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INSUFFICIENT MECHANISTIC UNDERSTANDING OF BIOSYNTHESIZED (BIOGENIC/GREEN) NANOPARTICLES IN HUMAN APPLICATIONS: CHALLENGES, SIGNAL GAPS, AND PROTOCOL FOR TRANSFORMATION

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ABSTRACT

Biosynthesized (biogenic/green) nanoparticles (derived from plants, microbes, fungi, algae and biomolecules) have emerged as promising alternatives to chemically synthesized nanomaterials due to their low-cost, eco-friendly production and intrinsic bioactivity. Despite explosive growth in publications, mechanistic understanding of their interactions with human biological systems remains inadequate including physicochemical reproducibility, identification of capping biomolecules, nano bio interactions including protein corona formation, cellular uptake pathways, in vivo biodistribution or clearance, and longterm toxicity. Taken together, these deficiencies hinder clinical translation. This review considers the current mechanistic evidence, highlights methodological and analytical limitations, and proposes a multipronged research roadmap including standardized characterization, corona profiling, multi-modal imaging, omicsguided assays, and improved regulatory frameworks due to advance biosynthesized nanoparticles toward safe human use.

KEYWORDS Green nanoparticles, Mechanistic insufficiency, reproducibility, capping, research roadmap etc.

1. INTRODUCTION

Biosynthesized or "green" nanoparticles (biogenic nanoparticles) are produced using biological systems such as plant extracts, bacteria, fungi, yeast, algae, and isolated biomolecules.[1,3] These systems act as natural reducing, stabilizing and capping agents, enabling energy-efficient and environmentally benign nanoparticle generation.[4] Biogenic nanoparticles have shown antimicrobial, anticancer, anti-inflammatory, antioxidant and imaging activities.[5,7] However, although their pledge, translation into human biomedical applications remain minimal. The core barrier is a lack of mechanistic clarity i.e., how exactly these biologically complex nanoparticles interact with human cells, tissues, immune system, and metabolic components is still poorly understood.[8,10]

Study Design and Rationale

The study was conceptualized as a hybrid research project, integrating elements from both qualitative and quantitative paradigms. The primary objective was not only to gather relevant scientific information but also to critically examine and synthesize current findings to identify the specific insufficient mechanistic understanding of green nanomedicine.[7] Special emphasis was placed on understanding the molecular level pharmacological and biochemical mechanisms lack age of their interactions with human biological systems remains inadequate including physicochemical reproducibility, identification of capping biomolecules, nano bio interactions including protein corona formation, cellular uptake pathways, in vivo biodistribution or clearance, and longterm toxicity which are involved in hindrance of clinical translation.[8]]

Given the complex and interdisciplinary nature of nanomedicine, the study was structured to incorporate multiple evidence-gathering techniques, thereby enhancing the toughness and reliability of the conclusions. The design rationality also included triangulation with using different methods and sources to cross-verify results of ensuring both internal and external validity. [9]

Data Collection Strategy

Data were collected from a wide array of sources to ensure comprehensive coverage of the research topic. The strategy consisted of the following key components

1. Systematic Literature Review (SLR): A well-defined protocol was established to conduct the SLR. This included the development of research questions, inclusion and exclusion criteria, search strategy formulation, and quality assessment. Databases such as PubMed, Scopus, and Web of Science were systematically searched using specific Boolean operators, medical subject headings (MeSH), and keyword combinations like "nanoparticles," "biogenic or green nanoparticles," "signal gap," and "protocol transformation"[10]
2. Non-systematic Literature Review: While the SLR ensured the inclusion of peer-reviewed and high-quality studies, non-systematic approaches were also used to capture emerging and grey literature. This included journal articles, clinical trial reports, white papers, and review articles published outside of indexed databases. This method allowed for the incorporation of new findings, expert perspectives, and less formalized knowledge that may not have passed through traditional peer-review processes but still hold academic value.[11]
3. Meta-Analysis and Metadata Evaluation: Where available, data from multiple studies were pooled and statistically analyzed to identify common trends, enigma, and knowledge insufficiency. Meta-analytical tools were used to assess effect sizes, heterogeneity, and publication bias, especially in clinical studies comparing biosynthesized and conventional treatments.[12,13]
4. Integrated Review and Umbrella Review: To provide a macro-level synthesis of findings, integrated and umbrella reviews were conducted. This involved summarizing the outcomes of various systematic reviews and meta-analyses into a single, coherent narrative. It allowed for the comparison of multiple intervention types, nano level mechanisms of arising difficulties of formulations used in diseases and patient populations.[14]
5. Rapid and Methodological Reviews: Rapid reviews were conducted in sub-topics that are rapidly evolving, such as plant and microbial, algal and yeast mediated synthesis, process, physicochemical, surface bound and reproducible insufficiency, protein corona, uptake level such as antimicrobial and anticancer fate, organ level accumulation, assay and omics tools and regulatory and transformational barriers[15] Methodological reviews regarding green nanoparticles were also performed to analyze the techniques, study designs, and essential other strategies used in prior research, helping to assess the overall quality and reproducibility of existing findings.[16]

Sources and Digital Tools

To support this extensive methodology, data were retrieved from both conventional academic repositories and cutting-edge digital tools

- Conventional Databases: Core academic platforms including PubMed, Scopus, Google Scholar, Science direct, IEEE Xplore and Web of Science were used for sourcing peer-reviewed journal articles, reviews, and clinical trial reports.[17]
- AI- and similar other based Search Platforms: Emerging AI platforms such as Semantic Scholar, Elicit, Chat GPT, Prisma, Python, visualization tools and Research Rabbit were employed to assist with automatic keyword extraction, context-based relevance scoring, and citation network analysis. These tools enhanced the efficiency and accuracy of identifying high-impact and thematically relevant research articles.[18]
- Unsystematic Sources: To ensure the inclusion of timely and cutting-edge insights, unsystematic information's were gathered from non-traditional platforms such as institutional repositories, conference abstracts, webinars, medical news outlets, and preprint servers (e.g., bioRxiv, medRxiv). These sources were critically evaluated for credibility and relevance before being incorporated into the study.[19]

This study employed a comprehensive and multi-dimensional methodological framework aimed at investigating the theme of mechanistical insufficiency regarding methodological and analytical basis that are responsible for the ineffectiveness of nano-sized drug delivery systems. In light of the increasing clinical relevance of biosynthesized nanoparticles especially in treating critical diseases such as various types of cancer and other relevant complications.

2. METHODS OF BIOSYNTHESIS

2.1 Plant-mediated synthesis

Plant extracts deliver polyphenols, terpenoids, flavonoids, amino acids, sugars and organic acids that function as reducing and capping agents.[24,26] Variability in plant species, extraction conditions, solvent composition and phytochemical content causes substantial physicochemical diversity in the resulting Nanoparticles.[27,29]

2.2 Microbial synthesis

Bacteria, actinomycetes and fungi generate intra- and extracellular Nanoparticles through enzymatic reduction pathways.[30,32] The presence of biomolecules like enzymes, proteins, metabolites etc. changes nanopartcles

surface chemistry dramatically compared to chemical synthesis.[33,34]

2.3 Algal and yeast-mediated synthesis

Algal polysaccharides and proteins offer strong stabilizing matrices,[35,36] whereas yeast systems allow controlled metal ion uptake and nucleation.[37]

2.4 Influence of process variables

pH, temperature, precursor concentration, reaction time and biomass composition cause wide variation in NP size, shape, crystallinity and surface coatings.[38,40] Due to these process variables reproducibility remains a major challenge.

3. Characterization Challenges

Biogenic Nanoparticles often carry a complex, poorly defined corona of natural biomolecules, making standard characterization insufficient.

3.1 Incomplete physicochemical reporting

Most studies report only UV–Vis, TEM and FTIR.[41] could able to characterize biogenic nanoparticles, while ignoring critical parameters including hydrodynamic diameter and polydispersity (DLS), zeta potential, capping layer thickness, quantification of adsorbed biomolecules and crystallinity and phase purity.

3.2 Difficulties in identifying surface-bound biomolecules

Due to the diversity of phytochemicals or microbial metabolites, identification of capping molecules using LC–MS/MS, NMR or proteomics is rarely performed.[42,44] and is very difficult.

3.3 Lack of batch reproducibility

Different plant batches, growth seasons, fermentation states or extraction solvents cause drastic inconsistency in NP physicochemical properties.[45.,46]

4. Nanobio Interactions

These include Protein corona formation, Cellular uptake pathways and Intracellular fate and understanding their nano–bio interaction is central to predicting human outcomes.

4.1 Protein corona formation

When Nanoparticles enter biological fluids, proteins adsorb to their surface forming a “corona” dictating cellular uptake pathway, biodistribution, immune recognition and toxicity. However, corona profiling for these particles is rarely conducted.[47,49]

4.2 Cellular uptake pathways

Biogenic Nanoparticles may utilized as clathrin-mediated endocytosis, caveolae-mediated endocytosis, micropinocytosis and phagocytosis. Yet only a small fraction of lessons map uptake routes mechanistically.[50,52]

4.3 Intracellular fate

Intracellular rates including endosomal escape, lysosomal degradation, ion release kinetics, ROS generation and mitochondrial damage.[53,55] which are still unknown and barriers in the exact use of nanoparticles.

5. Mechanisms of Biological Activity

5.1 Antimicrobial mechanisms

Proposed anti microbiological mechanisms are metal-ion release and enzyme inactivation, ROS generation, membrane disruption, DNA damage etc.[56,58] But the precise contribution of each mechanism varies widely depending on plant or microbial capping molecules.[59]

5.2 Anticancer mechanisms

Commonly ascribed pathways are mitochondrial depolarization, caspase activation, oxidative stress, inhibition of proliferation signaling pathways.[60,62] Still, these are varied greatly regarding dose, NP identity and cellular context.

6. In Vivo Biodistribution, Clearance and Toxicity

These are consisting of organ accumulation, immune interactions, genotoxicity and oxidative stress and long-term fate.

6.1 Organ accumulation

Studies demonstrate accumulation in liver, spleen, lungs, kidney and brain.[63,66]

But pharma cokinetic models still remaining in underdeveloped.

6.2 Immune interactions

Immune activation or suppression remains poorly characterized.[67,69]

Capping biomolecules may act as pathogen-associated molecular patterns, but the statistics are sparse.

6.3 Genotoxicity and oxidative stress

These include DNA fragmentation, chromosomal aberrations and oxidative markers.[70,71] and their mechanisms remain unclear yet.

6.4 Long-term fate

Do biosynthesized Nanoparticles biodegrade? The answer is often, yes — but not always.

Do they persist? The answer is, it depends on material and do they get excreted? The answer is

yes, but the rate depends heavily on size, for examples-

<5 nm

- Cleared rapidly via kidneys (urine)
- Minimal persistence

5–20 nm

- Some renal clearance
- Some accumulation in liver/spleen

20–200 nm

- Mainly captured by reticuloendothelial system (RES)
  - Liver
  - Spleen
  - Lymph nodes
- Excretion is slower; occurs via bile → feces
  >200 nm
- Very little excretion
- Mostly retained or broken down slowly

The following table summarizes the features of biodegradable nanoparticles regarding biodegradability, persistency and excretion pattern.

Table 1: Features of biodegradable nanoparticles regarding biodegradability, persistency and excretion pattern.

Nanoparticle Type	Biodegradable?	Persistent?	Excretion Route
Gold (Au)	No	High	Very slow, biliary
Silver (Ag)	Partial (ions)	Medium	Urine + feces
Zinc Oxide (ZnO)	Yes (dissolves)	Low	Urine
Copper Oxide (CuO)	Partial	Low–Medium	Urine + feces
Iron Oxide (Fe_3O_4)	Yes	Low	Natural iron metabolism
Plant- or microbial-coated nanoparticles	Coating = biodegradable	Less persistent than synthetic	Faster clearance

Long-term studies of the above are scarce.[72,73]

7. Analytical & Methodological Gaps are listed below

1. **Lack of standardized assays** for ROS, apoptosis, genotoxicity, and immunotoxicity.[73,74]
2. **Underuse of omics tools** (transcriptomics, proteomics, metabolomics) to map mechanisms.[63,64]
3. **Limited multi-modal imaging** (TEM + confocal + ICP–MS mapping)[65]
4. **Almost no protein corona profiling**[76,77]
5. **Scarce pharmacokinetics and pharmacodynamics (PK and PD) studies**[81]

8. Regulatory and Translational Barriers are listed below-

1. Regulatory bodies favor chemically well-defined nanomaterials, not heterogeneous biosynthesized ones.[82,83]
2. Quality control is difficult due to batch variability.[84]
3. Few clinical examples exist[85] which are not able to explore and features the exact potentiality of these agents.
4. **Safety dossiers** require long-term toxicity, reproductive studies, and PK data which are mostly absent.[86,87]

9. Endorsements & Research Protocol

Have to must ensure standardized characterization toolkit including i. TEM, SEM, XRD, FTIR ii. DLS, zeta potential iii. LC–MS/MS proteomics/metabolomics for capping layer, iv. ICP–MS for exact quantification.

9.2 Corona-aware nanoparticle design

Have to must ensure the study and tailor including i. hard/soft corona composition, ii. impact on uptake, toxicity, immunogenicity.

9.3 Multi-modal mechanistic assays

Have to must ensure combination including i. live-cell imaging ii. Omics iii. mitochondrial assays and iv. gene expression mapping.

9.4 In vivo PK/PD models

Have to must ensure the uses including i. whole-body imaging, ii. organ ICP–MS, iii. repeated-dosing studies.

9.5 Regulatory alignment

Have to must ensure adaptation of frameworks compatible with EMA, FDA and ISO nanoparticle guidance.

10. CONCLUSION

Although biosynthesized nanoparticles hold significant promise for human applications, mechanistic understanding remains the principal bottleneck. The field must transition from descriptive synthesis-oriented studies to rigorous mechanistic, multi-modal analyses. Implementing standardized characterization, corona profiling, omics-guided mechanistic assays, and robust in-vivo models will be essential for safe and effective clinical application.

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