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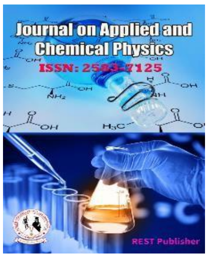

Eco-Friendly Metal Complex Nanozymes: Emerging Tools in Diagnostics and Therapeutics

Gaurav Prakash
Agra College, Agra, Uttar Pradesh, India.
Corresponding Author Email: gauravprakashbhu@gmail.com

Abstract: *Eco-friendly metal complex nanozymes represent a rapidly evolving class of catalytic nanomaterials engineered to mimic natural enzymes while adhering to green chemistry principles. Traditional nanozyme synthesis relies on hazardous reductants, toxic solvents, and energy-intensive conditions, resulting in materials with limited biocompatibility and notable environmental burdens. Green synthetic approaches—including plant-mediated phytochemical reduction, microbial templating, bio macromolecular scaffolding, mechanochemical processing, and aqueous low-temperature fabrication—yield metal complex nanozymes with enhanced safety, improved catalytic efficiency, and reduced ecological impact. These nanozymes exhibit versatile catalytic behaviours, such as peroxidase-, oxidase-, catalase-, superoxide dismutase-, and Fenton-like activity that support advanced diagnostic and therapeutic applications. Expanded diagnostic uses include colorimetric biosensors, electrochemical platforms, fluorescence-based sensing, wearable devices, and imaging-guided systems. Therapeutic applications range from antioxidant and antimicrobial treatments to cancer chemodynamic therapy, immunomodulation, wound healing, and metabolic disease intervention. Despite significant promise, challenges remain regarding toxicity, biodegradation, environmental persistence, and clinical translation. This extended review provides an in-depth examination of eco-friendly synthesis strategies, catalytic mechanisms, biomedical applications, and future research directions, including machine-learning-driven design, bioinspired catalysis, and circular chemistry frameworks.*

Keywords: *nanozymes; green chemistry; metal complexes; sustainable catalysis; diagnostics; therapeutics; coordination chemistry.*

1. INTRODUCTION

Nanozymes—engineered nanomaterials with intrinsic enzymatic properties—have emerged as transformative tools in modern biotechnology, medicine, and environmental science. Their catalytic robustness, cost-effectiveness, and structural tunability offer clear advantages over natural enzymes, which are often fragile, expensive to isolate, and sensitive to temperature and pH [1–3]. Among the various classes of nanozymes, metal complex nanozymes hold distinctive value because transition metals such as Fe, Cu, Mn, Co, Ni, Ce, and noble metals closely resemble the catalytic centres found in natural metalloenzymes [4,5].

Metal complex nanozymes leverage **coordination chemistry**, enabling precise control of metal–ligand geometry, electron transfer behaviour, and redox cycling—all of which critically determine catalytic activity. Their ability to mimic peroxidase, oxidase, catalase, superoxide dismutase (SOD), nitrate reductase, and Fenton chemistry positions them as multifunctional catalytic tools across biomedical sectors [6–8].

Despite their promise, the *traditional* synthesis of nanozymes remains problematic. Conventional methods commonly employ hazardous reductants (e.g., $NaBH_4$, hydrazine), organic solvents (DMF, ethanol, toluene), surfactants (PVP, CTAB), and high-temperature processes. These contribute to: Cytotoxicity, environmental contamination, regulatory barriers, poor biodegradability limited clinical readiness [9–11].

In contrast, **eco-friendly synthesis**, inspired by green chemistry principles, aims to reduce or eliminate hazardous substances while enhancing biocompatibility, biodegradability, and catalytic stability [12]. Green routes frequently yield nanozymes with superior surface chemistry, improved physiological interactions, and reduced toxicity, making them better suited for biomedical applications such as cancer therapy, biosensing, and wound healing [13–15].

This expanded review covers:

1. advanced eco-friendly synthesis strategies
2. catalytic mechanisms and structure–activity relationships
3. *greatly expanded* diagnostic
4. toxicity, environmental considerations, and clinical challenges
5. future directions in predictive design, bioinspired chemistry, and sustainable nanotechnology

2. GREEN SYNTHETIC STRATEGIES FOR METAL COMPLEX NANOZYMES

Eco-friendly synthesis is centered on minimizing environmental impact, reducing toxic reagents, lowering energy consumption, and improving biological compatibility. Below, each major strategy is expanded with deeper scientific explanation and mechanistic interpretation.

2.1 Plant-Mediated Synthesis

Plants offer abundant secondary metabolites—including polyphenols, flavonoids, alkaloids, terpenoids, organic acids, and sugars—capable of reducing metal ions and forming metal–ligand complexes. These molecules serve as: natural reductants, capping agents, chelating ligands, structural stabilizers [16].

Mechanistic Insight

Polyphenols (e.g., tannic acid, catechins) form coordination networks with Fe^{3+}, Cu^{2+}, or Mn^{2+}. These complexes exhibit strong redox activity due to electron-donating hydroxyl groups, enabling peroxidase- and oxidase-like catalysis [17].

Advantages

Renewable and biodegradable, Compatible with biomedical use, reduces synthesis temperature requirements, produces highly hydrophilic, dispersible nanozymes

Applications

Fe–tannin nanozymes synthesized using tea or grape seed extracts enhance glucose sensing due to strong peroxidase-like activity [18]. Cu–polyphenol nanozymes synthesized from bark extracts exhibit strong antimicrobial oxidase-like performance [19].

2.2 Microbial Templating and Biomineralization

Microorganisms act as **biomineralization platforms**, using intracellular enzymes, redox systems, and surface biomolecules to guide the formation of metal complexes [20].

Mechanistic Basis

Metal ion reduction occurs via: oxidoreductase enzymes, extracellular polymeric substances, cell wall functional groups (phosphate, carboxyl, amine groups) [21]

Unique Benefits: Highly controlled nucleation and growth, Physiological synthesis conditions, Eco-friendly metal recycling potential, Enhanced biological compatibility

Examples

Fungi-mediated Mn nanozymes demonstrate superior oxidase-like behavior useful in pathogen detection [22], while bacteria-templated Fe complexes show high antimicrobial efficacy due to synergistic ROS generation [23].

2.3 Biomacromolecular Scaffolding

Biomacromolecules provide natural, biodegradable frameworks for metal coordination.

Common scaffolds: proteins (BSA, collagen, casein), polysaccharides (chitosan, alginate, dextran), DNA and RNA, peptide amphiphiles

Functional Roles: metal ion chelation, particle size control, steric stabilization, enhanced targeting through functional groups [24]. Biomacromolecule-assisted nanozymes exhibit improved biocompatibility and controlled catalytic behavior.

2.4 Mechanochemical and Solvent-Free Synthesis

Mechanochemical processes rely on mechanical energy to initiate reactions without solvents.

Scientific Advantages

zero hazardous waste, direct metal–ligand integration, high reproducibility, energy efficiency [25]. Fe–gallic acid nanozymes produced mechanochemically show enhanced peroxidase-like catalysis and antimicrobial activity [26].

2.5 Green Hydrothermal and Low-Temperature Approaches

Water-based hydrothermal systems at 80–120 °C allow the formation of crystalline metal complexes without toxic additives.

Advantages

lower energy consumption, eco-friendly solvents, controlled crystallinity, compatibility with bioligands [27]. Examples include Fe–chitosan nanozymes with exceptional stability and catalytic strength [28].

2.6 Bioinspired Eco-Friendly MOF Nanozymes

Metal–organic frameworks synthesized using bio-derived ligands (catechol, tannic acid, amino acids) offer: tunable pore size, high surface area, multiple catalytic active sites biodegradability [29]. Such MOFs mimic multi-enzyme systems, enhancing both diagnostic and therapeutic capabilities.

3. CATALYTIC MECHANISMS OF ECO-FRIENDLY METAL COMPLEX NANOZYMES (EXPANDED)

Metal complex nanozymes derive their catalytic functions from the redox characteristics of transition metals and the electron-donating or electron-withdrawing nature of their coordinating ligands. These molecular-level interactions dictate the kinetics, thermodynamics, and selectivity of catalytic pathways.

3.1 Peroxidase-Like Catalytic Mechanisms

Peroxidase-mimicking nanozymes catalyze the oxidation of classical substrates such as TMB, ABTS, and OPD in the presence of H_2O_2.

Mechanistic Basis

The catalytic cycle involves: **Metal redox cycling** between M^{n+} and $M^{(n-1)+}$, Activation of H_2O_2 to produce high-valent metal–oxo intermediates, Electron transfer to chromogenic substrates, Turnover regeneration of the metal center [30]. Fe-based nanozymes follow a mechanism analogous to horseradish peroxidase (HRP), while Cu-based systems often exhibit enhanced electron-transfer rates due to their variable oxidation states [31].

Factors Improving Activity: Polyphenol ligands enhance electron transfer, Biomolecular scaffolds increase substrate affinity, MOF architectures provide accessible catalytic pores, Mechanochemical synthesis yields small, high-surface-area complexes

3.2 Oxidase-Like Catalysis

Oxidase-mimicking nanozymes catalyze substrate oxidation using dissolved oxygen as an electron acceptor, eliminating the need for H_2O_2.

Mechanistic Highlights: Direct electron transfer to O_2, Formation of superoxide radicals ($O_2{\bullet}^-$), Metal–ligand complexes stabilize reactive oxygen intermediates [32]. Oxidase-like nanozymes are widely used in antimicrobial systems and tumor oxygenation modulation.

3.3 Catalase-Like Activity

Catalase-like nanozymes decompose hydrogen peroxide into water and oxygen via:

$2H_2O_2 \rightarrow 2H_2O + O_2$

Biomedical Importance

This function is particularly beneficial in: ROS-induced tissue damage, inflammatory microenvironments, hypoxic tumor regulation [33]. Metal complexes containing Fe or Mn frequently show catalase-like behavior due to favorable redox potentials.

3.4 Superoxide Dismutase (SOD)-Like Activity

SOD-mimicking nanozymes catalyze the dismutation of superoxide radicals:

$2O_2^{\bullet -} + 2H^+ \rightarrow H_2O_2 + O_2$

Transition metals like Mn and Cu alternate efficiently between oxidation states, enabling continuous radical scavenging [34].

Implications: Anti-inflammatory therapy, Neuroprotection, Mitigation of oxidative stress in chronic disease.

3.5 Fenton and Fenton-Like Catalysis

Fenton-like reactions involve metal ions reacting with H_2O_2 to produce hydroxyl radicals (•OH):

$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {\bullet}OH + OH^-$

Relevance to Therapy: Chemodynamic cancer therapy (CDT), Photodynamic therapy enhancement, antimicrobial action [35]. Green ligands modulate ROS generation rates, improving safety and selectivity.

4. EXPANDED APPLICATIONS IN DIAGNOSTICS

Eco-friendly metal complex nanozymes have significantly transformed diagnostic science due to their high catalytic efficiency, environmental sustainability, tunability, and excellent compatibility with point-of-care and wearable devices. Below, each diagnostic domain is deeply expanded with scientific rationale and practical examples.

4.1 Colorimetric Biosensing

Colorimetric biosensing is one of the most mature application areas for nanozymes. The enzyme-like catalytic behavior enables rapid, visible color changes in response to analytes.

4.1.1 Glucose Detection

Traditional glucose sensors use HRP + GOx pairs. Nanozymes replace HRP, offering: higher stability, cost-effectiveness, no denaturation at high temperature or pH [36]. Fe–polyphenol complexes exhibit strong peroxidase-like activity, promoting TMB oxidation to produce intense blue signals proportional to glucose concentration.

4.1.2 Heavy Metal Ion Detection

The oxidase/peroxidase-like activity of Cu-, Mn-, and Fe-complex nanozymes facilitates selective heavy metal detection: Cu–tannin oxidase mimics detect Hg^{2+} at low nanomolar levels [37], Fe–polyphenol systems identify Pb^{2+} and Cr^{6+} contaminants.

4.1.3 Food Safety Testing

Nanozymes detect: pesticide residues, microbial contamination, spoilage indicators such as biogenic amines. Plant-derived nanozymes reduce toxicity concerns for food diagnostics [38].

4.2 Electrochemical Biosensing (Expanded)

Electrochemical biosensors benefit greatly from nanozymes due to their enhanced electron-transfer capabilities.

Advantages: Lower detection limits, Faster charge-transfer kinetics, Broadened detection ranges, Integration into flexible platforms. Green-synthesized Cu nanozymes detect dopamine with remarkable sensitivity because Cu redox cycling accelerates electron flow at electrode interfaces [39]. Fe-based MOFs increase surface conductivity, improving nitrite and H_2O_2 sensing [40].

4.3 Fluorescent, Chemiluminescent, and Photoluminescent Sensing

Metal complex nanozymes generate ROS that trigger luminescent reactions.

Applications: ultrasensitive detection of cancer biomarkers, live-cell ROS imaging, immunoassay signal amplification. Fe–chitosan catalase-mimics enhance chemiluminescence in immunoassays by controlling endogenous H_2O_2 levels [41].

4.4 Paper-Based and Portable Diagnostics

Eco-friendly nanozymes are ideal for disposable test strips because: they function without refrigeration, they operate under harsh environments, they are low-cost and environmentally benign

Applications include: rapid disease screening, water quality testing, food safety assays [42].

4.5 Wearable, Flexible, and Implantable Biosensors

Wearable biosensing is a rapidly growing field where nanozymes offer major advantages.

4.5.1 Sweat-Based Sensors

Wearable patches integrate nanozymes for real-time monitoring of: glucose, lactate, electrolytes, stress biomarkers (cortisol via oxidase-like reactions) [43].

4.5.2 Saliva and Tear Diagnostics

Metal complex nanozymes can be embedded in soft hydrogel matrices for non-invasive biomarker detection.

4.5.3 Smart Bandages

Wound-integrated nanozymes support monitoring of infection biomarkers through colorimetric or redox-based readouts.

4.6 Imaging-Based Diagnostics: Metal complex nanozymes serve as contrast agents for:

4.6.1 MRI Imaging: Fe-based nanozymes function as T1T2 contrast enhancers.

4.6.2 Photoacoustic Imaging: Cu-based nanozymes absorb near-infrared light, improving imaging depth.

4.6.3 Fluorescent Imaging: ROS-triggered fluorescence amplification supports tumor imaging [44].

5. TOXICITY, BIODEGRADATION, AND CHALLENGES (EXPANDED)

Although eco-friendly metal complex nanozymes offer improved safety compared to conventional nanozymes, several biocompatibility and environmental considerations remain. These concerns must be systematically assessed to ensure safe translation into clinical, agricultural, and environmental applications.

5.1 Metal Ion Release and Cytotoxicity

Metal complex nanozymes may release free metal ions (e.g., Fe^{2+}, Cu^{2+}, Co^{2+}), which can: catalyze uncontrolled ROS production, disrupt mitochondrial function, bind DNA and proteins, alter cellular redox signaling [36,37].

While green ligands—polyphenols, amino acids, polysaccharides—significantly reduce ion leakage, complete elimination remains challenging.

Mitigation Strategies: ligand engineering for tighter metal chelation, coating with biomacromolecules (BSA, chitosan), controlled-release architectures, pH-responsive disintegration in physiological or lysosomal environments.

5.2 Biodistribution, Accumulation, and Clearance

Nanozymes' fate in vivo depends on: size, surface charge, ligand type, metal–ligand stability, interaction with plasma proteins [38]. Potential concerns include: accumulation in the liver, kidney, or spleen, slow biodegradation, immune recognition and macrophage uptake, persistence in tissue microenvironments. Green synthetic strategies can reduce computational predicted toxicity and improve biodegradation profiles.

5.3 Environmental Persistence and Ecotoxicological Risk

Although eco-friendly synthesis reduces production toxicity, the environmental behavior of nanozymes after disposal is still poorly understood. Potential ecological risks include: bioaccumulation in aquatic organisms, soil microbial disruption, metal ion release into ecosystems, long-term effects on food chains [39]. Environmental safety must be evaluated through: life-cycle assessment (LCA), soil/water degradation studies, ecotoxicology testing on plants, algae, and invertebrates.

5.4 Clinical Translation Challenges

Transitioning nanozymes to clinical products requires overcoming several bottlenecks like Standardization of Synthesis, Regulatory Framework Limitations [40].

5.4.3 Large-Scale Manufacturing

Scaling up biological or plant-mediated synthesis requires: reproducibility, controlled ligand composition, stable reaction conditions

5.4.4 Long-Term Safety Data

Longitudinal in vivo studies are limited, especially concerning chronic exposure and biodegradation pathways.

6. FUTURE DIRECTIONS (EXPANDED)

Eco-friendly metal complex nanozymes represent an emerging frontier in sustainable nanomedicine. Several scientific, technological, and regulatory advancements will shape their future.

6.1 Machine Learning–Driven Nanozyme Discovery

Machine learning (ML) and artificial intelligence (AI) offer predictive capabilities for: selecting optimal metal–ligand combinations, predicting toxicity, simulating catalytic pathways, optimizing synthesis parameters, screening thousands of green ligands in silico [41–43]. AI-driven modeling can drastically reduce experimental trial-and-error, accelerating innovation.

6.2 Bioinspired Catalytic Engineering

Drawing inspiration from natural metalloenzymes, researchers are developing nanozymes with tailored: active-site geometries, substrate-binding pockets, electron-transfer channels, redox-active moieties [44]. Examples include mimics of: cytochrome P450, laccase, peroxidase, catalase, superoxide dismutase. These bioinspired complexes can improve catalytic selectivity, efficiency, and specificity.

6.3 Circular Chemistry and Sustainable Material Design

Circular chemistry emphasizes material reuse, recyclability, and minimal environmental impact.

Approaches: harvesting metal ions from industrial waste streams, using agricultural waste extracts as ligands, designing nanozymes that degrade into non-toxic metabolites, implementing closed-loop manufacturing systems [45]. This approach aligns nanozyme research with global sustainability agendas and UN SDGs.

6.4 Smart Theranostic Platforms

Future nanozymes will combine diagnostics + therapeutics into a single integrated system. Smart nanozymes will: respond to pH, temperature, enzymes, and redox gradients, release drugs or generate ROS only under diseased conditions, provide real-time imaging feedback, adjust catalytic activity dynamically [46]. Potential applications include: smart bandages, implantable sensors, adaptive cancer therapies, metabolic disease monitoring

6.5 Regulatory Science and Clinical Standards

To ensure safe translation, future work must establish: standardized toxicity assays detailed pharmacokinetics (ADME profiles), ISO-compliant nanomaterial characterization, GMP-compatible synthesis pipelines [47]. Strong collaboration between materials science, clinicians, toxicologists, and policymakers will be essential.

7. CONCLUSION

Eco-friendly metal complex nanozymes represent a transformative intersection of catalysis, green chemistry, and biomedicine. Their ability to mimic enzymatic processes while being produced through sustainable methods marks a paradigm shift in nanotechnology. Plant-derived ligands, microbial biomineralization systems, bio macromolecular scaffolds, mechanochemical synthesis, green hydrothermal techniques, and biodegradable MOFs have enabled the creation of nanozymes with superior catalytic behavior and enhanced biological compatibility.

These nanozymes support an extensive range of diagnostic and therapeutic applications—from colorimetric biosensing and electrochemical detection to antioxidant treatment, antimicrobial therapy, wound healing, and cancer chemodynamic therapy. Their multifunctionality and adaptability position them as powerful next-generation tools in precision medicine, point-of-care diagnostics, and regenerative healthcare.

However, to fully realize their potential, significant challenges must be addressed in toxicity mitigation, biodegradation control, environmental safety, and clinical translation. Future efforts integrating AI-driven design, bioinspired engineering, circular chemistry, and regulatory standardization will pave the way for safe, scalable, and globally impactful nanozyme technologies.

Eco-friendly metal complex nanozymes are not merely an alternative to traditional nanozymes—**they represent the future of sustainable nanomedicine**.

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