab et al., 2025)
Neem leaf (biogenic)	15–70	Moderate–High	Very Low	Moderate	Very Low	(El-Beltagi et al., 2024; Kapoor et al., 2024; Jeyaraj and Mary Saral, 2025; Jeeva et al., 2026; Halder et al., 2025; Saini et al., 2022; Tsegahun et al., 2025; Gemachu and Birhanu, 2024; Ajayan and Hebsur, 2020)
Other plant-biogenic	10–100	Moderate	Very Low	Moderate	Very Low	(Jha et al., 2023; Asif et al., 2023; Choudhary et al., 2023)

Plant-Mediated Biogenic Synthesis

Plant extract-based green synthesis exploits phytochemical molecules as reducing and capping agents to convert soluble zinc precursors into crystalline ZnO. The mechanistic sequence involves: (i) chelation of Zn^{2+} by phytochemical ligands; (ii) partial reduction generating amorphous zinc hydroxide intermediates; (iii) calcination converting intermediates to wurtzite ZnO; and (iv) final surface stabilisation by residual capping phytochemicals (Choudhary et al., 2023; Asif et al., 2023). Of all botanical sources reviewed in the recent literature, particles derived from Azadirachta indica exhibit the most favourable biological activity profile, a consequence of the remarkable phytochemical richness of neem tissues.

Neem (Azadirachta indica)-Mediated ZnO Nanoparticles

The Phytochemical Toolkit of Azadirachta indica

Azadirachta indica is native to the Indian subcontinent and cultivated throughout tropical and subtropical Asia, Africa, and South America. All plant parts — leaf, bark, seed, flower, fruit, and root — are rich in pharmacologically active secondary metabolites validated as antimicrobial, anti-inflammatory, anticancer, antidiabetic, and antioxidant agents in clinical and preclinical studies (El-Beltagi et al., 2024; Jha et al., 2023).

The phytochemicals principally involved in ZnO NP synthesis are: flavones (primary electron donors for Zn^{2+} reduction); organic acids (citric acid, ascorbic acid — pH buffering during nucleation); polyhydroxy limonoids (azadirachtin, nimbin, nimbolide surface capping and intrinsic anticancer/antimicrobial activity); phenolic acids (gallic acid, ellagic acid, tannic acid — antioxidant stabilisers); and enzymes facilitating enzymatic reduction pathways.

Synthesis Protocols: Leaves, Flowers, Bark, Seeds, and Peel

The standard neem leaf protocol involves adding 2–10 mL of neem leaf extract (6% w/v aqueous) to 1–4 mM zinc nitrate hexahydrate or zinc acetate dihydrate, with heating at 60–80 °C for 30–60 minutes under continuous stirring. Progressive nucleation is confirmed by a colour transition from colourless through pale yellow to deep yellow (Kapoor et al., 2024; Tsegahun et al., 2025).

The resulting precipitate is centrifuged, washed, dried, and calcined at 300–500 °C for 1–2 hours to yield phase-pure wurtzite ZnO NPs with zeta potentials exceeding ±30 mV. Optimal conditions are 60 °C, pH 8, and 4 hours reaction time. The diversity of available plant parts constitutes a synthesis toolbox of exceptional versatility, permitting modification of surface phytochemical composition while retaining the fundamental fabrication method. Seed- and bark-derived ZnO NPs (10–30 nm, XRD-confirmed) exhibit excellent combined antibacterial, photocatalytic, and supercapacitor performance, while flower-derived preparations demonstrate superior anticancer, DNA-binding, and antioxidant properties (Saini et al., 2022; Jeyaraj and Mary Saral, 2025).

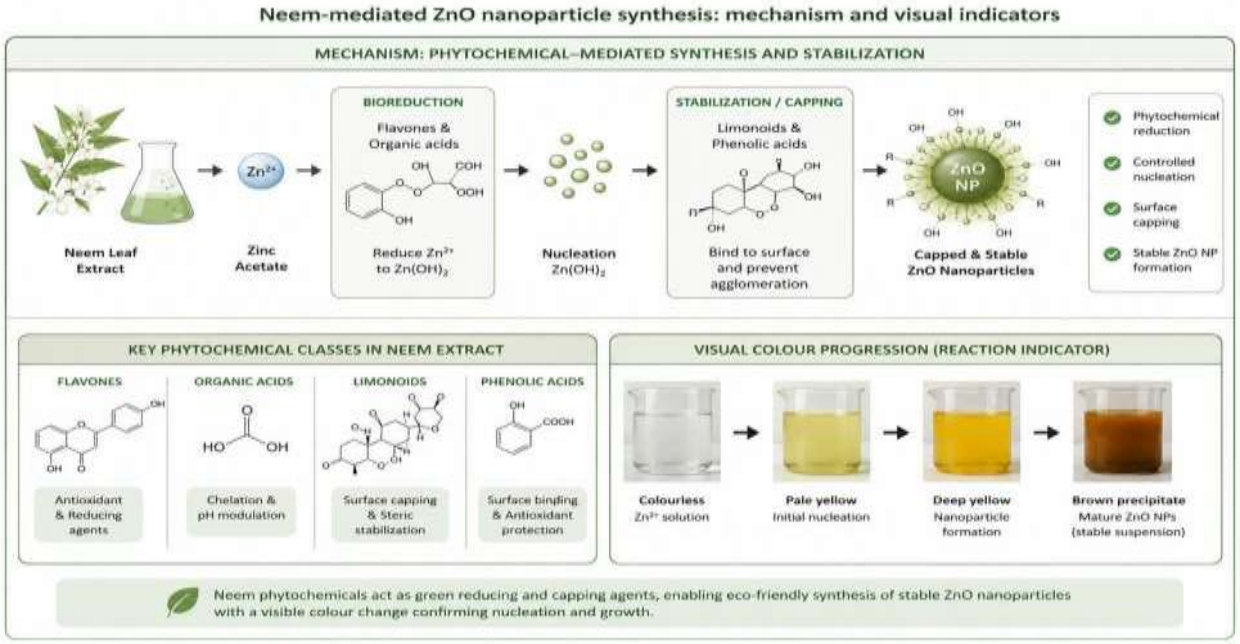

Figure 2. Neem-mediated ZnO NP synthesis mechanism. (Top) Phytochemical roles: flavones and organic acids reduce Zn^{2+}; limonoids and phenolic acids cap and stabilise the particle surface. (Bottom) Key phytochemical classes and visual colour progression from colourless to pale yellow to deep yellow to brown precipitate, confirming nanoparticle nucleation. (Original schematic.) The distinguishing feature of neem-ZnO NPs is their multi-component surface chemistry, which produces synergistic antibacterial, antifungal, anticancer, antidiabetic, and antioxidant effects exceeding those of either the extract or bare ZnO alone.

Table 2. Published studies on neem-mediated ZnO NP synthesis. Studies consistently confirm the quartzite phase and report particles largely in the 15-70 nm range across different plant parts

Plant Part	Precursor	Size (nm)	Morphology	Key Activity	References
Leaf extract	$Zn(NO_3)_2 \cdot 6H_2O$ (1 mM)	62.5	Spherical	Anticancer (HepG2, MCF-7), antibacterial	(El-Beltagi et al., 2024)
Leaf extract	Zinc acetate dihydrate	30–70	Hexagonal/spherical	Optimised synthesis; biomedical applications	(Kapoor et al., 2024)
Leaf extract	$Zn(NO_3)_2 \cdot 6H_2O$	UV peak 321 nm	Spherical	Antibacterial (E. coli, S. aureus)	(Tsegahun et al., 2025)
Leaf extract	Zinc acetate dihydrate	~25	Agglomerated	Antibacterial, antidiabetic (67.89%), antioxidant (53.77%)	(Jeeva et al., 2026)
Leaf extract	Zinc acetate	MIC 50 µg/mL	Reduced vs bare ZnO	Enhanced antibacterial (B. subtilis, S. aureus)	(Halder et al., 2025)
Leaf extract	$Zn(NO_3)_2 \cdot 6H_2O$	20–40	Spherical	DNA binding (CT-DNA), antibacterial	(Ajayan and Hebsur, 2020)
Leaf + Tulsi	Zinc precursor	100–300	Flake/flower-like	Characterisation baseline; agricultural	(Ajayan and Hebsur, 2020)
Seed & bark	Zinc acetate	10–30	Spherical/hexagonal	Antibacterial, photocatalytic, supercapacitor	(Saini et al., 2022)
Flower extract	Zinc acetate	30–60	Spherical	Anticancer, antibacterial, DNA-binding, antioxidant >80%	(Jeyaraj and Mary Saral, 2025)

Biological Applications of Neem-ZnO Nanoparticles

The biological application potential of neem-ZnO NPs encompasses antimicrobial, anticancer, antidiabetic, antioxidant, antifungal, and DNA-binding activities, operating through distinct but mechanistically interrelated pathways.

Antibacterial activity against E. coli, S. aureus, and B. subtilis yields inhibition zones of up to 19 mm at 50 µg/mL

— superior to comparable chemically synthesised ZnO NPs. The primary mechanistic triad of ROS-mediated membrane oxidation, Zn^{2+} ion-mediated membrane disruption, and direct nanoparticle-membrane contact is further augmented by the intrinsic antibacterial contribution of surface neem phytochemicals. Anti-biofilm activity against S. aureus and E. coli biofilm models has also been reported (El-Beltagi et al., 2024; Halder et al., 2025; Tsegahun et al., 2025).

Anticancer activity against HepG2, MCF-7, and A549 cell lines proceeds via ROS accumulation in the acidic tumour microenvironment, triggering caspase-3/9 activation, mitochondrial membrane depolarisation, and p53-mediated apoptosis. Consistently lower IC_{50} values for neem-ZnO NPs compared to chemically synthesised ZnO NPs or neem extract alone provide strong evidence for phytochemical synergy. pH-dependent Zn^{2+} dissolution in the acidic tumour microenvironment is proposed as the basis for cancer-selectivity observed across multiple studies (El-Beltagi et al., 2024; Jeyaraj and Mary Saral, 2025; Li et al., 2024).

Antidiabetic activity is demonstrated by glucose uptake inhibition (67.89%) and α-amylase inhibitory activity (63.03%), representing mechanistically relevant surrogates for glycaemic control in type-2 diabetes. These values exceed those of CuO and NiO NPs synthesised from the same botanical source. Antioxidant activity, assessed by DPPH radical scavenging, reaches 53.77% for leaf-derived preparations and exceeds 80% for flower extract-derived NPs (Jeeva et al., 2026; Jeyaraj and Mary Saral, 2025).

Table 3. Synopsis of reported biological activities of neem-mediated ZnO NPs. Concentration-dependent values vary with the target model and particle physicochemistry

Biological Activity	Target / Model	Effective Dose	Reported Outcome	References
Antibacterial	E. coli, S. aureus, B. subtilis	50–400 µg/mL	Inhibition zones 14–19 mm; anti-biofilm confirmed	(El-Beltagi et al., 2024; Jeeva et al., 2026; Halder et al., 2025; Tsegahun et al., 2025)
Anticancer	HepG2, MCF-7, A549	IC_{50} 15–60 µg/mL	Caspase-3/9 apoptosis; ROS-mediated; superior to chemical ZnO	(El-Beltagi et al., 2024; Jeyaraj and Mary Saral, 2025)
Antidiabetic	α-amylase; yeast glucose uptake	1–10 mg/mL	67.89% glucose uptake inhibition; 63.03% α-amylase inhibition	(Jeeva et al., 2026)
Antioxidant	DPPH radical scavenging	Conc.-dependent	53.77% DPPH scavenging; >80% inhibition (flower extract)	(Jeyaraj and Mary Saral, 2025; Jeeva et al., 2026)
Antifungal	C. gloeosporioides, A. alstroemeriae	5–10 mg/mL	Significant growth inhibition at 10 mg/mL	(Jeeva et al., 2026)
Photocatalysis	Methylene blue, Congo red	25–100 mg/L	>95% dye degradation in <120 min solar irradiation; outperformed CuO and NiO	(Gemachu and Birhanu, 2024)
DNA binding	Calf-thymus DNA (CT-DNA)	Spectroscopic	Groove-binding mode confirmed by CD spectroscopy	(Jeyaraj and Mary Saral, 2025)
Heavy metal removal	Pb^{2+} from aqueous solution	Contact time-dep.	Efficient Pb^{2+} removal; 8.5 nm pseudo-spherical NPs (Rietveld XRD)	(Gulab et al., 2025)

Broader Application Landscape of ZnO-Based Nanoparticles

Antimicrobial and Antiviral Applications

The three-mechanism killing model (ROS generation, Zn^{2+} ion release, direct membrane contact) extends across all morphologies, surface functionalisations, and particle sizes. MDR pathogens — MRSA, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Acinetobacter baumannii — have all been targeted, with MICs in the therapeutically achievable range for topical applications (Nan et al., 2024; Vagena et al., 2024). Ag-decorated ZnO nanocomposites demonstrate enhanced antibacterial activity (MIC 62.5 µg/mL vs. E. coli) attributable to localised surface plasmon resonance (LSPR)-enhanced charge separation. Antiviral activity of Ag-ZnO nanocomposites against coronavirus-family viruses via zinc ion interference with viral proteases represents an emerging mechanistic frontier (Al-Aaraji et al., 2025).

Oncology: Drug Delivery, PDT, and Targeted Nanomedicine

ZnO NPs loaded with doxorubicin, paclitaxel, or gemcitabine function as pH-responsive drug carriers exhibiting enhanced tumour spheroid penetration and cancer-selective cytotoxicity. Surface functionalisation with folate receptors, HER2 antibodies, and transferrin receptors defines the frontier of targeted ZnO NP nanomedicine (Gupta et al., 2023; Chawla et al., 2024).

Photodynamic therapy (PDT) exploiting ZnO NP-generated ROS under UV irradiation is constrained by the limited tissue penetration of UV light; upconversion or plasmonic coupling to NIR wavelengths represents the most promising unrealised advance in this area.

Photocatalysis and Doped/Composite ZnO Systems

Pristine ZnO NPs utilise approximately 4% of the solar spectrum. Metal doping (Ag, Ce, Co, Fe, Al, Mg) extends the absorption edge into the visible range; coupling with reduced graphene oxide (rGO) suppresses charge carrier recombination; and heterojunction architectures (CuO, TiO_2, g-C_3N_4, $BiVO_4$) establish interfacial electric fields promoting charge separation (Mohd Yusof et al., 2023; Alaizeri et al., 2026).

Al-doped ZnO/rGO nanocomposites achieve 95–99% photocatalytic and anticancer efficiency after 60–120 minutes of illumination. Ternary systems such as ZnO-MgO-Mn_2O_3 synthesised by Ocimum basilicum seed extract achieve 93% and 95% efficiency after 60 and 120 minutes of illumination, respectively (Alaizeri et al., 2026; Dananjaya et al., 2024).

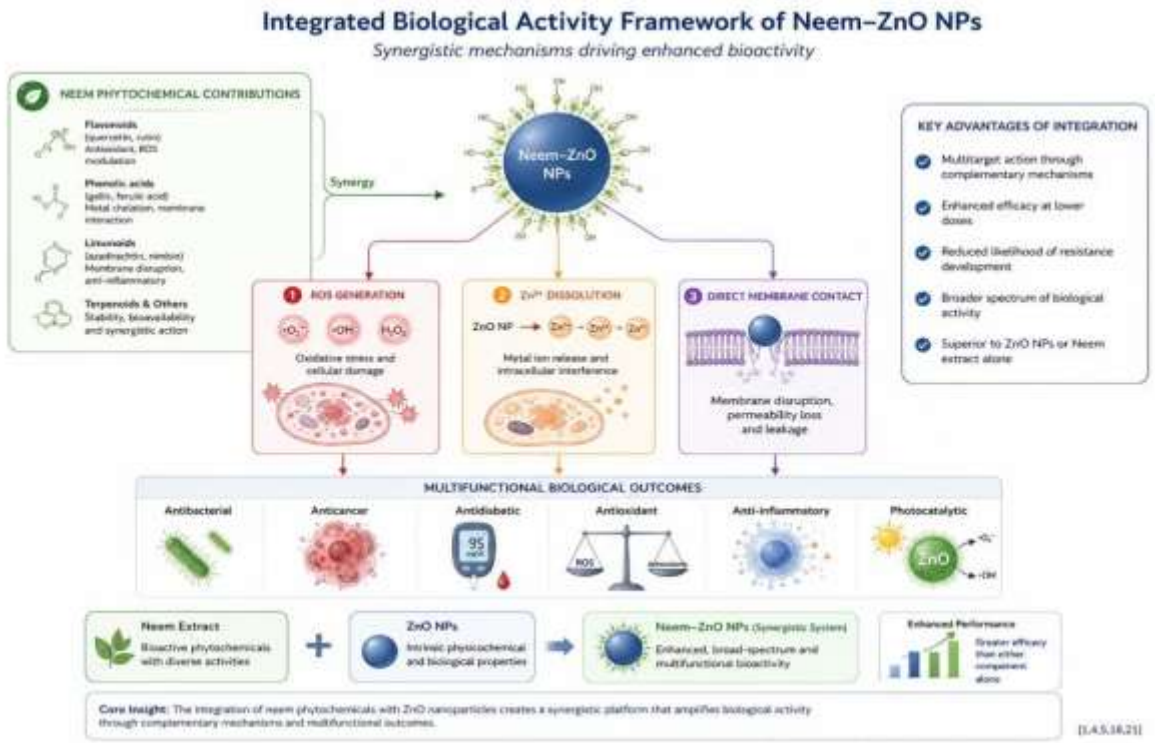

Figure 3. Integrated biological activity framework of neem-ZnO NPs. Central nanoparticle (blue) generates three primary mechanisms — ROS generation, Zn^{2+} dissolution, and direct membrane contact — amplified by synergistic neem phytochemical contributions (green box), producing multifunctional outcomes superior to either ZnO or neem extract alone (Original schematic)

Agricultural, Optoelectronic, and Sensing Applications

In optoelectronics, ZnO NPs serve as UV photodetectors, electron transport layers in perovskite solar cells, piezoelectric nanogenerators, and gas sensors (NO_2, H_2S, ethanol, VOCs). In biosensing, they enable detection of pharmaceutical contaminants and clinical biomarkers at sub-nanomolar concentrations (Ansari et al., 2024).

Nanotoxicology: Evidence, Mechanisms, and Risk Management

A responsible evaluation of ZnO NP applications demands rigorous toxicological scrutiny. Biodistribution studies across multiple exposure routes consistently identify the liver, kidney, lung, and spleen as principal organs of zinc accumulation, with the liver serving as the primary metabolic organ. The identity of the principal toxic species — intact ZnO NPs, dissolved Zn^{2+} ions, or a mixture — remains mechanistically unresolved, with significant implications for risk assessment and mitigation strategy design (Fujihara and Nishimoto, 2024; Chen et al., 2024; Havelikar et al., 2024).

Silica or biocompatible polymer coating of ZnO NPs demonstrably reduces both ROS generation and Zn^{2+} dissolution, constituting a viable engineering mitigation pathway. Systematic evaluation is needed with respect to physiologically relevant coating stability over time, particularly given the genotoxic endpoints identified in comet assays, micronucleus tests, and chromosomal aberration analyses (Fujihara and Nishimoto, 2024; Havelikar et al., 2024).

In the specific case of neem-ZnO NPs, surface-resident antioxidant phenolics and flavonoids may form a protective barrier against ROS generation in non-target tissues while remaining active in the ROS-rich tumour microenvironment. This hypothesis — mechanistically plausible but not yet validated in comparative toxicological studies — represents a specific and tractable research priority.

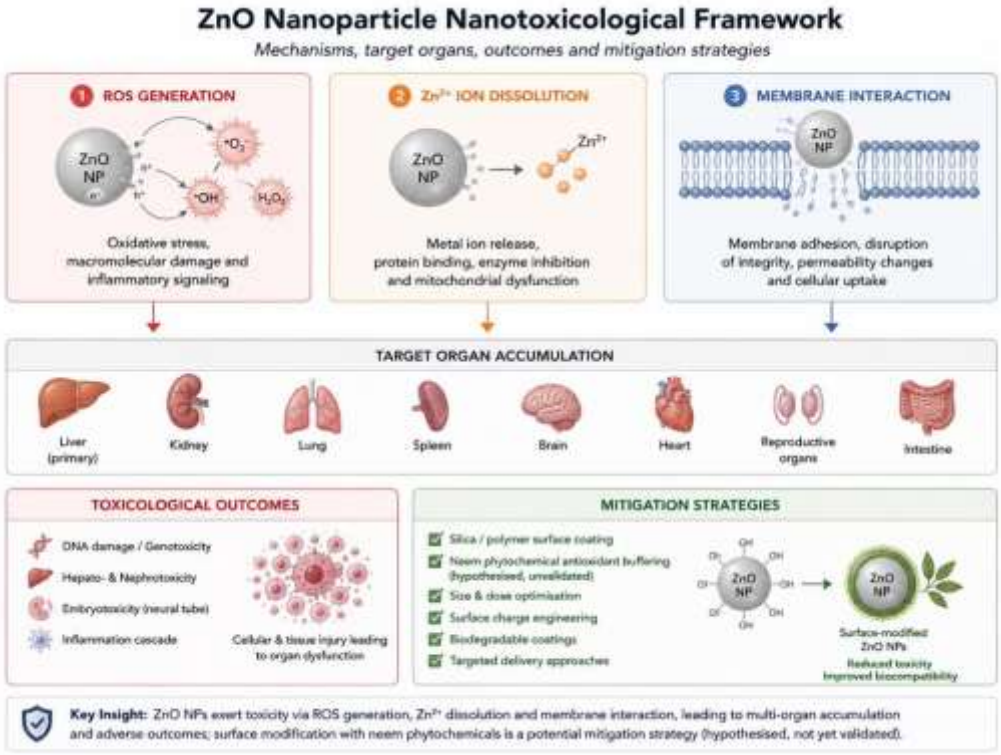

Figure 4 | ZnO NP nanotoxicological framework. Three primary mechanisms (ROS generation, Zn^{2+} ion dissolution, membrane contact) operate in parallel across target organs. Toxicological outcomes (red box) and mitigation strategies (green box), including neem phytochemical surface modifiers as a hypothesised but unvalidated strategy, are shown (Original schematic)

Table 4. Five Critical Research Gaps and Actionable Recommendation

Gap	Current Status	Priority Recommendation
Toxicology standardisation	Heterogeneous protocols; incomparable inter-laboratory datasets	OECD-analogous harmonised test guidelines; certified ZnO NP reference materials; mandatory characterisation reporting
Protein corona characterisation	Minimally characterised for ZnO NPs in physiological fluids	Quantitative proteomics (nLC-MS/MS); in situ biophysical characterisation; corona vs neem phytochemical coating
Visible-light photocatalysis	Charge carrier dynamics unclear in doped/composite ZnO systems	Transient absorption spectroscopy; operando XRD; Z-scheme heterojunction optimisation; single-atom catalysts
Clinical translation	<10 clinical trials globally despite extensive in vitro data	IND package development; large-animal pharmacokinetics; topical/localised solid tumour early-phase trials
Environmental fate & ecotoxicology	Transformation pathways and long-term ecotoxicity poorly mapped	LCA frameworks; regulatory concentration thresholds for surface water and soil; fate of neem phytochemicals

The most valuable contribution a review article can make is to define the structural gaps that are stalling progress from scientific knowledge to responsible real-world application. The five gaps enumerated below represent the most consequential areas requiring focused attention in ZnO NP research.

Gap 1: Nanotoxicology Standardisation

Interlaboratory comparability is currently precluded by cell-line heterogeneity, variable exposure metrics, non-

systematic endpoint selection, and inconsistent physicochemical reporting. The development of harmonised testing protocols — analogous to OECD TG guidelines for conventional chemicals — anchored in certified ZnO NP reference materials is an urgent and achievable priority.

Comparative toxicological studies of neem-ZnO NPs versus chemically synthesised counterparts under rigorously identical conditions are a critical unmet need.

Gap 2: Protein Corona Characterisation

ZnO NP surfaces are remodelled by protein corona formation upon entering physiological environments, fundamentally altering cellular uptake pathways, pharmacokinetics, immunological recognition, and targeting ligand accessibility. The pre-existing phytochemical coating of neem-ZnO NPs adds further complexity, modulating corona composition and pharmacokinetic predictability in ways that remain uncharacterised. Quantitative proteomics (nLC-MS/MS) combined with advanced biophysical methods represents a high-priority, feasible research programme.

Gap 3: Visible-Light Photocatalytic Mechanism

Charge carrier dynamics in modified ZnO systems — encompassing the roles of oxygen vacancy density, dopant spatial distribution, and interfacial electron transfer kinetics — remain mechanistically unclear. The contribution of surface phytochemical electron mediators to visible-light activity in neem-ZnO NPs has been postulated but not yet mechanistically elucidated (Alaizeri et al., 2026; Haiouani et al., 2024). Transient absorption spectroscopy, operando XRD, and the design of Z-scheme heterojunctions and single-atom catalysts are identified as key methodological priorities.

Gap 4: Clinical Translation Infrastructure

Despite an extensive body of in vitro and animal model evidence, clinical trials evaluating ZnO NP therapeutic potential are virtually absent globally. For neem-ZnO NPs, the regulatory challenges of characterising phytochemical surface modifiers and assuring physicochemical stability throughout formulation and storage must be addressed.

Development of IND packages, large-animal pharmacokinetic datasets, and early-phase trials in topical or localised solid tumour indications are the most tractable near-term steps.

Gap 5: Environmental Fate and Long-Term Ecotoxicology

Continuous environmental release of ZnO NPs from industrial effluents, agricultural runoff, cosmetic degradation, and textile leaching creates an escalating regulatory burden. Life-cycle assessment frameworks and regulatory concentration thresholds for surface water, soil, and biological matrices are urgently required (Fujihara and Nishimoto, 2024; Havelikar et al., 2024).

A key unresolved question is whether neem phytochemical surface coatings accelerate or retard environmental dissolution relative to bare ZnO NPs — a question with direct implications for environmental risk assessment.

Conclusions

This review has both celebrated genuine progress in ZnO NP research and offered critical evaluation where the literature overreaches available evidence. Neem-mediated synthesis of ZnO NPs stands as a thematic centrepiece demonstrating what intelligent green nanomaterial design can achieve: scalable, reproducible, environmentally benign particles with surface phytochemistry that synergistically amplifies every biological activity the ZnO NP platform offers. The multifunctionality of neem-ZnO NPs — encompassing MDR pathogen inhibition, tumour-microenvironment-targeted cytotoxicity, α-amylase inhibition (antidiabetic activity), antioxidant and antifungal activity, and photocatalytic degradation of organic pollutants — constitutes a range of biological capabilities unmatched by conventional drugs or materials.

The five research gaps identified in Section 7 define precisely what scientific effort is required to transform this laboratory excellence into real-world impact. The field does not require further demonstration of neem-ZnO NP biological activity in cell culture models. It requires mechanistic depth, rigorous in vivo comparisons, harmonised safety data, environmental fate characterisation, and the regulatory and clinical science infrastructure necessary for responsible translation commensurate with the promise these materials hold.

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Statements and Declarations

Data Availability statement

All relevant data are within the manuscript file.

Author's Contribution Statement

TA, SM, SH, and SY collected data and wrote manuscript equally. GZJ, MZS and NH edited final version. All authors have read the final manuscript and approve its submission.

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