TPM Vol. 32, No. S5, 2025
ISSN: 1972-6325
https://www.tpmap.org/

Open Access

GREEN SYNTHESIS AND BIOMEDICAL APPLICATIONS OF SELENIUM NANOPARTICLES AND ITS BASED NANOCOMPOSITE - A REVIEW

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Abstract

Selenium nanoparticles (SeNPs) have attracted growing attention in recent years due to their unique physicochemical properties and broad-spectrum biomedical activities, including antioxidant, antimicrobial, anti-inflammatory, and anticancer effects. This review provides a comprehensive overview of SeNPs, with a particular focus on the significance of green synthesis approaches utilizing plant extracts, microbial agents, and other biological resources. Green synthesis offers a sustainable, cost-effective, and biocompatible alternative to conventional chemical methods, resulting in nanoparticles with enhanced therapeutic efficacy and reduced toxicity. In addition to synthesis strategies, the review explores the biomedical relevance of SeNP-based nanocomposites, highlighting their applications in drug delivery systems, tissue engineering scaffolds, wound healing materials, and targeted cancer therapies. Key findings emphasize the role of SeNPs in regulating oxidative stress, promoting cell regeneration, and enabling smart delivery mechanisms. Finally, the review outlines current challenges in clinical translation such as scalability, standardization, and regulatory compliance while presenting a forward-looking perspective on the future integration of SeNPs into personalized medicine and advanced therapeutic platforms.

Keywords: Selenium nanoparticles (SeNPs), Green synthesis, Biomedical applications, Nanocomposites, Drug delivery systems

INTRODUCTION

The intersection of nanotechnology and medicine has ushered in a new era of innovation, with nanoscale materials playing a transformative role in diagnostics, therapeutics, and regenerative medicine(1). Nanoparticles, defined as materials with dimensions between 1 and 100 nanometers, exhibit unique physicochemical properties that differ significantly from their bulk counterparts. These include enhanced surface area-to-volume ratios, quantum effects, and improved reactivity, which enable superior performance in biomedical applications. As a result, nanotechnology offers new tools for addressing long-standing challenges in medicine, such as drug resistance, poor bioavailability, and systemic toxicity(2).

Among the diverse array of nanomaterials developed in recent years, SeNPs have garnered increasing attention due to their dual role as a bioactive element and a functional nanomaterial. Selenium is an essential micronutrient that participates in several physiological processes, primarily through its incorporation into selenoproteins(3). These proteins, including glutathione peroxidase and thioredoxin reductase, are critical in regulating oxidative stress, supporting immune function, and maintaining thyroid hormone metabolism. Despite its biological importance, selenium in its ionic or bulk forms is associated with narrow therapeutic windows and potential toxicity at higher doses. To overcome these limitations, the nanoformulation of selenium has emerged as a viable strategy, offering enhanced bioavailability, targeted delivery, and reduced systemic toxicity(4,5).

The green synthesis of selenium nanoparticles represents a significant advancement over traditional physical and chemical synthesis methods. Conventional approaches often involve the use of high temperatures, toxic solvents, and hazardous reducing agents such as sodium borohydride or hydrazine, which pose environmental and health risks(6). In contrast, green synthesis employs eco-friendly biological resources such as plant extracts, fungi, algae, and bacteria as both reducing and stabilizing agents. These biological systems are rich in phytochemicals, including polyphenols, flavonoids, alkaloids, and terpenoids, which facilitate the reduction of selenium precursors and simultaneously cap the resulting nanoparticles to enhance stability and bioactivity(7). This method not only

aligns with the principles of green chemistry but also results in nanoparticles with superior biocompatibility and multifunctional properties.

Moreover, the development of selenium-based nanocomposites which integrate SeNPs with other materials such as polymers, hydrogels, or metal oxides has opened new possibilities in biomedical research(8). These hybrid systems combine the therapeutic potential of selenium with the mechanical strength, biodegradability, and functional versatility of the composite matrix. Such nanocomposites have demonstrated promising results in areas including antimicrobial therapy, anti-inflammatory treatment, cancer inhibition, wound healing, and antioxidant defense(9). By tailoring the composition, structure, and surface chemistry of these nanocomposites, researchers can design multifunctional platforms that address complex clinical needs(10).

In recent years, several studies have reported the successful use of green-synthesized SeNPs in various biomedical applications, with enhanced efficacy and minimal side effects. Their ability to selectively induce apoptosis in cancer cells, inhibit microbial growth, scavenge free radicals, and accelerate tissue regeneration has positioned SeNPs as valuable candidates in nanomedicine(11). In addition, advances in nanofabrication techniques have enabled the development of smart delivery systems that release SeNPs in a controlled and site-specific manner, thereby improving therapeutic outcomes(12).

Despite the encouraging progress, several challenges remain. These include the need for standardized synthesis protocols, comprehensive toxicological evaluations, scalability for industrial production, and a clearer regulatory pathway for clinical translation. Additionally, the long-term stability and in vivo behavior of SeNPs and their composites require further investigation to fully harness their biomedical potential(13).

Therefore, the purpose of this review is to provide a comprehensive and critical overview of the current status and future prospects of selenium nanoparticles and their nanocomposites synthesized via green approaches. The article will begin by discussing the biological significance of selenium, followed by an in-depth analysis of green synthesis techniques and characterization methods. It will then explore the integration of SeNPs into nanocomposite systems and examine their biomedical applications, including antioxidant, antimicrobial, anti-inflammatory, anticancer, and wound healing properties. Finally, the review will address the challenges and future directions needed to advance these nanomaterials from laboratory research to clinical application.

Green Synthesis of Selenium Nanoparticles

Green synthesis of SeNPs offers an eco-friendly and sustainable alternative to conventional chemical and physical methods. By utilizing natural extracts from plants, microorganisms, and algae, this approach enables the reduction of selenium precursors into stable and biologically active nanoparticles, often with enhanced biocompatibility and catalytic efficiency. The method avoids toxic solvents, high energy input, and hazardous byproducts, making it suitable for both biomedical and environmental applications(14).

Biological Resources Used

Green synthesis of SeNPs utilizes a wide range of biological resources to convert selenium precursors into nanoscale selenium, offering a sustainable and non-toxic alternative to traditional chemical methods. This approach relies on natural compounds such as phytochemicals from plants, microbial enzymes, or algal polysaccharides which act as both reducing and stabilizing agents, allowing for precise control over nanoparticle size, shape, and surface chemistry(15). Compared to chemical synthesis, green methods are more environmentally friendly, cost-effective, and biocompatible, making them particularly suitable for biomedical and environmental applications(16).

Plant extracts

Figure 1: Biomedical applications of green synthesized selenium nanoparticles

Plant extracts represent the most widely studied biological system for SeNPs synthesis due to their rich phytochemical content and ease of scalability. Several medicinal and food-based plants have been reported to successfully produce bioactive SeNPs(17). For instance, *Diospyros montana* bark extract generates SeNPs within

a 100–150 nm size range and shows strong antioxidant activity (IC_{50} = 24.72 µg/mL) along with effective antibacterial action against both Gram-positive and Gram-negative bacteria(18). Similarly, *Hibiscus esculentus* L. (okra) extract yields spherical SeNPs around 62 nm in size, which are capable of degrading methylene blue dye with 98.3% efficiency and exhibit anticancer activity with an IC_{50} of 20.46 µg/mL against AGS gastric cancer cells(19). *Punica granatum* (pomegranate) has also been used to synthesize biocompatible SeNPs with dose-dependent cytotoxicity against MCF-7 breast cancer cells, suggesting its potential in antitumor therapy. In addition, traditional medicinal plants like plantain (*Plantago lanceolata*), yarrow (*Achillea millefolium*), and nettle (*Urtica dioica*) have been employed to produce SeNPs with size-dependent antioxidant capacity(20). The mechanism by which these plant extracts mediate synthesis involves polyphenols, alkaloids, and terpenoids reducing selenium ions (SeO_3^{2-} or SeO_4^{2-}) to elemental selenium (Se^0), followed by stabilization through phytochemical capping(21,22).

Microorganisms (bacteria, fungi)

In addition to plants, microbial systems particularly bacteria and fungi offer unique advantages for SeNP biosynthesis. These organisms reduce selenium ions through either intracellular or extracellular mechanisms, facilitated by enzymes such as reductases or by proteins secreted into the surrounding medium(23). For example, *Agrobacterium* species have been shown to produce nanoscale SeNPs using microbial reductase systems, while lactic acid bacteria perform extracellular reduction via protein-mediated processes, resulting in highly stable and low-toxicity nanoparticles(24). Fungi also participate in SeNP biosynthesis using mycelial biomass or culture filtrates, with growing applications in drug delivery and environmental remediation. Microbial systems are advantageous for their reproducibility and precise control over nanoparticle crystallinity and size, which can be fine-tuned by modifying parameters such as pH, temperature, and incubation duration(25).

Algal sources

Although less commonly explored, algae are emerging as sustainable biofactories for SeNP synthesis. Marine algae, in particular, have demonstrated the ability to reduce selenium ions through intracellular or extracellular processes, although specific algal species are less well-documented in current literature(26). Algal polysaccharides act as natural capping agents, contributing to enhanced nanoparticle stability, dispersity, and biological compatibility. The use of algae in green synthesis offers rapid production and generates minimal byproducts, aligning well with the goals of green chemistry and environmental sustainability(27).

The synthesis conditions play a critical role in determining the physicochemical properties of the resulting SeNPs. Optimal synthesis temperatures have been reported around 45–50°C, particularly in the case of *Hibiscus esculentus*, while a neutral to slightly acidic pH (~6) is generally favorable for nanoparticle stability(28). Characterization techniques such as UV-Visible spectroscopy (with absorption peaks ranging from 256–289 nm), transmission electron microscopy (TEM), scanning electron microscopy (SEM), and Fourier-transform infrared spectroscopy (FTIR) are commonly used to confirm successful synthesis, assess morphology, and identify phytochemical interactions(29).

Despite its advantages, green synthesis still faces certain challenges. One of the main issues is the variability in plant extract composition, which can affect reproducibility and require extensive optimization to maintain consistent nanoparticle size and activity(30). Moreover, microbial systems, though highly precise, face limitations in scalability and are often more complex to maintain under sterile conditions. Addressing these challenges through standardization and innovation particularly by exploring underutilized systems like algae could enhance the applicability of green-synthesized SeNPs in industrial and clinical settings(31,32).

Therefore, biological systems provide a sustainable and effective platform for the green synthesis of SeNPs, bridging the gap between environmental responsibility and biomedical innovation. Future research should focus on optimizing extraction protocols, improving reproducibility, and scaling up production to fully harness the potential of green nanotechnology(33).

Mechanisms of Green Synthesis

Reduction of selenium salts

The green synthesis of selenium nanoparticles (SeNPs) involves a complex interplay of biological mechanisms that drive the reduction, stabilization, and functionalization of selenium precursors into nanoscale particles(34). This eco-friendly process utilizes a variety of biological resources such as plant extracts, fungi, bacteria, and algae that are rich in enzymes, proteins, and phytochemicals capable of reducing selenium salts like sodium selenite or selenate to elemental selenium (Se^0). The reduction mechanism typically begins with the electron donation from bioactive compounds most notably polyphenols and flavonoids present in plant extracts which convert selenium ions into SeNPs(35). In microbial systems, the reduction may occur intracellularly or extracellularly, often facilitated by metabolic pathways and enzymatic activities that produce uniform and functional nanoparticles(36,37).

Stabilization and capping agents in plant-based synthesis

In plant-mediated synthesis, phytochemicals serve a dual purpose: they not only reduce selenium ions but also act as natural capping agents that stabilize the formed nanoparticles(38). Molecules such as proteins, secondary

metabolites, and polysaccharides bind to the surface of SeNPs, preventing agglomeration and promoting size uniformity(39). For example, antioxidants like curcumin from *Curcuma longa* not only facilitate the reduction process but also enhance the biological activity of the synthesized nanoparticles through surface interactions. These phytochemical coatings influence not only the structural integrity of SeNPs but also their biological compatibility, functionality, and shelf-life(40).

Influence of phytochemicals on particle properties

The nature and concentration of these bio-reducing agents significantly influence the physical and functional properties of SeNPs. For instance, higher concentrations of reducing agents generally lead to a more rapid reduction process, which in turn results in smaller nanoparticles due to faster nucleation rates(21). Moreover, the type of phytochemical present can determine particle morphology, surface charge, and reactivity. Specific phytochemicals can even enhance biological functions such as antioxidant and antimicrobial activity by increasing the surface reactivity of the nanoparticles(41).

Factors Influencing Green Synthesis

Several environmental and reaction parameters also govern the outcome of SeNP synthesis. pH is a critical factor, with neutral to slightly acidic conditions (around pH 6) often promoting both effective reduction and nanoparticle stability(42). Temperature plays a key role by affecting reaction kinetics; moderate temperatures (approximately 45–50°C) are typically optimal, as they facilitate enzymatic activity while preserving the structural integrity of sensitive biomolecules. Reaction time is another crucial determinant, where shorter durations tend to produce smaller nanoparticles, whereas prolonged exposure may lead to particle aggregation and larger sizes due to continued growth(43). Additionally, the concentration of selenium precursors directly impacts the rate of nanoparticle formation; higher concentrations may accelerate reduction but can also lead to larger or polydisperse particles if not properly controlled(44).

Ultimately, the interplay between these factors' biological agent composition, environmental conditions, and precursor concentration determines the final size, shape, and stability of SeNPs. For example, SeNPs synthesized using *Withania somnifera* extract were reported to be as small as 22 nm, offering increased reactivity and bioavailability. Spherical nanoparticles are generally preferred due to their uniformity and consistency in biomedical applications. Stability is equally important, and successful capping with biomolecules ensures the colloidal suspension remains stable over time without aggregation, making the nanoparticles suitable for therapeutic use(25).

Overall, the green synthesis of selenium nanoparticles is governed by biologically driven reduction and stabilization processes, influenced by phytochemical composition and synthesis conditions such as pH, temperature, reaction time, and precursor concentration. A deep understanding of these mechanisms allows researchers to fine-tune synthesis protocols, enabling the production of SeNPs with desired properties for diverse biomedical and environmental applications.

Characterization Techniques for SeNPs

Characterization of selenium nanoparticles (SeNPs) is a critical step in evaluating their physicochemical properties, understanding their behavior in biological environments, and ensuring their suitability for various applications. Multiple analytical techniques are employed to assess the size, morphology, crystallinity, surface chemistry, and stability of SeNPs, particularly those synthesized via green methods. These techniques provide comprehensive insights that guide the optimization of synthesis protocols and the design of functional nanomaterials for biomedical, environmental, and catalytic uses(23).

One of the most commonly used techniques is UV-Visible spectroscopy, which helps confirm the formation of SeNPs by detecting the characteristic surface plasmon resonance (SPR) peak. Typically, SeNPs display a distinct absorption peak around 256 nm, which indicates successful reduction of selenium salts and nanoparticle formation(45). Variations in the intensity and position of this peak provide useful information about particle concentration and size. Complementing this, Fourier-transform infrared spectroscopy (FTIR) is employed to identify the functional groups and chemical bonds associated with SeNPs(16). FTIR analysis confirms the presence of capping agents—such as proteins, polysaccharides, or secondary metabolites—derived from plant or microbial extracts. These functional groups play a crucial role in stabilizing the nanoparticles and enhancing their bioactivity(46).

To determine the crystalline nature of the nanoparticles, X-ray diffraction (XRD) analysis is utilized. This technique reveals whether the synthesized SeNPs are crystalline or amorphous, based on their diffraction patterns. Such information is important for predicting nanoparticle reactivity, solubility, and long-term stability(47). Morphological characteristics are best visualized through scanning electron microscopy (SEM) and transmission electron microscopy (TEM). SEM provides detailed surface images, allowing for observation of particle shape, size distribution, and aggregation. In contrast, TEM offers higher-resolution imaging that enables direct measurement of nanoparticle diameter at the nanometer scale, along with insights into their internal structure and crystallinity(48).

Dynamic light scattering (DLS) and zeta potential analysis are additional techniques that assess the behavior of SeNPs in colloidal suspension. DLS measures the hydrodynamic diameter of particles in solution, providing information on size distribution and potential agglomeration. Smaller hydrodynamic sizes generally indicate better dispersion and bioavailability. Zeta potential analysis, on the other hand, evaluates the surface charge of nanoparticles. This parameter is crucial for assessing colloidal stability, as higher absolute zeta potential values (positive or negative) reflect stronger electrostatic repulsion between particles, thereby preventing aggregation(49,50).

Together, these characterization techniques offer a comprehensive understanding of selenium nanoparticles synthesized via green methods. They help researchers optimize reaction conditions and tailor the properties of SeNPs for specific biomedical applications, such as targeted drug delivery, antioxidant therapy, antimicrobial coatings, and environmental detoxification. Ultimately, precise and thorough characterization ensures that SeNPs meet the necessary standards for safety, functionality, and performance in real-world settings.

Selenium-Based Nanocomposites

SeNPs are attracting considerable attention due to their multifunctional properties and broad applicability in fields such as biomedicine, agriculture, and environmental remediation. These nanocomposites are formed by integrating selenium nanoparticles into various structural matrices including polymers, metals, metal oxides, hydrogels, and scaffolds which significantly enhances their physicochemical characteristics, biological compatibility, and therapeutic potential. The resulting hybrid materials benefit from the intrinsic bioactivity of selenium and the mechanical or functional enhancements provided by the supporting matrix, leading to synergistic effects that are valuable in both clinical and industrial contexts(51).

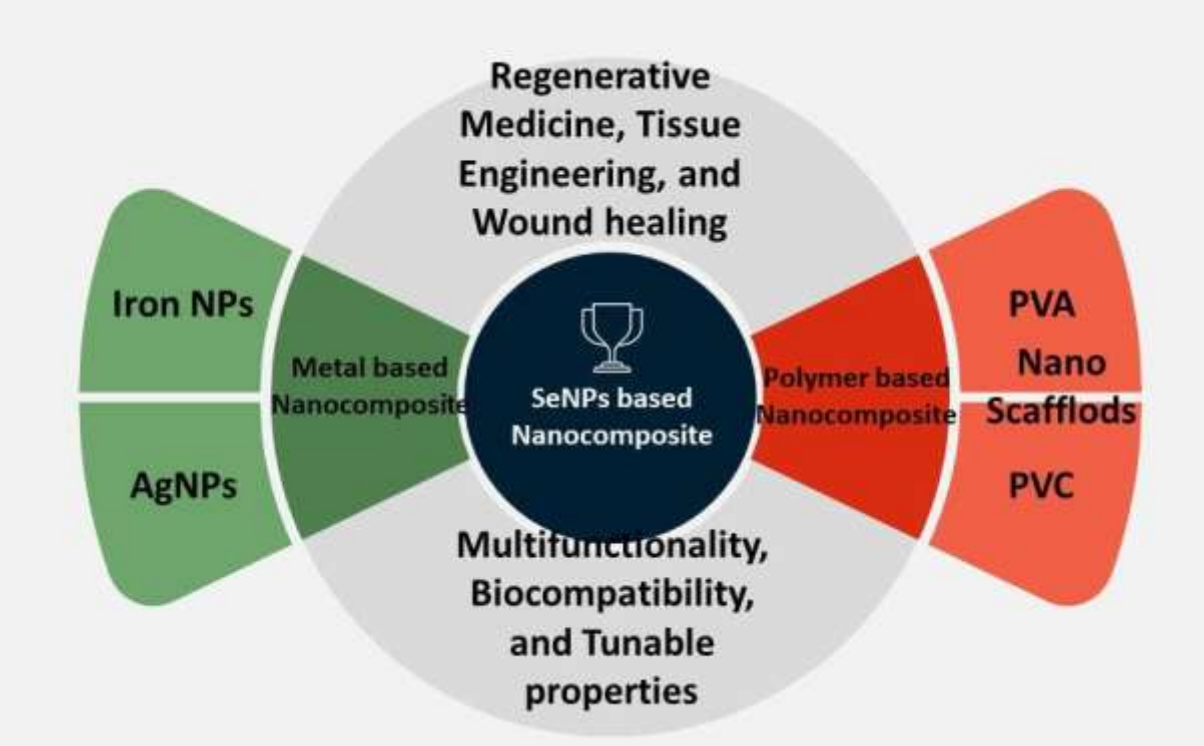

Figure 2 :Overview of SeNP-based nanocomposites combining metal and polymer components for enhanced biocompatibility and wound healing applications.

One of the most explored categories is polymer-based nanocomposites, where SeNPs are embedded within natural or synthetic polymer matrices. Natural polysaccharides such as arabinogalactan, starch, and kappa-carrageenan are widely used due to their biodegradability, non-toxicity, and stabilizing ability(52). These polysaccharide-based SeNP composites have demonstrated biological efficacy, such as fungicidal activity against *Phytophthora cactorum*, while maintaining environmental safety by preserving beneficial rhizospheric microorganisms. In contrast, synthetic polymers like polyethylene glycol (PEG) and polyvinyl alcohol (PVA) provide enhanced stability and dispersibility of SeNPs, especially in biomedical formulations such as drug delivery systems. These polymers offer a high degree of customization, enabling controlled release and improved solubility of selenium-based therapeutics(53,54).

Another promising class involves metal and metal oxide hybrid nanocomposites, which combine selenium nanoparticles with other functional nanomaterials to create dual-purpose or multifunctional systems. For example, selenium combined with iron oxide nanoparticles (IONPs) forms a magnetic nanocomposite suitable for targeted cancer therapy(55). The magnetic responsiveness of iron oxide enables guided delivery to tumor sites, while

selenium contributes its anticancer properties through oxidative stress modulation and apoptosis induction. Similarly, zinc sulfide-selenium nanocomposites have been reported for their enhanced photocatalytic activity. These materials demonstrate high efficiency in degrading organic dyes under ultraviolet light, highlighting their potential for wastewater treatment and environmental cleanup applications(56).

In biomedical engineering, hydrogels and scaffolds integrated with SeNPs are increasingly used for regenerative medicine, tissue engineering, and wound healing. Hydrogels embedded with SeNPs serve as smart drug delivery systems, capable of releasing therapeutic agents in a controlled manner while supporting cell viability(57). The inclusion of selenium enhances the hydrogel's antimicrobial and antioxidant activity, which is critical for accelerating wound healing and preventing infection. Scaffold-based systems further extend this functionality by providing structural support that mimics the extracellular matrix, promoting cellular attachment, proliferation, and differentiation. When infused with SeNPs, these scaffolds not only offer mechanical strength but also deliver selenium's therapeutic benefits locally and sustainably(58).

The broad utility of selenium-based nanocomposites extends beyond biomedicine. In agriculture, these composites have been explored for their ability to improve plant growth, enhance crop resilience, and provide protection against microbial pathogens. In environmental contexts, they are used for the photocatalytic degradation of pollutants, contributing to the removal of dyes and toxins from contaminated water sources. Their multifunctionality, biocompatibility, and tunable properties make them promising candidates for integrated solutions across sectors(53).

Therefore, selenium-based nanocomposites represent a dynamic and versatile class of materials, distinguished by their enhanced bioactivity, environmental safety, and application-specific adaptability. By integrating SeNPs with polymers, metals, or hydrogel matrices, researchers have developed systems that address pressing challenges in healthcare, agriculture, and environmental sustainability. Continued advancements in the synthesis and functionalization of these nanocomposites will likely lead to the next generation of smart, responsive, and targeted nano-enabled solutions.

Methods of Nanocomposite Fabrication

The fabrication of selenium-based nanocomposites involves a range of techniques designed to integrate selenium nanoparticles (SeNPs) into various matrix materials, thereby enhancing their physical, chemical, and biological functionalities. The choice of fabrication method significantly influences the final properties of the nanocomposite, including nanoparticle dispersion, mechanical integrity, biocompatibility, and release profiles. Among the most effective and widely adopted approaches are in situ synthesis, surface modification and conjugation, and electrospinning or embedding techniques(59).

In situ synthesis

In situ synthesis is one of the most efficient methods for producing nanocomposites with homogeneously distributed selenium nanoparticles. In this process, the precursor materials for both the SeNPs and the matrix often a polymer are combined in a single reaction system under controlled conditions, such as optimized temperature and pH(60). Nanoparticles form within the matrix in real time, leading to enhanced interfacial interactions and preventing agglomeration. This method provides uniform nanoparticle dispersion and improved mechanical and thermal properties, making it particularly valuable for the development of SeNP-polymer composites used in drug delivery and antimicrobial applications(61).

Surface modification and conjugation

Surface modification and conjugation techniques are widely employed to improve the compatibility, dispersibility, and functional performance of SeNPs within a composite material. This can be achieved either through covalent bonding, where chemical reactions attach functional groups directly onto the surface of SeNPs, or via physical adsorption involving non-covalent interactions such as van der Waals forces(62). These modifications stabilize the nanoparticles, reduce aggregation, and enhance their interaction with the host matrix. Furthermore, surface-functionalized SeNPs can be tailored for specific biomedical functions, including enhanced targeting, prolonged circulation time, or improved therapeutic efficacy in drug delivery systems(63).

Electrospinning and embedding techniques

Electrospinning and embedding techniques represent another class of fabrication methods particularly suitable for creating SeNP-integrated nanofibrous structures. In electrospinning, a polymer solution containing selenium nanoparticles is exposed to a high-voltage electric field, which stretches the solution into ultrafine fibers that are collected on a solid substrate(64). The resulting nanofibers possess high surface area-to-volume ratios, contributing to superior mechanical strength, enhanced bioactivity, and controlled drug release kinetics. Embedding techniques, on the other hand, involve physically incorporating SeNPs into a polymer matrix followed by processes such as solvent casting or compression molding to form films, gels, or other structured composites. These techniques are commonly used in developing wound dressings, scaffolds for tissue engineering, and filtration membranes, where structural integrity and biological responsiveness are critical(65,66).

Together, these fabrication methods offer versatile platforms for producing selenium-based nanocomposites with application-specific properties. By optimizing the synthesis parameters such as nanoparticle loading, surface

chemistry, and matrix composition researchers can tailor the performance of SeNP composites for diverse fields, including nanomedicine, agriculture, environmental remediation, and electronic devices. Continued innovation in fabrication techniques will be essential for scaling up production and translating these multifunctional materials into practical, real-world solutions.

Biomedical Applications of Selenium Nanoparticles and Nanocomposites

SeNPs and their nanocomposites have gained substantial interest in biomedical research due to their potent antioxidant properties and broad therapeutic potential. Among their various functionalities, the ability to combat oxidative stress stands out as a critical feature, especially in the prevention and treatment of diseases associated with excessive reactive oxygen species (ROS), such as cancer, cardiovascular conditions, and neurodegenerative disorders. The antioxidant efficacy of SeNPs is attributed to their unique nanoscale structure, surface reactivity, and their role in modulating cellular redox balance(67).

Antioxidant Activity

SeNPs exhibit antioxidant activity through multiple mechanisms. One of the primary pathways is direct scavenging, wherein SeNPs interact with ROS including hydroxyl radicals and superoxide anions by donating electrons. This electron transfer neutralizes these reactive species, thereby minimizing oxidative stress and cellular damage. Another important mechanism involves the enhancement of enzymatic activity, particularly of selenoenzymes such as glutathione peroxidase and thioredoxin reductase(68). These enzymes play a central role in detoxifying peroxides and maintaining redox homeostasis in cells. Furthermore, SeNPs may exert their effects at the genetic level by influencing gene regulation, specifically by upregulating the expression of antioxidant defense genes. This gene modulation promotes the intrinsic antioxidant capacity of the cell, contributing to long-term protection against oxidative injury(69).

Compared to conventional antioxidants like vitamins C and E, selenium nanoparticles offer distinct advantages. Their higher efficacy in scavenging ROS has been reported in various studies, largely due to their large surface area-to-volume ratio, which enhances reactivity and cellular interaction. In addition, SeNPs demonstrate favorable biocompatibility, with reduced toxicity and improved bioavailability at therapeutic doses(51). Unlike some synthetic antioxidants that may exert pro-oxidant effects at high concentrations, SeNPs maintain a more consistent safety profile. Importantly, SeNPs are also multifunctional, exhibiting not only antioxidant activity but also significant antimicrobial and anticancer effects. This versatility makes them highly suitable for integration into therapeutic systems aimed at addressing complex pathophysiological conditions(70).

The antioxidant capacity of SeNPs supports a wide range of biomedical applications, including their use in nanodrug delivery systems, tissue engineering, and chronic wound management. Their ability to reduce oxidative stress while simultaneously enhancing cellular repair and immune responses provides a dual therapeutic benefit, especially in the treatment of inflammatory and degenerative diseases. Continued exploration into the antioxidant mechanisms and biological interactions of SeNPs will further solidify their role as a promising class of nanotherapeutics in modern medicine(71,72).

Antimicrobial Activity

SeNPs have demonstrated considerable antimicrobial potential, positioning them as promising agents in the fight against infectious diseases. Their broad-spectrum activity, coupled with biocompatibility and multifunctional properties, makes SeNPs attractive alternatives or adjuncts to conventional antimicrobial therapies. The mechanisms by which SeNPs exert their antimicrobial effects are multifaceted, primarily involving oxidative stress induction, disruption of microbial membrane integrity, and inhibition of biofilm formation(73).

One of the primary antimicrobial mechanisms of SeNPs is the generation of reactive oxygen species (ROS), which induces oxidative stress within microbial cells. This oxidative damage leads to lipid peroxidation, protein dysfunction, and DNA fragmentation, culminating in cell death. The ROS generated by SeNPs also compromise membrane integrity, causing leakage of cytoplasmic contents and loss of essential intracellular components(74). For example, SeNPs have been shown to damage the microbial cell membrane, leading to cytoplasmic leakage and reduced viability in pathogens such as *Pseudomonas fluorescens*. Studies have specifically noted that SeNPs synthesized using *Lactobacillus casei* effectively disrupt the membranes of bacterial cells, contributing to their antimicrobial efficacy(75). In addition, SeNPs are known to inhibit biofilm formation, a critical survival mechanism used by many pathogenic bacteria. By preventing biofilm development, SeNPs render microbes more vulnerable to both immune responses and conventional treatments, thereby enhancing therapeutic outcomes(76).

The spectrum of antimicrobial activity exhibited by SeNPs encompasses both Gram-positive and Gram-negative bacteria. Commonly tested bacterial strains such as *Staphylococcus aureus* and *Escherichia coli* have shown sensitivity to SeNPs, with inhibition zones reported in various in vitro studies(77). Beyond bacterial pathogens, SeNPs also demonstrate antifungal activity, particularly against *Candida albicans*, suggesting their utility in treating fungal infections. While data on their antiviral properties are limited, preliminary findings hint at potential antiviral effects, although further studies are needed to substantiate this role(78).

When compared to conventional antimicrobial and antioxidant agents, SeNPs offer several noteworthy advantages. In terms of efficacy, SeNPs often outperform traditional antioxidants like vitamins C and E in ROS

scavenging, owing to their nanoscale size and high surface-area-to-volume ratio, which enhance their reactivity and cellular interaction. Regarding biocompatibility, SeNPs are generally well-tolerated and less likely to induce adverse effects compared to synthetic antibiotics, which can disrupt the microbiome or lead to antimicrobial resistance(79). Moreover, SeNPs are multifunctional, exhibiting both antimicrobial and antioxidant activities simultaneously. This dual-action capability is especially beneficial in clinical settings, where managing oxidative stress and infection concurrently can improve healing and recovery(80).

Overall, selenium nanoparticles exhibit robust antimicrobial activity through mechanisms that include oxidative stress induction, membrane disruption, and biofilm inhibition. Their effectiveness against a broad range of bacterial and fungal pathogens, combined with their favorable safety profile and multifunctionality, highlights their potential as innovative therapeutic agents. Continued investigation into their modes of action and in vivo efficacy will further clarify their role in future antimicrobial strategies.

Anti-inflammatory Potential

SeNPs have emerged as promising anti-inflammatory agents due to their ability to modulate key inflammatory pathways and restore immune homeostasis. Chronic inflammation underlies the pathogenesis of numerous diseases, including cancer, cardiovascular disorders, respiratory illnesses, and neurodegenerative conditions. SeNPs, with their unique redox-active properties and nano-scale bioavailability, offer a multifaceted approach to managing inflammation by targeting both pro-inflammatory mediators and oxidative stress(81).

One of the primary mechanisms through which SeNPs exert their anti-inflammatory effects is the inhibition of pro-inflammatory cytokines. Studies have consistently shown that SeNPs can significantly reduce the levels of tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) cytokines that play central roles in propagating the inflammatory cascade(82). By suppressing these mediators, SeNPs help to attenuate the immune response in inflamed tissues. Simultaneously, SeNPs have been reported to enhance the production of anti-inflammatory cytokines, particularly interleukin-10 (IL-10), which contributes to the resolution of inflammation and supports tissue repair(83). This dual modulation fosters a shift from a pro-inflammatory to an anti-inflammatory environment, thereby promoting recovery. In addition, SeNPs are known to reduce oxidative stress, which is closely linked to chronic inflammation. By increasing the activity of antioxidant enzymes such as glutathione peroxidase and superoxide dismutase, SeNPs neutralize reactive oxygen species (ROS), thus preventing oxidative damage that exacerbates inflammation(84).

The therapeutic implications of these mechanisms have been explored in several models of chronic inflammatory diseases. In chronic respiratory disorders, SeNPs particularly those conjugated with bioactive compounds like chlorogenic acid have demonstrated the ability to reduce lung inflammation and oxidative injury. These effects are partially mediated through the polarization of macrophages toward an anti-inflammatory phenotype. In the realm of cancer therapy, SeNPs contribute to the suppression of inflammation-associated tumor progression(85). For instance, SeNPs synthesized from *Baliospermum montanum* not only exerted anticancer effects but also significantly downregulated pro-inflammatory cytokines, highlighting their role as dual-action agents. In neurological disorders, SeNPs have shown promise in mitigating neuroinflammation(86). Animal models of stress-induced depression have revealed that SeNPs can reduce inflammatory markers in the brain while also limiting oxidative stress, suggesting their potential in managing neurodegenerative diseases such as Alzheimer's and Parkinson's(87). Furthermore, the application of SeNPs in wound healing has demonstrated anti-inflammatory and pro-regenerative effects. When incorporated into wound dressings, SeNPs not only suppress local inflammation but also promote tissue regeneration by modulating redox balance and cytokine profiles(15).

Anticancer Applications

SeNPs have gained increasing attention in oncology due to their dual functionality as therapeutic agents and drug delivery platforms. Their ability to selectively induce apoptosis in cancer cells while sparing healthy tissues, combined with their adaptability for targeted drug delivery, positions them as promising candidates in the development of next-generation cancer treatments. The nanoscale size, surface reactivity, and biocompatibility of SeNPs allow them to interact effectively with tumor microenvironments, modulate cellular signaling pathways, and enhance the efficacy of chemotherapeutic agents(88).

One of the key anticancer mechanisms of SeNPs is their capacity to induce apoptosis, or programmed cell death, in malignant cells. This is primarily achieved through the generation of reactive oxygen species (ROS) within cancer cells, leading to oxidative stress that disrupts cellular homeostasis and activates intrinsic apoptotic pathways. This effect has been documented across various cancer models, including pancreatic carcinoma and cervical cancer, with SeNPs demonstrating dose-dependent cytotoxicity as indicated by IC_{50} values within effective therapeutic ranges(89). In addition to ROS generation, SeNPs also contribute to DNA damage, a critical trigger for apoptosis. Treated cancer cells often exhibit nuclear condensation, fragmentation, and disruption of mitochondrial membrane potential—hallmarks of apoptosis that indicate the nanoparticles' effectiveness in compromising cancer cell viability. Moreover, SeNPs influence hypoxia-related signaling by interfering with hypoxia-inducible factors (HIFs). By downregulating HIF activity, SeNPs sensitize cancer cells to apoptosis even under low oxygen conditions commonly found in solid tumors(90).

Beyond their intrinsic anticancer properties, SeNPs serve as efficient nanocarriers for drug delivery and targeted therapy. Their high surface-to-volume ratio and tunable surface chemistry enable the encapsulation of chemotherapeutic agents, improving drug solubility, stability, and controlled release at the tumor site(47). Functionalization of SeNPs with ligands such as antibodies or peptides allows for targeted delivery, where nanoparticles selectively bind to overexpressed receptors on cancer cells. This targeting minimizes off-target effects, reduces systemic toxicity, and increases drug accumulation within tumor tissues. In recent developments, SeNPs have also been employed in combination therapies, enhancing the efficacy of conventional treatments such as radiotherapy and photothermal therapy. For instance, selenium-loaded scaffolds combined with laser irradiation have shown synergistic tumor suppression effects, offering a novel strategy for localized cancer therapy(91).

Therefore, selenium nanoparticles hold substantial promise as both direct anticancer agents and multifunctional drug delivery platforms. Their ability to modulate oxidative stress, induce apoptosis, and enable targeted drug delivery supports their application across a wide range of tumor types. As research continues to uncover new mechanisms and refine their formulation, SeNPs are poised to contribute significantly to the future of personalized and precise cancer therapy(92,93).

Wound Healing Properties

One of the primary ways SeNPs facilitate wound healing is by stimulating cell proliferation and migration, particularly of fibroblasts, which are essential for collagen synthesis and extracellular matrix remodeling. Studies involving NIH3T3 murine fibroblast cells have shown that SeNPs enhance cell viability and proliferation, thereby accelerating wound closure. In addition to promoting cellular activity, SeNPs are known to modulate the inflammatory response, which is critical for preventing delayed healing and tissue damage(94,95). By reducing levels of pro-inflammatory cytokines such as IL-6 and TNF-α, SeNPs create a more favorable microenvironment for tissue repair and regeneration. Furthermore, SeNPs have been associated with enhanced angiogenesis, an essential process for delivering oxygen and nutrients to regenerating tissues. Their ability to support new blood vessel formation contributes to improved granulation tissue development and overall wound healing outcomes(96).

The efficacy of SeNPs in wound care is further enhanced through their incorporation into nanogel and nanofiber systems, which allow for sustained release and localized action. In nanogel-based platforms, SeNPs are encapsulated within hydrophilic polymer networks that maintain a moist wound environment and enable controlled delivery. For example, bacterial cellulose/gelatin hydrogels containing SeNPs have demonstrated excellent mechanical strength, biocompatibility, and antibacterial properties, making them ideal for use as wound dressings(97). These hydrogels not only prevent infection but also exhibit antioxidant activity that protects cells from oxidative stress during the healing process. Similarly, electrospun nanofibers loaded with SeNPs offer a large surface area and structural mimicry of the native extracellular matrix, which promotes cell attachment and proliferation. These nanofibrous mats act as both physical barriers and bioactive platforms, facilitating fibroblast activation, collagen deposition, and overall tissue regeneration(98).

Emerging research further supports the role of SeNPs in effective wound healing. Myco-synthesized SeNPs, for instance, have been shown to significantly reduce wound area and healing time in animal models while lowering bacterial load and supporting epithelial regeneration(99). In another study, SeNPs integrated into bacterial cellulose/gelatin hydrogels improved wound healing in rats by enhancing granulation tissue formation and collagen alignment. Moreover, hybrid formulations combining selenium with zinc oxide nanoparticles have demonstrated synergistic effects, including disruption of microbial biofilms and faster wound closure, underscoring the versatility of SeNP-based composites for treating infected or chronic wounds(100,101).

Toxicological and Biocompatibility Considerations

As SeNPs continue to gain momentum in biomedical research, evaluating their toxicological and biocompatibility profiles becomes increasingly important. Understanding how SeNPs interact with biological systems both at the cellular and organismal levels is crucial to ensure their safe integration into therapeutic and diagnostic applications(102). Compared to conventional selenium compounds, SeNPs have been shown to offer a more favorable safety profile, largely due to their tunable physicochemical properties and targeted delivery capabilities(103).

In vitro cytotoxicity studies provide the first line of evidence for assessing the safety of SeNPs. Research across various cell lines has consistently demonstrated that SeNPs, particularly those functionalized with biocompatible agents, exhibit reduced cytotoxicity compared to traditional selenium salts like sodium selenite. For instance, SeNPs stabilized with olive-derived polyphenols showed significantly lower toxicity in human hepatocellular carcinoma (HepG2) and colorectal adenocarcinoma (Caco2) cell lines, suggesting enhanced compatibility with human cells(104). The cytotoxic behavior of SeNPs, however, is influenced by several factors, including particle size, surface charge, and the nature of the stabilizing agents. These variables can modulate cellular uptake, oxidative stress responses, and apoptosis induction, indicating that SeNPs may elicit distinct effects depending on their formulation and the target cell type(105).

In vivo studies, particularly those using zebrafish and rodent models, further validate the biocompatibility of SeNPs. Zebrafish embryos, which offer advantages such as transparency, genetic similarity to humans, and rapid development, have been employed to assess nanoparticle toxicity. Findings suggest that SeNPs, when administered at therapeutic concentrations, do not induce significant developmental abnormalities or behavioral changes(106). Similarly, rodent studies have provided reassuring data on systemic tolerance. For example, bovine serum albumin (BSA)-coated SeNPs administered to mice showed no detectable damage to major organs and maintained normal physiological parameters, underscoring their safety for potential clinical use. These studies reinforce the idea that SeNPs, especially when surface-modified, can be safely utilized for biomedical interventions(107).

Nevertheless, the dose-dependent nature of SeNP toxicity must be carefully considered. While lower concentrations typically exhibit minimal cytotoxic effects, excessive doses can trigger oxidative stress, mitochondrial dysfunction, and cellular apoptosis. This biphasic response highlights the need for rigorous dose optimization in both preclinical and clinical settings(108). To address this, comprehensive safety assessments including histopathological analyses, oxidative stress markers, and long-term toxicity evaluations are essential to establish therapeutic windows and safe exposure levels. Notably, functionalization strategies can improve SeNP safety by enhancing their biocompatibility, targeting ability, and degradation profiles. This makes functionalized SeNPs particularly suitable for sensitive applications such as cancer therapy, tissue regeneration, and drug delivery(109).

CHALLENGES AND LIMITATIONS

Despite the growing interest in selenium nanoparticles SeNPs for biomedical applications, their successful clinical translation faces several critical challenges. Addressing issues related to stability, scalability, reproducibility, regulatory compliance, and long-term safety is essential for unlocking the full therapeutic potential of SeNP-based technologies(110).

One major hurdle is the stability and scalability of green synthesis methods. While eco-friendly routes using plant extracts, microbes, or other biological systems are widely appreciated for their sustainability and biocompatibility, the physical and chemical stability of green-synthesized SeNPs can be highly sensitive to external factors such as pH, temperature, and ionic strength(111). This instability can lead to aggregation or changes in particle morphology, potentially compromising their therapeutic efficacy. Furthermore, scaling up these biosynthesis methods from laboratory to industrial levels presents technical barriers. Maintaining consistency in nanoparticle size, shape, and surface chemistry at large production scales remains a significant limitation, hindering commercialization efforts(112).

Another key challenge lies in standardization and reproducibility. Variability in the biological sources used for nanoparticle synthesis, such as differences in phytochemical content among plant extracts or strain-specific differences in microbes, can lead to batch-to-batch inconsistencies in nanoparticle properties. The lack of universal protocols for SeNP synthesis and characterization limits the ability to reproduce results across different laboratories or production environments(113). Moreover, standardized and validated characterization techniques are urgently needed to define critical parameters, including particle size, shape, zeta potential, crystallinity, and biological activity. These parameters must be correlated with therapeutic outcomes to guide the design of reproducible and functional nanomaterials(114).

From a translational perspective, regulatory concerns and clinical barriers also impede progress. The current regulatory framework for nanomaterials is still in development, with limited specific guidelines addressing the safety, toxicity, and environmental impact of selenium-based nanostructures. Regulatory agencies require detailed data on pharmacokinetics, biodistribution, degradation, and long-term safety before approving any clinical applications(115). However, such data are often lacking or incomplete for SeNPs, particularly regarding their interaction with biological systems over prolonged periods. In addition, clinical translation necessitates rigorous preclinical validation, including well-controlled in vivo studies that assess efficacy, immunogenicity, and potential interactions with other drugs. The complexity of these assessments, coupled with limited funding and interdisciplinary collaboration, further slows the pathway to clinical adoption(116).

Future Perspectives

The future landscape of SeNPs in biomedicine is highly promising, with transformative potential in precision drug delivery, personalized therapeutics, and clinical translation. Continued innovation in nanoengineering, combined with interdisciplinary collaboration, is expected to drive SeNPs toward more advanced and clinically viable applications(117).

One key area of advancement lies in the development of smart delivery systems using SeNP composites. Functionalization of SeNPs with disease-specific ligands, such as antibodies, peptides, or aptamers, can enable targeted drug delivery, ensuring that therapeutic agents accumulate preferentially in diseased tissues while sparing healthy cells(118). This precision reduces systemic toxicity and enhances treatment efficacy, especially in

oncology. In addition, SeNPs are emerging as powerful platforms for combination therapies, enabling the co-delivery of chemotherapeutics, gene therapies, or anti-inflammatory agents within a single nanocarrier. Such synergistic strategies may prove especially effective in combating drug-resistant cancers or chronic inflammatory diseases. Furthermore, the integration of stimuli-responsive mechanisms triggered by pH, temperature, redox conditions, or external light will enable dynamic, site-specific drug release, offering a level of control that conventional delivery systems cannot achieve(119).

SeNPs also hold strong potential for integration into personalized medicine, a domain that emphasizes individualized therapeutic strategies based on patient-specific biomarkers and disease profiles. In this context, SeNPs can be tailored to interact with particular molecular targets, ensuring biomarker-driven precision therapy. Beyond treatment, their inherent optical properties open avenues for real-time imaging and diagnostic monitoring, allowing clinicians to track therapeutic responses non-invasively and adjust interventions accordingly. Advances in surface modification and formulation will continue to improve the biocompatibility of SeNPs, making them more suitable for long-term use and repeat dosing in sensitive patient populations(120).

In parallel, the expansion of clinical research and translational initiatives will be crucial in bridging the gap between laboratory findings and real-world medical applications. Despite numerous preclinical successes, SeNPs still require robust validation through well-designed clinical trials that assess their safety, pharmacokinetics, and therapeutic efficacy in humans. Such studies will lay the groundwork for regulatory approvals and broader clinical acceptance(121,122). To support this transition, there is an urgent need for the establishment of clear regulatory frameworks that specifically address the unique properties and safety considerations of nanomaterials. These frameworks must include standardized protocols for nanoparticle characterization, toxicological testing, and risk assessment. Ultimately, the successful deployment of SeNPs in healthcare will depend on interdisciplinary collaboration among material scientists, clinicians, pharmacologists, and regulatory bodies to address these complex challenges and accelerate clinical translation(123,124).

CONCLUSION

SeNPs have emerged as multifunctional nanomaterials with remarkable biomedical potential, owing to their unique physicochemical properties, controlled reactivity, and biocompatibility. This review has highlighted the diverse green synthesis strategies employed using plant extracts, microbial agents, and biopolymers, which offer eco-friendly, cost-effective, and scalable alternatives to conventional chemical routes. These green synthesis approaches not only ensure environmental sustainability but also contribute significantly to the enhanced biological activity and safety profile of SeNPs by incorporating bioactive capping agents derived from natural sources.

The biomedical applications of SeNPs are broad and expanding. Their demonstrated antioxidant, anti-inflammatory, antimicrobial, anticancer, and wound healing properties position them as promising candidates for drug delivery systems, tissue engineering platforms, and targeted therapeutics. The ability of SeNPs to induce apoptosis in cancer cells, modulate immune responses, and support tissue regeneration underscores their versatility across various therapeutic domains. Furthermore, their integration into advanced systems such as nanogels, nanofibers, and smart delivery platforms enhances their efficacy and application-specific performance. Reinforcing the importance of green synthesis, this approach aligns with the global shift toward sustainable nanotechnology. It not only reduces the toxicological risks associated with conventional synthesis but also enables the generation of biocompatible nanoparticles with improved therapeutic outcomes. Green-synthesized SeNPs represent a convergence of safety, functionality, and ecological responsibility-critical factors in the development of clinically viable nanomedicines.

Looking forward, the clinical translation of SeNPs will depend on overcoming challenges related to synthesis standardization, long-term safety validation, and regulatory approval. Nonetheless, advances in smart delivery, personalized medicine, and interdisciplinary collaboration are likely to accelerate the integration of SeNPs into mainstream healthcare. With continued research and innovation, selenium nanoparticles are poised to become key components of next-generation biomedical technologies, offering safer and more effective solutions to complex health challenges.

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