Natural Resources for Human Health
eISSN: 2583-1194

Original Research

Received 22 March 2026
Revised 15 April 2026
Accepted 05 May 2026

Natural Resources for Human Health 2026, Vol. 6 (3): 759–766

KEYWORDS:
selenium nanoparticles; biogenic synthesis; green nanotechnology; structure–activity relationship; antioxidant mechanisms; Nrf2–Keap1; oxidative stress; nanotoxicology

Biogenic Synthesis of Selenium Nanoparticles: Structure-Activity Relationships and Antioxidant Mechanisms

Makhzuna Mukhsinova[1], Sorabh Lakhanpal[2], Tharani Munusamy[3], Nallusamy Duraisamy[4], Amanveer Singh[5], S. Andrew John Silvester[6], Kunal Dadhich[7]

[1]Department of Childhood Diseases in Family Medicine, Tashkent State Medical University, Tashkent, Uzbekistan, mukhsinovamakhzuna@gmail.com
[2]School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab 144411, India, sorabh.lakhanpal@lpu.co.in
[3]Research, Meenakshi Academy of Higher Education and Research, tharani@maher.ac.in
[4]Department of Research, Meenakshi Academy of Higher Education and Research, nallu@maher.ac.in
[5]Centre for Research Impact & Outcome, Chitkara University Institute of Engineering and Technology, Chitkara University, Rajpura, Punjab 140401, India, amanveer.singh.orp@chitkara.edu.in
[6]Department of Neuroscience, School of Allied Health Sciences, Vinayaka Mission's Puducherry Campus, Vinayaka Mission's Research Foundation (DU), Tamil Nadu, India, andrewjohn.aj@gmail.com
[7]Department of Pharmaceutical Chemistry, Parul Institute of Pharmacy, Parul University, Vadodara, Gujarat, India, kunal.dadhich39000@paruluniversity.ac.in

ABSTRACT: Selenium nanoparticles (SeNPs) have emerged as redox-active nanomaterials that combine the biological relevance of selenium with size-dependent physicochemical properties. This review examines biogenic SeNP production, the relationships between structural attributes and biological performance, and the mechanisms underlying antioxidant activity. Plants, bacteria, fungi, yeasts, algae, and isolated biomolecules can reduce selenium oxyanions to elemental selenium while simultaneously generating a surface corona that influences nucleation, growth, colloidal stability, cellular interactions, and toxicity. Synthesis variables—including pH, temperature, reaction time, precursor concentration, extract composition, and biomass ratio—govern particle size, morphology, crystallinity, charge, aggregation, and dissolution. These characteristics determine protein adsorption, membrane interaction, cellular uptake, intracellular selenium availability, and ultimately the balance between antioxidant and pro-oxidant effects.

At appropriate exposures, biogenic SeNPs may support glutathione peroxidase and thioredoxin reductase systems, increase glutathione, activate Nrf2–Keap1–ARE signaling, limit reactive oxygen and nitrogen species, preserve mitochondrial function, and reduce lipid, protein, and DNA oxidation. Reported applications include protection in metabolic, inflammatory, neurodegenerative, hepatic, renal, and reproductive models, as well as antimicrobial and anticancer strategies in which controlled oxidative stress may be desirable. Translation remains limited by inconsistent biological starting materials, incomplete nanoparticle characterization, variable dose reporting, insufficient

Natural Resources for Human Health
eISSN: 2583-1194

pharmacokinetic evidence, and a lack of standardized long-term safety studies. Future progress requires quality-by-design synthesis, reference materials, mechanistically linked structure–activity datasets, physiologically relevant models, and transparent reporting. Biogenic SeNPs are promising antioxidant platforms, but their clinical value depends on reproducible manufacture and exposure-specific safety evaluation.

1. INTRODUCTION

Selenium is a trace element that is known to play a role in the regulation of the redox status through 25 human selenoproteins, such as glutathione peroxidases, thioredoxin reductases and iodothyronine deiodinases, which participate in the metabolism of thyroid hormones, immunity, reproduction and cell survival. Both deficiency and toxicity are detrimental, and the relatively small window between requirement and toxicity makes supplementation a tricky business. (3) Distribution, metabolism and biological effect are strongly affected by selenium speciation (inorganic selenite and selenate are not pharmacologically equivalent to elemental selenium or organic selenomethionine). The advantages of SeNPs are that, at the nanoscale, Se can possess a high surface area, be rendered more reactive, and exhibit decreased acute toxicity in many experimental systems compared to soluble inorganic forms. (4) Biological identity is not restricted to the selenium core, but is defined as a combination of size, morphology, crystallinity, surface charge, aggregation state, dissolution and the corona of adsorbed biomolecules or biogenic origin. (5) Biogenic synthesis involves usage of plant extracts, microorganisms or purified biomolecules as a reducing and stabilizing system, which reduces the use of harsh reductants and increases the production of naturally capped particles with potentially useful bioactivity. As detailed in Figure 1, the selenium oxyanions are reduced to elemental selenium via nucleation and growth processes that are influenced by the reaction conditions, followed by biomolecular capping that influences downstream function of the colloid. The aim of this review is to combine the key biogenic production pathways, discuss the characterisation required to define the structure of SeNP, and link physicochemical properties to bioavailability and antioxidant activity, and critically evaluate safety and translational challenges. Special attention is directed towards exposure dependent redox properties, as the same material can be protective in antioxidant activity in normal tissues, and may create oxidative damage at high levels or in susceptible cells. (7)

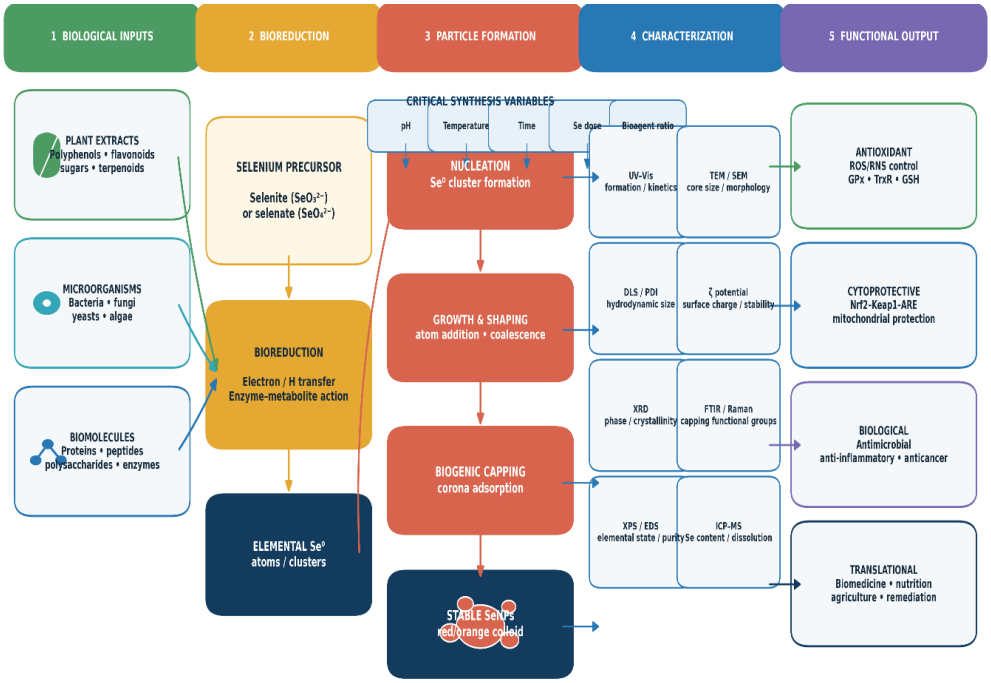

Figure 1. Biogenic synthesis of selenium nanoparticles using plants, microorganisms, and biomolecules.

2. BIOGENIC SYNTHESIS AND CHARACTERIZATION OF SELENIUM NANOPARTICLES

The most typical pathways for the biogenic synthesis of SeNP involve the use of selenite or selenate and the reduction properties of plant metabolites, microbial enzymes or isolated macromolecules. The plant extracts provide polyphenols, flavonoids, sugars, organic acids, terpenoids and proteins which chelate the selenium ions and are bound to the surface of the particle as stabilizing ligands. Bacteria can recover by intracellular or extracellular reduction via respiratory detoxification, redox enzymes, glutathione related pathways and secreted metabolites, but intracellular recovery may complicate purification. Fungi and yeasts provide high biomass along with good metal tolerance, and also have good amounts of extracellular proteins while algae provide pigments, polysaccharides and phenolic compounds that can undergo reduction and capping. Purified polysaccharides, proteins, peptides and microbial exopolymers can be used to enhance compositional control and can lead to narrower particle distributions than crude extracts (10). The presence of nanoparticles is typically confirmed by a red to orange color, and a characteristic UV–visible response, but color is not a definitive identifier of nanoparticles. Primary size and morphology should be determined by transmission or scanning electron microscopy, hydrodynamic diameter and polydispersity should be reported by dynamic light scattering, dispersion behavior by zeta potential, and surface groups, elemental state and selenium content by FTIR, Raman spectroscopy, XPS or ICP-based methods. Nucleation, growth, aggregation, yield, and corona composition are affected by (12) reaction pH, temperature, reaction time, concentration of precursor, extract-to-precursor ratio, agitation, oxygen availability, and post-synthesis purification. Table 1 shows the information that should be reported for synthesis–property–application, which is compared with representative biological sources. Interpretable comparisons of biological effects require batch controls, blank extracts, measurement of residual precursor, storage stability, sterility or endotoxin testing, as well as both mass and particle-based dose metrics. Standardized workflows are particularly crucial as they can alter the reducing capacity of biological materials depending on the season, geographic location, growth phase, and extraction, and thus affect the final product of SeNP. (14)

Table 1. Biological sources, synthesis conditions, physicochemical characteristics, and applications of biogenic selenium nanoparticles.

Biological system	Principal reducing/capping components	Key process variables	Expected SeNP attributes	Representative applications
Plant extracts	Polyphenols, flavonoids, sugars, proteins, terpenoids	Species, plant part, extraction, pH, temperature, precursor ratio	Often spherical; variable corona and size distribution	Antioxidant, antimicrobial, anti-inflammatory
Bacteria	Reductases, thiols, proteins, extracellular polymers	Strain, growth phase, oxygen, precursor tolerance, recovery	Intracellular or extracellular; protein/EPS capped	Bioremediation, antimicrobial, biomedical
Fungi and yeasts	Secreted enzymes, proteins, polysaccharides	Biomass, incubation time, pH, aeration, downstream purification	High-yield extracellular particles; strong biomolecular capping	Antioxidant, anticancer, agriculture
Algae	Pigments, phenolics, proteins, sulfated polysaccharides	Species, light, salinity, extract concentration	Polysaccharide-rich corona; potentially stable colloids	Nutraceutical, antimicrobial, environmental

Biological system	Principal reducing/capping components	Key process variables	Expected SeNP attributes	Representative applications
Purified biomolecules	Polysaccharides, peptides, proteins, enzymes	Molecular weight, purity, ligand:Se ratio, ionic strength	Better-defined corona and tunable stability	Drug delivery, targeted and mechanistic studies

3. STRUCTURE–ACTIVITY RELATIONSHIPS OF BIOGENIC SELENIUM NANOPARTICLES

Biogenic SeNPs do not act solely in response to the nominal selenium concentration, but rather by a complex structure–exposure relationship. Smaller particles tend to have higher specific surface area and potentially to be able to dissolve, adsorb biomolecules, or enter cells more easily, but can also aggregate or cause toxicity if the delivered intracellular dose is too high. (15) Shape and crystallinity modify exposed facets, defect density, chemical reactivity and dissolution kinetics, and broad size distributions could obscure the identity of the subpopulation responsible for a measured response. The surface charge has an effect on the stability of the colloids and their interaction with membranes but may vary significantly in the presence of serum and gastrointestinal fluid or in cell culture media. The biogenic corona is especially noteworthy as these proteins, polysaccharides and polyphenols can inhibit aggregation, have inherent antioxidant activity, influence protein adsorption and mediate receptor-mediated uptake. Therefore, the effects of the biological material must be compared with the effects of the precursor, biological-extract, and corona materials to separate the effects of the selenium core from the effects from surface-associated molecules. The nature of the activity (from the intact particles, released selenium species, or both) is determined by dissolution or transformation, which depends on pH, ionic strength, thiols, enzymes, and residence time. Structural properties influence the nano–bio interface which in turn determines uptake, intracellular selenium availability, antioxidant signaling and tissue protection as shown in Figure 2. An optimized particle can be used for slow release selenium and for using it as part of the mechanisms that support selenoprotein function without causing a high transient load, while an unstable or very reactive particle can lead to aggregation, an overload of selenium, mitochondrial disturbance, and pro-oxidant injury. (20) For meaningful structure–activity studies, matched batches that differ only by one feature are desirable, so is complete characterization in relevant media, quantitative uptake and dissolution measurements, and dose–response modeling based on both administered and cellular doses. These can then be used in multivariate analysis and/or quality-by-design methods to determine critical material attributes and establish a reproducible design space for antioxidant applications. (21)

Natural Resources for Human Health
eISSN: 2583-1194

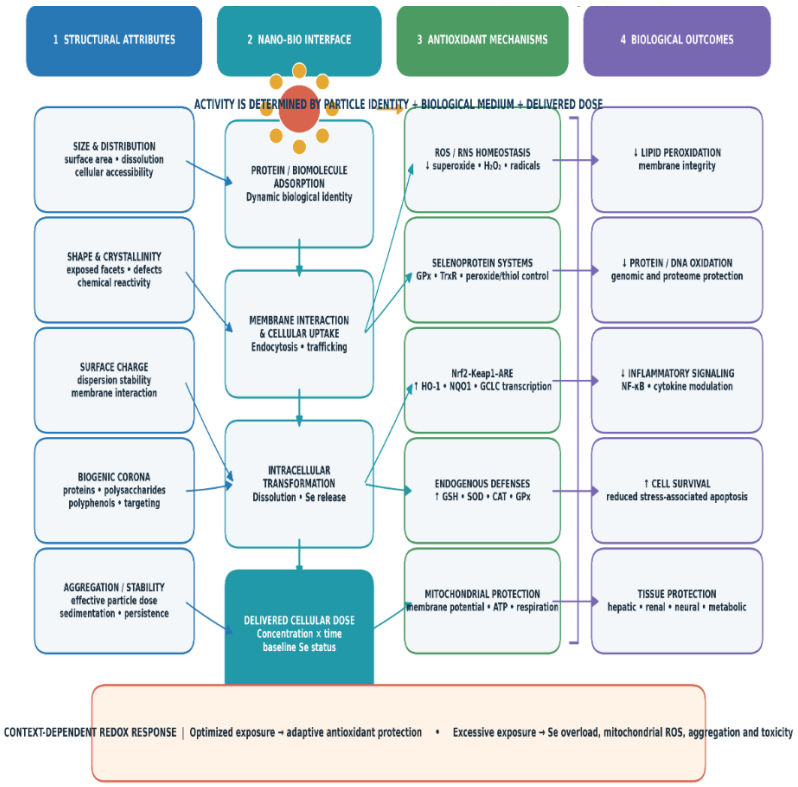

Figure 2. Structure–activity relationships governing the antioxidant activity of biogenic selenium nanoparticles.

4. ANTIOXIDANT MECHANISMS AND BIOLOGICAL APPLICATIONS

Biogenic SeNPs can modulate oxidative stress in the direct chemical interactions, but more significantly, via cellular antioxidant systems. Reducing molecules and phenolics found in surface preparations may be able to scavenge radicals in cell-free assays which is not indicative of in vivo efficacy and should be confirmed by showing uptake, metabolism, and pathway engagement. The release and/or metabolic availability of selenium from SeNPs can facilitate the production or function of glutathione peroxidases and thioredoxin reductases, which may facilitate peroxide elimination, thiol redox regulation and the regeneration of antioxidant networks. (23) SeNP has also been shown to act as an activator of Nrf2, its dissociation from Keap1-dependent repression, nuclear translocation, and activation of genes that contain antioxidant response elements, such as HO-1, NQO-1 and glutathione metabolism enzymes. In experimental models these responses can raise glutathione, superoxide dismutase, catalase and glutathione peroxidase activity and lower malondialdehyde, protein carbonylation, inflammatory signaling and oxidative DNA injury. Mitochondrial protection can be achieved by maintaining membrane potential, minimizing electron leakage, ATP homeostasis and apoptosis suppression due to stress. These mechanisms have been successfully applied to studies of hepatic, renal, metabolic, neurodegenerative, reproductive, inflammatory, and ischemic injury models. (26) Table 2 will sort mechanism end points (MEPs), models, and safety observations to evaluate claims. A different interpretation is needed for its antimicrobial and anticancer applications: controlled ROS generation, mitochondrial depolarization and apoptosis can be protective in the one biological context and pro-oxidant in another, hence a pro-oxidant formulation can be protective in one case and pro-oxidant in another. Cell and animal studies continue to dominate the evidence, there is a great deal of variability in synthesis, dose units, comparator, exposure duration, and endpoint selection. An evaluation of antioxidant activity should include chemical assays of antioxidant activity, cell-based redox imaging, enzyme activity and gene expression, mitochondrial endpoints, oxidative damage markers, pharmacokinetics, histopathology, and functional outcomes. Mechanistic inhibitors and/or genetic models are required to prove causation, rather than simply a correlation between SeNP treatment and indices of antioxidant markers. (28)

Table 2. Antioxidant mechanisms, experimental models, biological outcomes, and toxicity considerations of biogenic selenium nanoparticles.

Mechanistic domain	Representative measurements	Typical experimental models	Interpretation	Essential safety controls
Radical and peroxide control	DPPH/ABTS, ROS probes, H_2O_2, lipid peroxidation	Cell-free systems; stressed cells	Screening only unless supported by cellular evidence	Assay interference and extract/corona controls
Selenoenzyme support	GPx and TrxR activity; selenium speciation	Cells, liver, kidney, metabolic models	Improved peroxide and thiol-redox regulation	Compare selenite, selenate, SeMet and elemental Se
Nrf2–Keap1–ARE signaling	Nrf2 translocation; HO-1, NQO1, GCLC expression	Oxidative, inflammatory and toxicant models	Adaptive cytoprotective transcription	Pathway inhibition or genetic validation
Endogenous defenses	GSH/GSSG, SOD, CAT, GPx; MDA and carbonyls	Cell and animal disease models	Network-level antioxidant response	Time course, dose response, baseline Se status
Mitochondrial protection	Membrane potential, ATP, respiration, apoptosis	Neuronal, hepatic, renal and cardiac models	Reduced mitochondrial ROS and cell injury	Cellular uptake, dissolution and viability
Context-dependent pro-oxidation	ROS, depolarization, caspases, DNA damage	Tumor cells and microorganisms	May contribute to anticancer/antimicrobial action	Normal-cell selectivity and systemic toxicity

5. SAFETY, CHALLENGES, FUTURE PERSPECTIVES, AND CONCLUSION

The major hurdle in the translation of bioengineered SeNPs is the translation of a variable biological product into a reproducible and exposure-controlled nanomedicine or functional ingredient. Safety margins are small, and toxicity of nanoparticles may be size-dependent, surface chemistry-dependent, aggregation-dependent, dissolution-dependent, dose-dependent, route-dependent, frequency-dependent and condition-dependent. Inadequate short-term cytocompatibility: genotoxicity, immunotoxicity, reproductive effects, organ accumulation, selenium speciation, excretion and recovery following repeated exposure should be studied. Protein corona and blood or gastrointestinal fluid changes can affect biodistributions and uptake by liver, spleen, and mononuclear phagocyte systems can result in tissue-specific exposure. Seasonal variation in plant extracts, microbial strain drift, endotoxin or biomaterial contamination, residual selenium salts, inconsistent purification of extracts and scale dependent mixing and oxygen transfer are also manufacturing challenges. (32) Progress depends on the use of authenticated biological sources, specified critical quality attributes, validated assays, reference batches, stability-indicating methods and reporting standards which link synthesis parameters to particle identity and biological response. Long-term studies with an adequate number of animals and adequate benckmarking of selenium comparators, physiologically relevant models, disease-relevant models and sex-balanced animals should be conducted before clinical testing (33). The classification, good manufacturing practice (GMP), evaluation of environmental risk, and justified specifications for size distribution, elemental state, corona composition, potency, impurities and release will be necessary for regulatory development. Finally, the use of

biogenic SeNPs is a versatile platform to modulate oxidative stress; however, the safety and efficacy of "green" synthesis is not guaranteed. They must be manufactured reproducibly, structure-activity relationships have to be mechanistically understood and shown to have an antioxidant benefit within a well-defined therapeutic window. (35)

Declarations

Acknowledgment: The authors gratefully acknowledge the support and guidance received during the preparation of this manuscript.

Conflict of Interest: The authors declare that they have no conflict of interest.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

[1] National Institutes of Health, Office of Dietary Supplements. Selenium: Fact Sheet for Health Professionals. Bethesda (MD): NIH; 2025.
[2] Rayman MP. Selenium and human health. Lancet. 2012;379(9822):1256-1268. doi:10.1016/S0140-6736(11)61452-9.
[3] Fairweather-Tait SJ, Bao Y, Broadley MR, Collings R, Ford D, Hesketh JE, et al. Selenium in human health and disease. Antioxid Redox Signal. 2011;14(7):1337-1383. doi:10.1089/ars.2010.3275.
[4] Zhang T, Qi M, Wang G, et al. Recent research progress on the synthesis and biological effects of selenium nanoparticles. Front Nutr. 2023;10:1183487. doi:10.3389/fnut.2023.1183487.
[5] Hosnedlova B, Kepinska M, Skalickova S, et al. Nano-selenium and its nanomedicine applications: a critical review. Int J Nanomedicine. 2018;13:2107-2128. doi:10.2147/IJN.S157541.
[6] Mikhailova EO. Selenium nanoparticles: green synthesis and biomedical applications. Molecules. 2023;28(24):8125. doi:10.3390/molecules28248125.
[7] Khurana A, Tekula S, Saifi MA, Venkatesh P, Godugu C. Therapeutic applications of selenium nanoparticles. Biomed Pharmacother. 2019;111:802-812. doi:10.1016/j.biopha.2018.12.146.
[8] Ikram M, Javed B, Hassan SWU, et al. Biomedical potential of plant-based selenium nanoparticles: a comprehensive review on therapeutic and mechanistic aspects. Int J Nanomedicine. 2021;16:249-268. doi:10.2147/IJN.S295053.
[9] Fesharaki PJ, Nazari P, Shakibaie M, Rezaie S, Banoee M, Abdollahi M, et al. Biosynthesis of selenium nanoparticles using Klebsiella pneumoniae and their recovery by a simple sterilization process. Braz J Microbiol. 2010;41(2):461-466. doi:10.1590/S1517-83822010000200028.
[10] Zare B, Babaie S, Setayesh N, Shahverdi AR. Isolation and characterization of a fungus for extracellular synthesis of small selenium nanoparticles. Nanomed J. 2013;1(1):13-19.
[11] Ramamurthy CH, Sampath KS, Arunkumar P, et al. Green synthesis and characterization of selenium nanoparticles and its augmented cytotoxicity with doxorubicin on cancer cells. Bioprocess Biosyst Eng. 2013;36(8):1131-1139. doi:10.1007/s00449-012-0867-1.
[12] Ibrahim SSS, et al. Recent progress in the green synthesis, characterization, and applications of selenium nanoparticles. BIO Integration. 2024. doi:10.15212/bioi-2024-0063.
[13] Wadhwani SA, Shedbalkar UU, Singh R, Chopade BA. Biogenic selenium nanoparticles: current status and future prospects. Appl Microbiol Biotechnol. 2016;100(6):2555-2566. doi:10.1007/s00253-016-7300-7.
[14] Shakibaie M, Khorramizadeh MR, Faramarzi MA, Sabzevari O, Shahverdi AR. Biosynthesis and recovery of selenium nanoparticles and the effects on matrix metalloproteinase-2 expression. Biotechnol Appl Biochem. 2010;56(1):7-15. doi:10.1042/BA20090234.
[15] Huang B, Zhang J, Hou J, Chen C. Free radical scavenging efficiency of nano-Se in vitro. Free Radic Biol Med. 2003;35(7):805-813. doi:10.1016/S0891-5849(03)00428-3.
[16] Zhang JS, Gao XY, Zhang LD, Bao YP. Biological effects of a nano red elemental selenium. Biofactors. 2001;15(1):27-38. doi:10.1002/biof.5520150103.
[17] Nel AE, Mädler L, Velegol D, et al. Understanding biophysicochemical interactions at the nano-bio interface. Nat Mater. 2009;8(7):543-557. doi:10.1038/nmat2442.
[18] Monopoli MP, Åberg C, Salvati A, Dawson KA. Biomolecular coronas provide the biological identity of nanosized materials. Nat Nanotechnol. 2012;7(12):779-786. doi:10.1038/nnano.2012.207.

[19] Loeschner K, Hadrup N, Qvortrup K, et al. Distribution of selenium in rats following repeated administration of selenium nanoparticles or selenite. Part Fibre Toxicol. 2014;11:11. doi:10.1186/1743-8977-11-11.
[20] Wang H, Zhang J, Yu H. Elemental selenium at nano size possesses lower toxicity without compromising the fundamental effect on selenoenzymes. Free Radic Biol Med. 2007;42(10):1524-1533. doi:10.1016/j.freeradbiomed.2007.02.013.
[21] Geng L, et al. Recent advances towards selenium nanoparticles: synthesis, structure-activity relationships and applications. Foods. 2025;14(21):3640.
[22] Kong H, Yang J, Zhang Y, Fang Y, Nishinari K, Phillips GO. Synthesis and antioxidant properties of gum arabic-stabilized selenium nanoparticles. Int J Biol Macromol. 2014;65:155-162. doi:10.1016/j.ijbiomac.2014.01.011.
[23] Rotruck JT, Pope AL, Ganther HE, Swanson AB, Hafeman DG, Hoekstra WG. Selenium: biochemical role as a component of glutathione peroxidase. Science. 1973;179(4073):588-590. doi:10.1126/science.179.4073.588.
[24] Liu HJ, Qin Y, Zhao ZH, Zhang Y, Yang JH, Zhai DH, et al. Biogenic nanoselenium particles effectively attenuate oxidative stress-induced intestinal epithelial barrier injury by activating the Nrf2 antioxidant pathway. ACS Appl Mater Interfaces. 2017;9(13):11761-11770. doi:10.1021/acsami.7b03377.
[25] Ye XQ, et al. Biogenic selenium nanoparticles synthesized with alginate oligosaccharides improve antioxidant capacity and immune function. Antioxidants. 2023;12(11):1973.
[26] Duntas LH, Benvenga S. Selenium: an element for life. Endocrine. 2015;48(3):756-775. doi:10.1007/s12020-014-0477-6.
[27] Hariharan H, Al-Harbi N, Karuppiah P, Rajaram SK. Microbial synthesis of selenium nanocomposite using Saccharomyces cerevisiae and its antimicrobial activity. Enzyme Microb Technol. 2012;50(4-5):241-246. doi:10.1016/j.enzmictec.2011.12.009.
[28] Grudniak AM, et al. Mechanism of antioxidant activity of selenium nanoparticles obtained by green synthesis. Int J Nanomedicine. 2025.
[29] Nuttall KL. Evaluating selenium poisoning. Ann Clin Lab Sci. 2006;36(4):409-420.
[30] Hadrup N, Ravn-Haren G. Acute human toxicity and mortality after selenium ingestion: a review. J Trace Elem Med Biol. 2020;58:126435. doi:10.1016/j.jtemb.2019.126435.
[31] Weekley CM, Harris HH. Which form is that? The importance of selenium speciation and metabolism in the prevention and treatment of disease. Chem Soc Rev. 2013;42(23):8870-8894. doi:10.1039/C3CS60272A.
[32] Menon S, Shrudhi Devi KS, Agarwal H, Shanmugam VK. Efficacy of biogenic selenium nanoparticles from an extract of ginger towards evaluation on antimicrobial and antioxidant activities. Colloid Interface Sci Commun. 2019;29:1-8. doi:10.1016/j.colcom.2018.12.004.
[33] ISO/TR 13014:2012. Nanotechnologies—Guidance on physico-chemical characterization of engineered nanoscale materials for toxicologic assessment. Geneva: International Organization for Standardization; 2012.
[34] Faria M, Björnmalm M, Thurecht KJ, et al. Minimum information reporting in bio-nano experimental literature. Nat Nanotechnol. 2018;13(9):777-785. doi:10.1038/s41565-018-0246-4.
[35] OECD. Guidance document on aquatic and sediment toxicological testing of nanomaterials. Paris: Organisation for Economic Co-operation and Development; 2020.