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Streptomyces-Mediated Green Synthesis of Nanoparticles: Mechanisms, Applications, and Future Perspectives

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ABSTRACT

Streptomyces species are prolific producers of bioactive secondary metabolites, enzymes, and reducing agents, making them attractive biotechnological platforms for the eco-friendly synthesis of metallic and metal oxide nanoparticles. Their ability to generate nanoparticles under mild and sustainable conditions has stimulated growing interest in biomedical, agricultural, and environmental applications. This review evaluates the current knowledge on *Streptomyces*-mediated nanoparticle biosynthesis, focusing on the underlying synthesis mechanisms, biological applications, cytotoxicity profiles, limitations, and future research directions. Published literature on the biosynthesis of silver, gold, zinc oxide, copper oxide, iron oxide, and selenium nanoparticles by *Streptomyces* species was critically examined. Particular attention was given to nanoparticle formation mechanisms, physicochemical characteristics, therapeutic potential, and safety considerations. The reviewed studies demonstrate that *Streptomyces*-derived nanoparticles exhibit diverse bioactivities, including antimicrobial, antioxidant, wound-healing, and anticancer effects. Their biological performance is strongly influenced by physicochemical parameters such as particle size, morphology, surface charge, concentration, and exposure duration. Although these nanomaterials can selectively induce cancer cell death through reactive oxygen species generation, mitochondrial dysfunction, and apoptosis, evidence also indicates potential adverse effects in normal cells, including oxidative stress, DNA damage, inflammation, and organ toxicity. Important knowledge gaps remain regarding long-term biodistribution, bioaccumulation, immunogenicity, and environmental fate. Despite their considerable promise, the translation of *Streptomyces*-derived nanoparticles into clinical and commercial applications is constrained by limited standardization, scalability challenges, insufficient long-term toxicity data, and evolving regulatory requirements. Future integration of synthetic biology, omics technologies, and advanced nanoparticle engineering may improve safety, reproducibility, and functional performance, supporting the responsible development of these nanomaterials while addressing remaining translational hurdles.

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INTRODUCTION

Nanotechnology has transformed modern science through the development of nanoparticles (NPs) possessing unique physicochemical properties, including high surface-area-to-volume ratios, enhanced reactivity, and improved catalytic performance. These characteristics have enabled diverse applications in medicine, agriculture, environmental remediation, and industry (Abuzeid et al., 2023; Eweis et al., 2024; Protik et al., 2026). Despite these advantages, conventional physical and chemical methods of nanoparticle synthesis often require substantial energy inputs, costly equipment, and hazardous chemicals, raising concerns regarding environmental sustainability and potential health risks (Abuzeid et al., 2023; Protik et al., 2026).

Green synthesis has emerged as a sustainable alternative that utilizes biological systems and their metabolites to produce nanoparticles under environmentally friendly conditions. Among biological approaches, microbial-mediated synthesis has attracted considerable attention because microorganisms employ enzymes, proteins, polysaccharides, and secondary metabolites as natural reducing and stabilizing agents, allowing efficient nanoparticle formation with enhanced biocompatibility (Eweis et al., 2024).

Among microbial producers, *Streptomyces* species are particularly attractive because of their remarkable metabolic diversity and ability to synthesize a wide range of bioactive compounds that facilitate nanoparticle production. Recent studies have demonstrated the successful biosynthesis of metallic and metal oxide nanoparticles using *Streptomyces*, with reported applications in antimicrobial therapy, cancer treatment, wound healing, biosensing, and drug delivery (Anjum et al., 2024; El-Naggar et al., 2024; Lin et al., 2025). In particular, *Streptomyces*-derived nanoparticles have shown promise in addressing antimicrobial resistance through mechanisms such as membrane disruption, reactive oxygen species (ROS) generation, and interference with microbial metabolic processes (Anjum et al., 2024; Kerdtoob et al., 2024).

Despite these promising applications, significant challenges remain before *Streptomyces*-mediated nanoparticles can be translated into clinical and commercial use. A major limitation is the absence of standardized cytotoxicity assessment protocols, as studies frequently employ different

cell models, nanoparticle concentrations, exposure periods, and analytical methods, leading to inconsistent and difficult-to-compare results (Kong et al., 2011; Awashra & Młynarz, 2023). Furthermore, most safety evaluations remain limited to in vitro investigations, while comprehensive data on biodistribution, bioaccumulation, pharmacokinetics, long-term toxicity, and organ-specific effects are still scarce (Elnady et al., 2022; Zhang et al., 2024). Another important knowledge gap is the limited number of head-to-head studies comparing the safety and efficacy of biogenic nanoparticles with chemically synthesized counterparts under standardized experimental conditions, making it difficult to determine their relative translational advantages (Składanowski et al., 2016). Therefore, this review critically examines the mechanisms underlying *Streptomyces*-mediated nanoparticle biosynthesis, summarizes their biomedical and biotechnological applications, evaluates current evidence on cytotoxicity and biocompatibility, and identifies key translational challenges, including standardization, scalability, long-term safety assessment, and regulatory considerations. Future research directions required to support the safe and effective development of *Streptomyces*-derived nanomaterials are also discussed.

MATERIALS AND METHODS

This review employed a systematic and reproducible approach to identify, evaluate, and synthesize published studies on *Streptomyces*-mediated nanoparticle biosynthesis and their applications. The methodology was designed in accordance with established systematic review principles to ensure transparency, comprehensiveness, and scientific rigor (Iravani et al., 2020; Singh et al., 2022).

Literature Search Strategy

A comprehensive literature search was conducted using four major scientific databases: Scopus, Web of Science, PubMed, and Google Scholar. Relevant studies were identified using combinations of the following keywords and Boolean operators:

i. "*Streptomyces* nanoparticles"
ii. "biosynthesis of nanoparticles"
iii. "microbial nanotechnology"
iv. "green synthesis"
v. "actinomycetes-mediated nanomaterials"

The search strings were combined using AND, OR, and NOT to maximize retrieval of relevant studies while minimizing irrelevant records. Additionally, backward, and forward citation tracking of key articles was performed to identify important studies that may not have been retrieved during the initial search.

Eligibility Criteria

Inclusion Criteria

Studies were included if they:

i. Were published in peer-reviewed journals.
ii. Were available in full text and written in English.
iii. Reported the biosynthesis of metallic or metal oxide nanoparticles using *Streptomyces* species.
iv. Investigated synthesis mechanisms, characterization, biological applications, toxicity, or prospects of *Streptomyces*-derived nanoparticles.
v. Were published between 2015 and 2025 to capture recent scientific developments.

Exclusion Criteria

Studies were excluded if they:

i. Were duplicate records.
ii. Were conference abstracts, editorials, book chapters, or non-peer-reviewed articles.
iii. Focused on nanoparticle synthesis by microorganisms other than *Streptomyces* without providing relevant comparative insights.
iv. Provided insufficient experimental detail or scientific validity.
v. Were review articles, although these were consulted to identify additional primary studies.

Study Screening and Selection

Retrieved articles underwent a multi-stage screening process involving title review, abstract assessment, and full-text evaluation. Duplicates were removed before eligibility assessment. Studies meeting the inclusion criteria were selected for detailed analysis. The study selection process is summarized in Figure 1.

Data Extraction and Synthesis

Relevant data were extracted from eligible studies, including:

i. *Streptomyces* species used
ii. Type of nanoparticles synthesized
iii. Synthesis mechanism
iv. Physicochemical characteristics
v. Biological and biomedical applications
vi. Toxicity and biocompatibility findings
vii. Reported limitations and prospects

The extracted information was synthesized qualitatively to identify emerging trends, technological advances, evidence gaps, and future research priorities in *Streptomyces*-mediated nanotechnology.

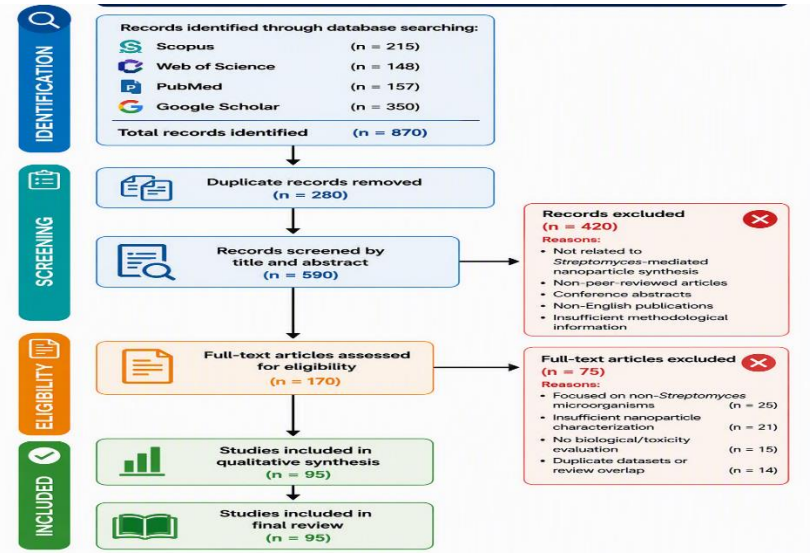

Figure 1: PRISMA-based study selection workflow for the review

RESULTS AND DISCUSSION

Mechanisms of Nanoparticle Biosynthesis

The biosynthesis of nanoparticles by *Streptomyces* species occurs through complex biochemical pathways involving enzymatic reduction, metabolite interactions, and cellular defense mechanisms. These processes can be broadly categorized into intracellular and extracellular synthesis routes, both of which are regulated by microbial metabolic activity and environmental conditions. In addition, diverse biomolecules play critical roles in the reduction, capping, and stabilization of the synthesized nanostructures (Iravani et al., 2020; El-Naggar et al., 2022).

Intracellular Synthesis

Intracellular nanoparticle synthesis involves the transport of metal ions across the microbial cell wall into the cytoplasm, where they are subsequently reduced to their elemental form. This reduction process is primarily mediated by intracellular enzymes such as NADH-dependent reductases, including nitrate reductase, as well as electron shuttle molecules involved in cellular respiration (Duran et al., 2011; Li et al., 2011).

Recent studies have demonstrated that *Streptomyces* species utilize their intrinsic redox systems to detoxify metal ions, leading to the nucleation and growth of nanoparticles within the cytoplasmic matrix (Khan et al., 2024; Singh et al., 2021). These nanoparticles are often localized within specific cellular compartments, suggesting regulated biosynthetic pathways linked to metal stress responses.

Although intracellular synthesis offers controlled nanoparticle formation with uniform morphology, it often requires downstream processing steps such as cell disruption and purification, which can limit its scalability for industrial applications (Ghosh et al., 2020; Ahmed et al., 2023).

Extracellular Synthesis

Extracellular synthesis is widely regarded as a more practical and cost-effective approach for nanoparticle production. In this mechanism, *Streptomyces* species secrete enzymes, proteins, and secondary metabolites into the surrounding medium, which interact with metal ions and reduce them extracellularly.

Key biomolecules involved include reductase enzymes, electron shuttle compounds, and bioactive metabolites, which facilitate the conversion of metal ions into stable nanoparticles outside the cell (Ahmad et al., 2003; Bansal et al., 2005). Recent advancements have highlighted the role of extracellular polymeric substances (EPS) and secreted peptides in enhancing nanoparticle nucleation and stability (Roy et al., 2021; Kumar et al., 2022).

This method offers significant advantages, including ease of nanoparticle recovery, reduced processing complexity, and suitability for large-scale production. Consequently, extracellular biosynthesis has gained prominence in green nanotechnology applications and industrial bioprocessing (Iravani et al., 2020; El-Naggar et al., 2022).

Role of Biomolecules

Biomolecules produced by *Streptomyces* species play multifunctional roles in nanoparticle biosynthesis, acting as reducing, stabilizing, and capping agents. These molecules include proteins, enzymes, polysaccharides, phenolic compounds, and diverse secondary metabolites such as antibiotics and siderophores (Kuppusamy et al., 2016; Singh et al., 2018).

Recent investigations have shown that functional groups present in these biomolecules—such as hydroxyl, carboxyl, and amine groups—facilitate the reduction of metal ions while simultaneously binding to nanoparticle surfaces to prevent aggregation (Ahmed et al., 2023; Khan et al., 2024). Additionally, specific peptides and proteins can influence nanoparticle size, shape, and crystallinity, enabling controlled synthesis with tailored physicochemical properties.

Furthermore, secondary metabolites produced by *Streptomyces* contribute to enhanced antimicrobial activity of the synthesized nanoparticles through synergistic effects, thereby expanding their biomedical relevance (El-Naggar et al., 2022; Roy et al., 2021). These biomolecular interactions are crucial for improving nanoparticle stability, dispersibility, and functional performance in various applications, including drug delivery and antimicrobial therapies.

Applications of Streptomyces-Derived Nanoparticles

Nanoparticles biosynthesized by *Streptomyces* spp. have attracted considerable attention because of their diverse biological activities, environmentally friendly production, and broad applicability across biomedical, agricultural, and environmental sectors. Analysis of the published literature reveals several important trends regarding nanoparticle types, application areas, and the strength of supporting evidence.

Predominant Nanoparticle Types and Application Trends

Among the nanoparticles reported, silver nanoparticles (AgNPs) are by far the most extensively studied, followed by gold nanoparticles (AuNPs), while zinc oxide (ZnO), selenium (SeNPs), copper oxide (CuO), titanium dioxide (TiO_2), and iron oxide (Fe_3O_4) nanoparticles are comparatively less represented. The predominance of AgNPs reflects their well-established broad-spectrum antimicrobial activity against bacterial, fungal, and biofilm-forming pathogens, including multidrug-resistant organisms (Anjum et al., 2024; Ovais et al., 2018; Wypij et al., 2018). Gold nanoparticles represent the second most frequently investigated class due to their favorable biocompatibility and applications in cancer therapy, drug delivery, wound healing, biosensing, and diagnostic imaging (El-Naggar et al., 2024; Lin et al., 2025).

Antimicrobial Applications

Antimicrobial activity remains the most widely reported application of *Streptomyces*-derived nanoparticles. Silver nanoparticles synthesized by species such as *S. rochei, S. viridogens, S. coelicolor, S. avidinii, S. xinghaiensis,* and *S. spiralis* have demonstrated effective inhibition of pathogenic microorganisms through cell membrane disruption, protein denaturation, oxidative stress induction, and reactive oxygen species (ROS) generation (Ovais et al., 2018; Wypij et al., 2018; Anjum et al., 2024). Several studies also reported antibiofilm activity, suggesting potential utility against persistent infections that are resistant to conventional antibiotics.

Anticancer and Biomedical Applications

The second major research focus involves anticancer and nanomedicine applications. Gold nanoparticles synthesized by *S. albogriseolus, S. kasugaensis,* and *Streptomyces* sp. YJD18 have demonstrated the ability to induce apoptosis through ROS generation, mitochondrial dysfunction, DNA fragmentation, and caspase activation in cancer cell lines (El-Naggar et al., 2024; Lin et al., 2025). Similarly, ZnO nanoparticles from *S. baarnensis* and selenium nanoparticles from *S. griseoruber* have exhibited promising anticancer, antioxidant, and immunomodulatory properties (Kalaba et al., 2024; Elnady et al., 2022). In addition, iron oxide nanoparticles synthesized by *S. hygroscopicus* have shown potential for magnetic targeting, biosensing, and diagnostic imaging applications (Abuzeid et al., 2023).

Agricultural and Environmental Applications

Although less extensively studied than biomedical applications, *Streptomyces*-derived nanoparticles have demonstrated potential in agriculture and environmental remediation. Copper oxide nanoparticles synthesized by *S. sannanensis* and ZnO nanoparticles produced by *S. cyaneofuscatus* have shown activity against plant pathogens and may contribute to sustainable crop protection strategies (Eweis et al., 2024). Environmental applications include pollutant degradation, wastewater treatment, and antimicrobial surface coatings, particularly through TiO_2 and AgNP-based systems capable of generating ROS-mediated degradation of environmental contaminants (Eweis et al., 2024; Ovais et al., 2018).

Critical Evaluation of Current Evidence

Despite the encouraging findings reported across multiple application areas, the current evidence base remains dominated by laboratory-scale and in vitro studies. Most antimicrobial and anticancer claims are supported primarily by cell culture experiments, while comprehensive in vivo investigations, pharmacokinetic studies, and clinical evaluations remain limited. Furthermore, substantial variability exists in nanoparticle synthesis methods, characterization techniques, biological assays, and reporting standards, making direct comparison among studies difficult. Another notable limitation is the scarcity of studies assessing the long-term environmental fate, biodegradation, bioaccumulation, and ecological impacts of these nanomaterials. Likewise, relatively few investigations have directly compared *Streptomyces*-derived nanoparticles with chemically synthesized counterparts under standardized conditions.

Overall, current evidence strongly supports the potential of *Streptomyces*-mediated nanoparticles as multifunctional nanomaterials, particularly for antimicrobial and anticancer applications. However, further in vivo validation, environmental safety assessment, standardized characterization protocols, and comparative studies are required before their full translational potential can be realized.

Table 1: Nanoparticles Synthesized from *Streptomyces* and Their Applications

Nanoparticle Type	Representative *Streptomyces* Species	Main Mechanisms	Key Applications	References
Silver nanoparticles (AgNPs)	*S. rochei, S. coelicolor, S. avidinii*	Reactive oxygen species (ROS) generation, membrane disruption, protein denaturation, DNA damage	Antimicrobial, antibiofilm, wound healing	El-Batal et al. (2022); Abuzeid et al. (2023); El-Naggar et al. (2024)
Gold nanoparticles (AuNPs)	*S. albogriseolus, S. kasugaensis*	Apoptosis induction, antioxidant activity, mitochondrial dysfunction, drug loading capability	Anticancer therapy, drug delivery, biosensing	Ghosh et al. (2021); Singh et al. (2022); El-Naggar et al. (2024)
Zinc oxide nanoparticles (ZnO NPs)	*S. baarnensis, S. cyaneofuscatus*	ROS generation, oxidative damage, membrane permeability alteration	Antimicrobial agents, agricultural disease control, plant growth promotion	Khan et al. (2022); Abuzeid et al. (2023); El-Naggar et al. (2024)
Selenium nanoparticles (SeNPs)	*S. griseoruber*	Antioxidant activity, immune modulation, oxidative stress regulation	Anticancer, antimicrobial, antioxidant applications	El-Batal et al. (2022); Ghosh et al. (2021); Khan et al. (2022)
Copper oxide nanoparticles (CuO NPs)	*S. sannanensis*	Oxidative stress induction, membrane damage, enzymatic inhibition	Plant disease control, antimicrobial applications	Singh et al. (2022); Abuzeid et al. (2023)
Iron oxide (Fe_3O_4) and Titanium dioxide (TiO_2) nanoparticles	*S. hygroscopicus, S. capillispiralis*	Magnetic targeting, photocatalysis, ROS-mediated degradation of pollutants	Diagnostics, targeted drug delivery, bioremediation, environmental remediation	Iravani et al. (2020); Khan et al. (2022); El-Naggar et al. (2024)

The most extensively studied *Streptomyces*-derived nanomaterials are silver and gold nanoparticles, largely due to their potent antimicrobial and anticancer activities (Ghosh et al., 2021; Singh et al., 2022; Abuzeid et al., 2023). Silver nanoparticles primarily exert antimicrobial effects through ROS generation, membrane disruption, and cellular damage,

whereas gold nanoparticles are commonly investigated for anticancer and drug-delivery applications because of their biocompatibility and ability to induce apoptosis in tumor cells (El-Batal et al., 2022; El-Naggar et al., 2024).

Prospects of *Streptomyces*-Mediated Nanoparticles

The application of *Streptomyces*-mediated nanoparticle synthesis has gained considerable attention in recent years due to its alignment with global demands for sustainable nanotechnology, biomedical innovation, and cost-efficient industrial processes. *Streptomyces* species, renowned for their metabolic diversity and production of bioactive compounds, offer unique advantages in the green synthesis of nanoparticles. The following subsections highlight the key prospects associated with this emerging field.

Eco-Friendly Synthesis

One of the most significant advantages of *Streptomyces*-mediated nanoparticle production is its environmentally benign nature. Unlike conventional physicochemical synthesis methods, which often involve toxic solvents, hazardous reducing agents, and high energy consumption, biological synthesis leverages naturally occurring biomolecules such as enzymes, proteins, and secondary metabolites as reducing and stabilizing agents. This approach minimizes the generation of harmful by-products and reduces ecological pollution (Iravani, 2014; Thakkar et al., 2010).

Streptomyces species secrete a wide array of extracellular enzymes and bioactive compounds capable of reducing metal ions into nanoparticles under mild conditions of temperature and pH. This eliminates the need for extreme reaction environments, thereby decreasing energy requirements and supporting sustainable production practices. Furthermore, the use of renewable biological systems aligns with the principles of green chemistry and circular bioeconomy.

In the context of increasing environmental concerns and stricter regulatory frameworks governing industrial waste disposal, eco-friendly synthesis through *Streptomyces* offers a viable alternative for large-scale nanoparticle production. This is particularly relevant in developing countries where environmental protection and industrial growth must be balanced.

Cost-Effectiveness

Cost efficiency is another compelling advantage of *Streptomyces*-mediated nanoparticle synthesis. Conventional nanoparticle fabrication techniques, such as chemical reduction and physical vapor deposition, require sophisticated equipment, high energy input, and expensive reagents, thereby limiting their scalability and commercial viability. In contrast, microbial synthesis utilizes relatively simple culture media, standard fermentation techniques, and readily available substrates (Kumar et al., 2018).

Streptomyces species are easily cultured under laboratory and industrial conditions, with well-established fermentation technologies already in place due to their long-standing use in antibiotic production. The integration of nanoparticle synthesis into existing fermentation systems reduces infrastructure costs and facilitates industrial adoption.

Moreover, the use of inexpensive substrates, including agricultural and industrial waste materials as culture media components, further lowers production costs and contributes to resource optimization. This economic advantage makes *Streptomyces*-mediated synthesis particularly attractive for large-scale applications in sectors such as pharmaceuticals, environmental remediation, and agriculture.

Biocompatibility

Biocompatibility is a critical factor in the biomedical application of nanoparticles, including drug delivery, imaging, and antimicrobial therapy. Biogenic nanoparticles synthesized by *Streptomyces* often exhibit enhanced biocompatibility and reduced cytotoxicity compared to their chemically synthesized counterparts (Singh et al., 2018).

This improved safety profile can be attributed to the natural capping of nanoparticles by biological molecules such as proteins, polysaccharides, and secondary metabolites produced during biosynthesis. These capping agents not only stabilize the nanoparticles but also modulate their interaction with biological systems, reducing adverse effects on healthy tissues.

Additionally, the inherent bioactivity of *Streptomyces*-derived compounds may impart synergistic therapeutic properties to the nanoparticles, thereby enhancing their efficacy. For instance, antimicrobial nanoparticles synthesized by *Streptomyces* may exhibit dual functionality due to both metallic and microbial-derived bioactive components.

The potential for reduced immunogenicity and improved pharmacokinetics positions these nanoparticles as promising candidates for clinical translation in areas such as antimicrobial therapy, cancer treatment, and tissue engineering.

Functional Versatility

Another notable prospect of *Streptomyces*-mediated nanoparticles lies in their functional versatility. The surface properties of biogenic nanoparticles can be readily modified or inherently functionalized during synthesis through interactions with microbial metabolites. This facilitates enhanced performance across a wide range of applications (Kuppusamy et al., 2016).

Surface functionalization plays a crucial role in determining nanoparticle behavior, including stability, solubility, targeting ability, and interaction with biological systems. *Streptomyces*-derived nanoparticles often possess naturally functionalized surfaces that improve dispersion and prevent aggregation without the need for additional chemical modifications.

Furthermore, these nanoparticles can be tailored for specific applications through controlled synthesis conditions or post-synthesis modifications. Examples include:

i. Biomedical Applications: Targeted drug delivery, cancer therapy, antimicrobial coatings.
ii. Environmental Applications: Heavy metal removal, water purification, pollutant degradation.
iii. Agricultural Applications: Nano-fertilizers, plant disease control, growth promoters.

The adaptability of *Streptomyces* systems also allows for the synthesis of diverse nanoparticle types, including metallic (Ag, Au), metal oxides (ZnO, TiO_2), and hybrid nanostructures, further expanding their utility.

Limitations and Challenges of *Streptomyces*-Mediated Nanoparticles

Despite their considerable potential in nanomedicine, biotechnology, agriculture, and environmental applications, *Streptomyces*-mediated nanoparticles face several limitations that currently hinder their large-scale production, commercialization, and clinical translation. These challenges primarily relate to standardization, scalability, safety, stability, and regulatory compliance.

Lack of Standardization

One of the most significant challenges is the lack of standardized synthesis and characterization protocols. The physicochemical properties of nanoparticles, including size, shape, dispersity, and surface charge, are highly influenced by culture conditions such as pH, temperature, nutrient composition, incubation time, and metal precursor concentration. In addition, differences among *Streptomyces* species, strains, and metabolic activities contribute to variability in nanoparticle synthesis, resulting in poor reproducibility across studies and production batches (Grasso et al., 2020).

To address this limitation, recent studies have recommended the establishment of standardized operating procedures (SOPs) that precisely control biosynthesis conditions, purification processes, and quality assessment parameters (Zayerzadeh & Koohi, 2024; El-Naggar et al., 2024). The implementation of advanced characterization techniques, including dynamic light scattering (DLS), transmission electron microscopy (TEM), scanning electron microscopy (SEM), Fourier-transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), and zeta potential analysis, is also essential for ensuring consistency and comparability among studies (Kerdtoob et al., 2024; Kalaba et al., 2024). Furthermore, integrating omics-based approaches and systems biology tools may improve understanding of the biomolecules involved in nanoparticle reduction and stabilization, thereby enhancing process reproducibility and strain-specific optimization (Li et al., 2024).

Scalability Challenges

Although *Streptomyces*-mediated nanoparticle biosynthesis has been successfully demonstrated at the laboratory scale, industrial-scale production remains challenging. Biological systems are highly sensitive to environmental fluctuations, making it difficult to maintain consistent nanoparticle yield, quality, and productivity during large-scale fermentation (Fariq et al., 2017). Moreover, downstream processing steps such as nanoparticle recovery, purification, concentration, and stabilization remain technically demanding and economically expensive.

Advances in bioprocess engineering provide potential solutions to these challenges. Optimized bioreactor designs, automated fermentation systems, artificial neural networks (ANNs), and response surface methodology (RSM) have been shown to improve process control, nanoparticle yield, and production efficiency (El-Naggar et al., 2024). Additionally, metabolic engineering and synthetic biology approaches could enhance nanoparticle productivity through the genetic modification of *Streptomyces* strains to overexpress reducing enzymes, metal transporters, and stabilizing metabolites (Lin et al., 2025; Kalaba et al., 2024).

Safety and Toxicity Concerns

Safety remains a critical consideration for the biomedical application of *Streptomyces*-derived nanoparticles. Although biogenic nanoparticles are generally regarded as more biocompatible than chemically synthesized counterparts, they may still induce oxidative stress, inflammation, genotoxicity, and cytotoxic effects depending on their size, morphology, concentration, surface chemistry, and composition (Ovais et al., 2018). Smaller nanoparticles, in particular, possess larger surface-area-to-volume ratios and may generate elevated levels of reactive oxygen species (ROS), leading to cellular damage and apoptosis.

Furthermore, residual microbial metabolites and incomplete purification may influence biological interactions and toxicity profiles. Consequently, comprehensive toxicological evaluation frameworks are required. Recent studies advocate combining conventional cytotoxicity assays with advanced transcriptomic, proteomic, metabolomic, and lipidomic analyses to better understand nanoparticle-induced toxicity pathways (Li et al., 2024; Calé et al., 2025). Future research should also investigate long-term effects, including biodistribution, bioaccumulation, immunotoxicity, genotoxicity, reproductive toxicity, and ecological impacts, while adopting standardized toxicity-testing protocols to improve reliability and comparability of results (Zayerzadeh & Koohi, 2024). Comparative assessments between biologically and chemically synthesized nanoparticles are equally important for validating the proposed safety advantages of *Streptomyces*-mediated nanoparticles (Awashra & Młynarz, 2023).

Stability Issues

The long-term stability of biogenic nanoparticles remains another significant concern. During storage and application, nanoparticles may aggregate due to weak stabilization forces, leading to alterations in particle size, surface properties, biological activity, and therapeutic efficacy (Mittal et al., 2013). Environmental factors such as temperature, pH, ionic strength, and light exposure can further accelerate instability and reduce functionality.

Although *Streptomyces*-derived biomolecules act as natural capping and stabilizing agents, they may not always provide sufficient long-term protection. To improve nanoparticle stability, several advanced stabilization strategies have been proposed, including polymer coating, PEGylation, surface functionalization, nanoencapsulation, and lyophilization (Chávez-Hernández et al., 2024). Moreover, optimization of microbial capping agents and the development of smart nanocarriers and hybrid nanocomposites may further enhance colloidal stability, shelf-life, environmental tolerance, and targeted delivery efficiency (Kerdtoob et al., 2024; Lin et al., 2025).

Regulatory and Commercialization Barriers

Regulatory uncertainty represents a major obstacle to the commercialization of *Streptomyces*-mediated nanoparticles. Currently, there are no universally harmonized international guidelines governing nanoparticle synthesis, characterization, toxicity testing, environmental risk assessment, manufacturing standards, and product labeling (Grasso et al., 2020). Differences among national regulatory frameworks create additional challenges for product approval, market entry, and global distribution.

The unique hybrid nature of biogenic nanoparticles, which combines biological and nanotechnological components, further complicates classification and risk assessment. Recent studies have highlighted the urgent need for internationally accepted regulatory frameworks that address safety evaluation, environmental sustainability, quality control, and lifecycle management of nanoparticle-based products (Chávez-Hernández et al., 2024; Shin et al., 2026). Incorporating life-cycle assessment (LCA) approaches into regulatory policies would facilitate safer and more sustainable production, use, and disposal of nanomaterials (Chávez-Hernández et al., 2024).

Future Perspectives

Overall, the successful translation of *Streptomyces*-mediated nanoparticles from laboratory-scale research to industrial and clinical practice will depend on overcoming challenges related to reproducibility, large-scale manufacturing, toxicity

assessment, long-term stability, and regulatory compliance. Future progress will require standardized synthesis protocols, scalable bioprocess technologies, comprehensive toxicological frameworks, advanced stabilization methods, and harmonized international regulations (Fariq et al., 2017; Grasso et al., 2020; Ovais et al., 2018).

Emerging technologies such as artificial intelligence-driven bioprocess optimization, omics-based toxicity assessment, systems biology, metabolic engineering, and advanced drug-delivery platforms are expected to play crucial roles in addressing these limitations and accelerating the development of safe, sustainable, and clinically applicable *Streptomyces*-derived nanoparticle systems (El-Naggar et al., 2024; Li et al., 2024; Lin et al., 2025 Ahmad et al., 2026).

Future Perspectives of *Streptomyces*-Mediated Nanoparticles

The growing interest in *Streptomyces*-mediated nanoparticle biosynthesis reflects the significant potential of these microorganisms for sustainable nanomaterial production. Although numerous studies have demonstrated promising antimicrobial, anticancer, agricultural, and environmental applications, most evidence remains confined to laboratory-scale investigations and in vitro experiments (El-Naggar et al., 2024; Abuzeid et al., 2023). Consequently, future research should focus on addressing mechanistic, toxicological, standardization, and translational challenges to facilitate the practical deployment of *Streptomyces*-derived nanomaterials.

Standardization and Scalable Manufacturing

A major obstacle to commercialization is the absence of standardized synthesis and characterization protocols. Variations in *Streptomyces* strains, growth media, incubation conditions, pH, temperature, and metal precursor concentrations often result in nanoparticles with inconsistent physicochemical properties (Kuppusamy et al., 2016; Singh et al., 2022). Future research should establish standardized operating procedures for nanoparticle production and quality assessment, with emphasis on critical parameters such as particle size, morphology, crystallinity, surface charge, and colloidal stability (El-Naggar et al., 2024).

The integration of artificial intelligence, machine learning algorithms, and process analytical technologies may further improve process optimization and reproducibility. Such approaches can facilitate the transition from bench-scale synthesis to industrial manufacturing while ensuring consistent nanoparticle quality and performance (Karunakaran et al., 2023; El-Naggar et al., 2024).

Multi-Omics Approaches for Mechanistic Elucidation

Although enzymes, proteins, polysaccharides, and secondary metabolites have been recognized as major contributors to nanoparticle biosynthesis, the molecular mechanisms controlling metal ion reduction, nucleation, growth, and stabilization remain insufficiently understood (Singh et al., 2018; Ghosh et al., 2021).

Future studies should employ integrated multi-omics approaches, including:

i. Genomics to identify genes associated with metal tolerance and nanoparticle biosynthesis.
ii. Transcriptomics (RNA-Seq) to determine genes differentially expressed during nanoparticle formation.
iii. Proteomics to identify reductase enzymes and nanoparticle-capping proteins.
iv. Metabolomics to characterize bioactive metabolites involved in reduction and stabilization processes.
v. Systems biology frameworks to integrate multi-omics datasets and reveal regulatory networks governing nanoparticle synthesis (Singh et al., 2018; El-Naggar et al., 2024).

These approaches will provide mechanistic insights that can facilitate the rational design of nanoparticles with enhanced biological activity, stability, and specificity.

Genetic Engineering and Strain Improvement

Recent advances in synthetic biology and genome engineering have opened new opportunities for improving the nanoparticle-producing capabilities of *Streptomyces* species. Techniques such as CRISPR-Cas genome editing can be employed to overexpress metal-reducing enzymes, enhance electron transfer pathways, and optimize secondary metabolite production (Vijayan et al., 2018; Karunakaran et al., 2023).

Future engineering strategies may focus on:

i. Increasing nanoparticle production yields.
ii. Controlling nanoparticle size and morphology.
iii. Enhancing nanoparticle stability and functionality.
iv. Improving tolerance to metal ion toxicity.
v. Developing strains capable of producing multifunctional nanomaterials (Vijayan et al., 2018; El-Naggar et al., 2024).

Such developments could significantly improve process efficiency and support the large-scale production of customized nanomaterials for biomedical and environmental applications.

Comprehensive Toxicity and Safety Assessment

Despite increasing interest in biologically synthesized nanoparticles, comprehensive safety evaluation remains a major research gap. Current toxicity data are largely derived from short-term in vitro studies, whereas evidence from chronic in vivo investigations remains limited (Ovais et al., 2018; Khan et al., 2022).

Future studies should prioritize the evaluation of:

i. Biodistribution and tissue accumulation.
ii. Clearance and biotransformation pathways.
iii. Chronic and sub-chronic toxicity.
iv. Immunotoxicity and inflammatory responses.
v. Genotoxicity and DNA damage.
vi. Reproductive and developmental toxicity.
vii. Environmental persistence and ecotoxicological impacts (Khan et al., 2022; El-Naggar et al., 2024).

Particular attention should be given to priority toxicity endpoints such as oxidative stress biomarkers, cytokine expression profiles, histopathological changes, liver and kidney function markers, hematological parameters, and DNA damage assays. The establishment of internationally harmonized toxicological testing frameworks would facilitate regulatory approval and clinical translation (Ovais et al., 2018; Abuzeid et al., 2023).

7.5 Development of Multifunctional Nanomaterials

The future of *Streptomyces*-mediated nanotechnology lies in the development of multifunctional nanoplatforms capable of performing therapeutic, diagnostic, and environmental functions simultaneously. Advances in nanoparticle engineering and surface functionalization have enabled the design of sophisticated nanosystems with enhanced targeting capabilities and improved biological performance (Karunakaran et al., 2023).

Promising areas for future development include:

i. Theranostic nanoparticles combining disease diagnosis and treatment.

ii. Stimuli-responsive nanoparticles activated by pH, temperature, enzymes, light, or magnetic fields.
iii. Targeted drug-delivery systems incorporating ligands, peptides, or antibodies.
iv. Hybrid bio-nanocomposites integrating metallic nanoparticles with polymers and biomolecules.
v. Antimicrobial smart coatings for the prevention of multidrug-resistant infections (Ovais et al., 2018; Karunakaran et al., 2023).

Although these emerging applications appear promising, many remain supported primarily by preliminary laboratory findings. Therefore, extensive preclinical evaluation and validation are needed before practical implementation.

Regulatory and Translational Considerations

Beyond scientific advancement, successful commercialization of *Streptomyces*-derived nanoparticles will require compliance with regulatory frameworks governing nanomaterial production and safety. Future studies should adopt Good Manufacturing Practice (GMP) principles, validated characterization protocols, standardized toxicity assessment procedures, and quality-by-design approaches (Khan et al., 2022; El-Naggar et al., 2024).

Collaborative efforts involving microbiologists, nanotechnologists, toxicologists, clinicians, and regulatory authorities will be essential for translating laboratory discoveries into industrial and clinical applications.

CONCLUSION

Streptomyces-mediated nanoparticle synthesis represents a promising and sustainable approach to nanomaterial production, offering an environmentally friendly alternative to conventional physical and chemical methods. Through their diverse repertoire of enzymes, proteins, polysaccharides, and bioactive secondary metabolites, *Streptomyces* species can efficiently facilitate the synthesis and stabilization of a wide range of metallic and metal oxide nanoparticles. These nanomaterials have demonstrated considerable potential in antimicrobial therapy, cancer treatment, drug delivery, agriculture, environmental remediation, and biosensing applications.

Despite these advances, several critical barriers continue to constrain their broader translation. Major challenges include the lack of standardized synthesis and characterization protocols, variability in nanoparticle properties, limited scalability, insufficient long-term safety and toxicological data, and the absence of harmonized regulatory frameworks. Furthermore, much of the current evidence is derived from in vitro studies, while robust in vivo investigations and comparative assessments with chemically synthesized nanoparticles remain limited.

Addressing these gaps should be a priority for future research. Efforts should focus on standardized production and evaluation protocols, omics-based investigations to elucidate biosynthetic mechanisms, strain engineering to improve yield and reproducibility, comprehensive toxicity and biodistribution studies, and systematic assessments of environmental impacts. Equally important is the development of clear regulatory and quality-control frameworks to support responsible innovation.

In conclusion, *Streptomyces*-derived nanoparticles hold significant potential for advancing sustainable nanobiotechnology; however, their successful translation will require rigorous standardization, robust safety validation, scalable manufacturing strategies, and well-defined regulatory pathways before widespread clinical, industrial, or environmental implementation can be realized.

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