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Original article

Biosynthesis and Biomedical Applications of Selenium Nanoparticles Synthesized by Actinomycetes: A Review

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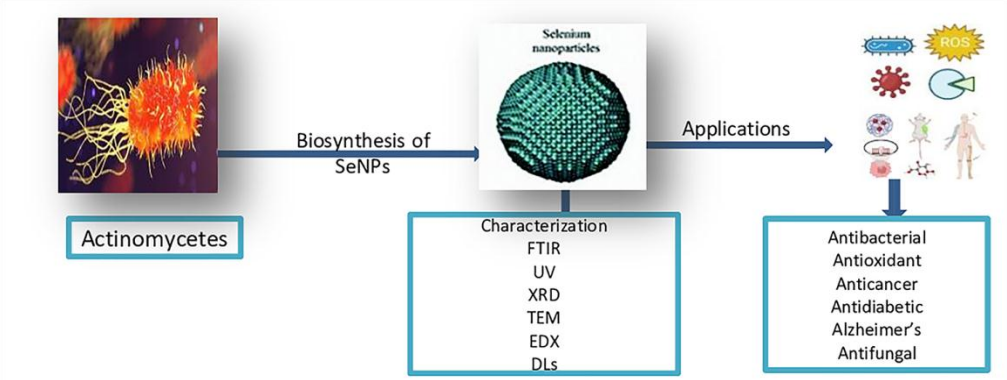
ABSTRACT

Selenium nanoparticles (SeNPs) have emerged as potential nanomaterials due to their biocompatibility, bioavailability, and low toxicity, making them ideal for a wide range of biomedical applications. Although SeNPs may be manufactured via physical, chemical, and biological processes, biological approaches are gaining popularity because of their environmental friendliness and improved bioactivity. Actinomycetes, as microbial systems, constitute a novel and underexplored platform for SeNP biosynthesis due to their unique metabolic capability, generation of bioactive compounds, and ability to create nanoparticles of regulated size and stability. These nanoparticles are confirmed and characterized using advanced analytical methods such as UV-Vis spectroscopy, FTIR, XRD, SEM, EDX, and DLS. This study emphasizes the unique function of actinomycetes in sustained SeNP synthesis and critically examines their medicinal uses, which range from antibacterial and antifungal activities to antioxidant, anticancer, and antidiabetic therapy. By stressing the benefits of actinomycete-mediated synthesis over traditional approaches, this work highlights actinomycetes' originality and future promise as efficient bio factories for SeNPs in biomedical research.

Graphical abstract



1. Introduction

Nanotechnology is a rapidly expanding science with many applications in health, agriculture, catalysis, and environmental management [1-2]. Nanoparticles (NPs), which generally range in size from 1 to 100 nm, have distinct physicochemical features due to their high surface-to-volume ratio and quantum effects. Metallic nanoparticles such as Zn, Cu, Mg, Au, Ti, and Ag have all been thoroughly researched for their biological applications [3, 4]. However, current physical and chemical synthesis methods are still hindered by high energy demands, hazardous byproducts, and limited scalability, emphasizing the need for safer and more sustainable methodologies [5].

Selenium (Se), a naturally occurring but scarce metalloid, is an essential micronutrient for immunity, antioxidant defense, aging, and tumor suppression [6-7]. Selenium nanoparticles (SeNPs) exhibit increased bioactivity, reduced toxicity, and improved bioavailability when compared to bulk selenium, making them highly appealing for biomedical applications such as antibacterial, antifungal, antioxidant, anticancer, and antidiabetic therapies [8]. Biogenic production of SeNPs has gained popularity as an environmentally acceptable and biocompatible alternative to conventional approaches.

Despite these developments, the majority of research has been on plants, fungi, or bacteria, and little is known about the role actinomycetes may play in SeNP production. Gram-positive bacteria with a high GC content and a fungal-like appearance, actinomycetes are well-known for producing a large number of bioactive secondary metabolites, such as enzymes, antibiotics, and anticancer drugs [9, 10]. Actinomycetes have a unique possibility to be used as prospective bio factories for the manufacture of SeNPs, since these biomolecules can act as natural reducing and stabilizing agents during nanoparticle creation.

The purpose of this work is to fill this research gap by concentrating on the production of SeNPs utilizing actinomycetes. To enhance their usage in medicine, the goals are to (i) describe what is now known about actinomycete-mediated SeNPs, (ii) emphasize their benefits over other biological systems, (iii) critically assess their biomedical uses, and (iv) identify knowledge gaps and future prospects.

2. Methodology

This study was carried out by methodically gathering and analyzing relevant material from a variety of internet databases and academic resources. Google Scholar, PubMed, Web of Science, and Scopus were the key databases examined, with pertinent books and journal articles from the university library supplementing the search. Selenium nanoparticles, actinomycetes, antioxidant, anticancer, microbial-mediated SeNPs, SeNP characterization, biocompatibility, cytotoxicity, and antibacterial were all employed, either alone or in combination.

The criteria for inclusion were as follows: studies had to (i) describe the biosynthesis of selenium nanoparticles using actinomycetes or other microbial systems, (ii) examine the physicochemical characterization of SeNPs (e.g., UV–Vis, FTIR, XRD, SEM, EDX, DLS), or (iii) assess biomedical applications like antioxidant, antimicrobial, anticancer, or anti diabetic activity. Only scholarly books published in English, conference proceedings, and peer-reviewed journal articles were taken into account.

Exclusion criteria: Studies were excluded if they (i) only addressed bulk selenium or non-nano selenium compounds, (ii) described physical or chemical synthesis techniques that did not involve biology, or (iii) came from non-peer-reviewed sources like news articles, opinion pieces, or unpublished reports, or (iv) lacked adequate methodological detail or characterization information. After the first search produced a large number of results, the irrelevant papers were filtered out by title and abstract. Methodological rigor and relevance to the review's goals were then assessed in full-text papers. A thorough and fair coverage of the biosynthesis processes, characterization techniques, and biological uses of actinomycete-mediated SeNPs was ensured by the selection of final references.

3. Results

3.1. Methods for the formation of Selenium Nanoparticles

The physical, chemical, and biological (green) methods are the three primary ways to biosynthesize SeNPs. Nanoparticles (Fig. 1). The benefits and drawbacks of each approach are presented in Table 1.

Environmentally friendly biosynthesis techniques provide a sustainable solution to the challenges of synthetic nanoparticle manufacturing, including the use of hazardous reagents, high energy consumption, and limited scalability. Green approaches enable safer, more affordable, and environmentally compatible nanoparticle production [8].

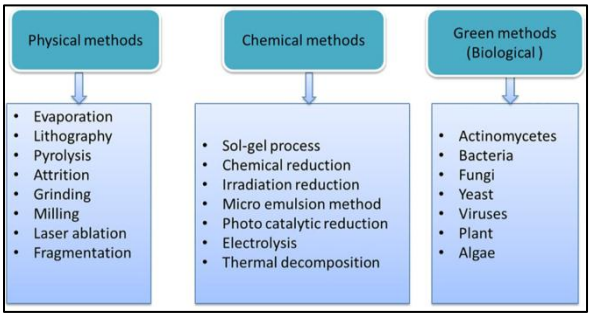


Fig. 1. Various techniques for creating selenium nanoparticles (SeNPs), categorized into physical, chemical, and green (biological) methods. Each pathway uses different mechanisms and has specific advantages and limitations in terms of scalability, cost, and biocompatibility.

3.2. Biological Methods (Green Synthesis)

Numerous microorganisms, including bacteria, fungi, yeasts, and actinomycetes have been successfully employed for nanoparticle biosynthesis. These biological systems are recognized as environmentally safe, cost-effective, and time-efficient platforms for producing nanoparticles compared with traditional physical and chemical methods [11].

3.2.1. Microorganisms in the biosynthesis of nanoparticles

To convert metal ions into stable nanoparticles, microorganisms use a variety of metabolic and enzymatic processes. Because each type of bacteria has unique benefits, they are useful platforms for green synthesis**.**

3.2.1.1. Fungi-based biosynthesis

Because fungi may mediate both external and intracellular activities, while the mechanisms are still poorly understood, they are being investigated extensively for the creation of nanoparticles [12]. Fungi, the biggest category of microbes, are crucial to nanotechnology, enzyme synthesis, and bioremediation [13]. Their benefits include a wide mycelial surface area, simplicity of downstream processing, and metal tolerance [14, 15]. Numerous species have been reported to create nanoparticles with high yield, stability, and economic viability, including *Aspergillus, Trichoderma, Verticillium, Rhizopus, Penicillium, and Fusarium* [16].

3.2.1.2. Bacteria-based biosynthesis

Because of their ease of culture, genetic versatility, and capacity to generate nanoparticles of various sizes and shapes, bacteria were historically the first microorganisms used in nanoparticle biosynthesis. However, fungi offer several benefits. The ability of bacterial systems to decrease harmful metal ions is noteworthy; for example,

silver ions may be converted into silver nanoparticles (AgNPs). For example, AgNPs with different morphologies were formed by a Pseudomonas strain that was isolated from the Antarctic ciliate *Euplotes focardii* [17]. This illustrates how adaptable bacterial systems are in the field of green nanotechnology.

Table (1): Comparative summary of selenium nanoparticle (SeNP) synthesis methods, highlighting typical techniques, advantages, limitations, and expected outcomes.

Synthesis Method	Examples / Sources	Advantages	Limitations	Characterization Techniques	Typical Outcomes / Applications
Physical methods	Laser ablation, ball milling, evaporation–condensation	Simple and rapid; no chemical reagents	High energy cost; poor Control of particle size requires advanced equipment	XRD, SEM, TEM, DLS	SeNPs with variable size; limited biomedical use due to agglomeration
Chemical methods	Chemical reduction, precipitation, hydrothermal, sol–gel	Large-scale production; good control over size/shape	Toxic solvents/reagents; possible cytotoxicity; low biocompatibility	UV–Vis, FTIR, XRD, SEM, EDX	SeNPs for catalysis, photocatalysis, and limited drug delivery
Biological methods (Green synthesis)	Bacteria, fungi, yeast, and plant extracts	Eco-friendly, cost-effective, biocompatible; metabolites act as reducing & capping agents	Slower synthesis; variability between organisms; optimization required	UV–Vis, FTIR, SEM, XRD, DLS, EDX	Biocompatible SeNPs with antimicrobial, antioxidant, anticancer, and antidiabetic effects.
Actinomycete-mediated synthesis	*Streptomyces, Nocardia, Rhodococcus, Thermoactinomycetes spp.*	Produces stable, polydisperse SeNPs; metabolites enhance bioactivity; high biomedical potential.	Slower growth; few mechanistic studies; scale-up challenges.	UV–Vis, FTIR, SEM, TEM, XRD, EDX, DLS.	SeNPs with strong antibacterial, antifungal, antioxidant, and anticancer activity; promising for drug delivery a nd biomedical research.

3.2.1.3. Yeast-based biosynthesis

Yeasts are a promising microbial platform in addition to bacteria and fungi. Yeasts are easy to grow, control, and scale in a lab setting since they are single-celled eukaryotic microorganisms. Yeasts, of which more than 1,500 species have been found, offer stable and regulated systems for the creation of nanoparticles, as extensively reported in the literature [18].

3.2.1.4. Actinomycetes-based biosynthesis

Actinomycetes are poorly studied but very promising options for the production of nanoparticles among microbial systems. Actinomycetes are well-known for their ability to produce antibiotics and other beneficial secondary metabolites [19, 20]. They may also naturally reduce and stabilize the development of nanoparticles [21]. Actinomycetes are efficient in the creation of extracellular and intracellular nanoparticles [22]. According to reports, they produce nanoparticles with potent biocidal properties, stability, and excellent polydispersity. While Streptomyces spp. have successfully created silver nanoparticles and selenium nanoparticles (SeNPs), examples of gold nanoparticles include Thermoactinomycetes sp., Rhodococcus sp., Streptomyces viridogens, Nocardia farcinica, Streptomyces hygroscopicus, and Thermomonospora sp. [16].

3.3. Actinomycetes' biosynthesis of SeNPs

According to Bahig et al. (2023) [23], after Se NPs are isolated, the most efficient strain of actinomycetes is utilized for the biogenic synthesis of SeNPs. After being added to an Erlenmeyer flask with 100 ml of nutritional broth, the actinobacterial inoculum of strain E3 was shaken at 180 rpm for five to seven days. Centrifugation, which was operated for 30 minutes at 5000 rpm, was used to extract the biomass from the cell supernatant. 100 mL of 1 mM Na2SeO3 in an aqueous solution was combined with 5 g of wet biomass, weighed, rinsed three times with sterile deionized water, and then incubated for 72 hours in a rotator shaker [24]**.** At the same time, a culture medium free of bacterial cells and a supernatant containing 1 mM of Na2SeO3 were used as positive and negative controls, respectively.

Using spectroscopy (200-800 nm) and visual inspection, the synthesis of selenium nanoparticles was confirmed.

Streptomyces sp. growth generates selenium nanoparticles both extracellularly and intracellularly, according to Bahig et al. (2023) [23]. Visual examination of the culture treated with sodium selenite at 32°C for five to seven days in the dark revealed a color shift from light yellow to brilliant red. According to Bajaj et al. (2012) [25], this signifies the production of red-colored elemental Se^0, which is a defining trait of selenium nanoparticles. The sodium selenite solution used as a negative control, however, did not exhibit any color change. There was no color change in control reactions using the bacterial-free growth media, which did not imply that bacteria were required for the bio fabrication of SeNPs.

Despite these benefits, actinomycete-mediated synthesis still has drawbacks. The obstacles include a lack of thorough mechanistic knowledge of the metabolic mechanisms underpinning nanoparticle creation, comparatively slower growth rates as compared to bacteria and yeasts, and challenges in adjusting culture settings for consistent nanoparticle yield. Achieving process standardization and increasing production scale continue to be major barriers to industrial use [26]. Nonetheless, actinomycetes' metabolic diversity and capacity to produce bioactive, functionalized nanoparticles make them a uniquely promising but underutilized platform for improving green nanotechnology in biomedici ne.

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3.4. Selenium nanoparticle (SeNP) characterizati

Size, shape, and other factors are studied to determine and define the structural properties of SeNP. The structural characteristics of Se NPs are examined using the following methods: Fourier Transform infrared spectroscopy(FTIR): to identify functional groups responsible for reduction and stabilization; Dynamic light scattering (DLS) and Zeta Potential: to assess particle size distribution and surface charge stability; Scanning and Transmission Electron Microscopy (SEM and TEM): to analyze the morphology, size, and surface structure; Ultraviolet (UV)-visible absorption spectral analysis: to identify the characteristic absorption peak of SeNPs; and, lastly, the size, shape, and other characteristics of SeNPs [27].

3.5. Application of SeNPs

The biological activities of selenium nanoparticles (SeNPs), such as their antifungal, anticancer, antioxidant, antibacterial, antidiabetic, and neuroprotective properties, have drawn a lot of attention. Although several studies demonstrate their potential, unsolved issues, including toxicity, stability, and dose optimization, continue to limit the practical translation of SeNPs. The main biological uses of SeNPs, as shown in Fig. 2, are critically assessed in the following subsections.

3.5.1. SeNPs as cytotoxic/anticancer agents

SeNPs' strong bioactivity, minimal systemic toxicity, and potential for functional design in biomedical applications are highlighted in recent initiatives to highlight their clinical translational potential [28]. The potential of SeNPs as anticancer agents was underlined by an in vitro investigation that revealed significant cytotoxicity at specific dosages (25 µL/mL) [29]. However, results differ depending on the kind of cancer, and clinical data are still inadequate. Before incorporating SeNPs into routine treatment, thorough comparative and clinical assessments are still required.

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3.5.2. SeNPs as Antioxidants

The antioxidant effectiveness of SeNPs with enhanced stability and safety is confirmed by new research. Strong antioxidant (and antibacterial) activity and good stability characteristics are displayed by green-synthesised SeNPs made from plant extracts [30]. When SeNPs are stabilized with *Moringa oleifera* polysaccharides, their stability and antioxidant qualities are further improved, providing improved storage and digestive resilience [31]. Furthermore, ultra-small lentinan-derived SeNPs (LNT-UsSeNPs) exhibit minimal immunosuppressive risk, improved ROS scavenging, blood–spinal cord barrier penetration, and neuroprotective effect across important signaling pathways [32]. Studies on dietary supplements in model species, such as fish, show increased activity of antioxidant enzymes without inducing oxidative stress [33].

3.5.3. SeNPs as Antibacterial Agents

A new SeNPs–Cu_2O nanocomposite shows strong activity against multidrug-resistant (MDR) Gram-positive and Gram-negative clinical isolates, indicating a viable approach against nosocomial infections [34]. Recent investigations build on classic antibacterial results. Comparative analyses of surface-modified SeNPs provide additional insight into the ways that surface chemistry and chemical structure affect antibacterial efficacy [35]. Long-term safety and resistance mechanisms, however, still need more research.

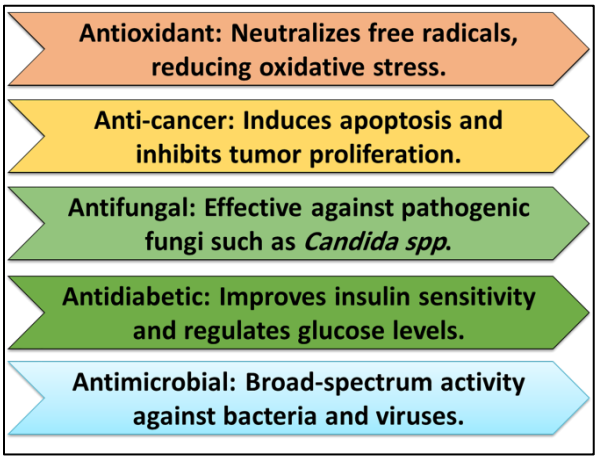

Fig. 2. Applications of selenium nanoparticles (SeNPs) in biomedical and therapeutic fields, illustrating their multifunctional roles including antioxidant, anticancer, antifungal, antidiabetic, and antimicrobial activities

3.5.4. Antidiabetic Activity

According to recent research, resveratrol-functionalized chitosan selenium nanoparticles (CS/Res/SeNPs) modulate the PI3K/AKT/mTOR sig-

naling pathway to provide hepatoprotective and antidiabetic benefits [36]. Preclinical in vitro and animal models are the primary sources of these encouraging results. The therapeutic promise of CS/Res/SeNPs in the treatment of type 2 diabetes and associated consequences must thus be confirmed by further research concentrating on bioavailability, pharmacokinetics, and clinical effectiveness in people.

3.5.5. Role of SeNPs in Alzheimer's Disease

The therapeutic potential of antioxidant-loaded nano carriers has been highlighted by the ability of chrysine-loaded lipid nanoparticles to reduce amyloid β-induced neuronal stress in Alzheimer's disease mice [37]. But a more recent study has particularly assessed selenium nanoparticles (SeNPs) in Alzheimer's disease models both in vitro and in vivo. By lowering β-amyloid aggregation, inhibiting tau hyper phosphorylation, decreasing oxidative stress and neuroinflammation, and even overcoming the blood–brain barrier to enhance cognitive outcomes in transgenic mouse models, SeNPs have been shown to have neuroprotective benefits, according to this review [38].

Despite these positive findings, the formulation, dose, method of administration, and particle size of SeNPs continue to influence therapeutic efficacy. Furthermore, conventional biomarkers, such as glutathione peroxidase (GSH-Px) activity and plasma selenium, only provide proxy indicators of neuroprotection. In Alzheimer's research, SeNPs should be considered experimental drugs rather than proven treatments until strong longitudinal human studies verify safety and efficacy.

3.5.6. Antifungal Activity

SeNPs have encouraging antifungal action against *Aspergillus terreus, Candida albicans, and Malassezia spp.* [39]. Functionalization with proteins or polysaccha rides increases their antifungal effectiveness and biocompatibility. SeNPs' antifungal properties and vast biological potential are confirmed by recent studies, which also highlight their high utilization rate and low toxicity (e.g., in modulating inflammatory diseases) [40].

3.6. Toxicity and Safety Evaluation of SeNPs

3.6.1. Comparative Toxicity Profile

SeNPs are consistently less hazardous than conventional forms of selenium, according to recent evaluations. SeNPs, for example, showed reduced acute and sub-chronic toxicity in lab animal models, with LOAEL of around 0.05 mg/kg/day and NOAL values of about 0.22 mg/kg/day for males and 0.33 mg/kg/day for females [41]. Furthermore, up to 2000 mg/kg, biosynthesized SeNPs (for example, by Bacillus halotolerans) showed no acute toxicity and had no negative impact on body weight, biochemical results, or histological liver and kidney markers [42].

3.6.2. Age-Dependent Biodistribution & Toxicity

SeNPs' toxicity and biodistribution are influenced by age; in a 28-day trial, SeNPs accumulated preferentially in the liver, testes, and kidney, with younger rats exhibiting stronger protective effects than adults [43].

3.6.3. Stability-Dependent Cytotoxicity

Ascorbic acid-stabilized SeNPs showed much increased toxicity (EC50 = 6.8 mg/L) towards NIH/3T3 cells, but SeNPs reduced by sodium borohydride were barely cytotoxic (EC50 >100 mg/L) [44]. This suggests that the synthesis process has a considerable impact on cytotoxicity.

3.6.4. Safety and Synthesizing Methods

According to thorough evaluations, SeNPs exhibit less toxicity and short-term negative effects than either inorganic or organic forms of selenium [45]. Furthermore, it was discovered that biologically produced SeNPs were less toxic and more biocompatible than bulk selenium in a veterinary setting [46].

4. Conclusion

Selenium is an essential micronutrient for the proper functioning of the body's biological and metabolic functions. This review validates the effectiveness of the biosynthetic process that uses bacteria, fungi, yeast, and actinomycetes to create selenium nanoparticles (SeNPs) with distinct physicochemical properties. Biological methods for creating Se NPs are less expensive, safe, and environmentally friendly than chemical reduction processes, which need hazardous chemicals, high temperatures, and an acidic pH. Use a range of techniques, such as UV-Vis, FTIR, SEM, TEM, EDX, XRD, DLS, and Zeta potential, to characterize the generated nanoparticles. The investigation focuses on the biosynthesis of Se NPs from actinomycetes. Se NPs have a variety of biological applications due to their superior characteristics. SeNPs are highly effective at preventing fatal diseases like diabetes, Alzheimer's, cancer, and drug-induced toxicity, according to numerous studies. Despite this, experts are still gravely concerned about the toxicity of nanoparticles.

In the near future, selenium nanoparticles from actinomycetes may find utility in pharmaceutical and nutritional supplements. It is possible to look into the possible uses of biogenic Se NPs as catalysts, drug delivery systems, and antiviral and anti-TB medicines. More precise clinical investigations are required to ascertain whether Se NPs are safe for human health. Much research is needed to understand how nano-selenium impacts the cytotoxicity and efficacy of radiation, chemotherapy, and cancer treatments, as well as to develop less costly and hazardous production methods. By enabling the precise release of selenium into the gastrointestinal tract and permitting its transport in organs that can change the nanoparticles' physicochemical properties, the development of innovative nanoparticle delivery systems can, in particular, offer substantial dietary and medicinal potential. More thorough clinical research is necessary to assess their pharmacokinetic characteristics and safety; nevertheless, in order to open the door for real-world applications. However, a major obstacle to clinical translation is still unresolved toxicity issues, as described in Section 6. Developing standard-

ized synthesis protocols for reproducibility, (i) conducting systematic in vivo and clinical trials, (ii) investigating mechanistic pathways such as immune interactions, micro biota balance, and ROS modulation, (iii) designing functionalized delivery systems to improve bioavailability and targeting, (v) conducting comparative studies against conventional therapies, and (vi) investigating combinatorial therapies that pair SeNPs with chemotherapy or radiation are some of the areas that future research should concentrate on. These avenues can help SeNP research go from preclinical promise to dependable clinical and industrial uses.

List of abbreviation

SeNPs selenium nanoparticles
NPs nanoparticles
AgNPs silver nanoparticles
FTIR Fourier Transform Infrared Spectroscopy
DLS Dynamic Light Scattering
SEM Scanning Electron Microscopy
TEM Transmission Electron Microscopy
UV Ultraviolet-Visible Spectroscopy
ROS Reactive Oxygen Species
GPx Glutathione peroxidase
RNS Reactive nitrogen species

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