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Review Article

Biological Activities of Selenium Nanoparticles: Molecular Mechanisms, Therapeutic Potential, and Safety Considerations

Hanif Amrulloh*, Claudia Maria Simonescu, Oman Zuas, Muhammad Saqib Khan, and Hamed Kioumarsi

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Abstract
Selenium nanoparticles (SeNPs) have emerged as structurally tunable, redox-active nanomaterials with multifaceted biological activities that extend beyond the capabilities of conventional selenium compounds. This review critically synthesizes current knowledge on the molecular mechanisms, therapeutic potential, and safety considerations underlying SeNP bioactivity. At the mechanistic level, SeNPs function as redox-responsive nanomodulators that regulate reactive oxygen species (ROS) in a dose- and context-dependent manner. Through modulation of glutathione peroxidase activity and Nrf2/Keap1 signaling, SeNPs reinforce endogenous antioxidant defenses, while controlled ROS amplification induces mitochondrial membrane depolarization, caspase activation, and apoptosis in malignant cells. In microbial systems, SeNPs exert multitarget effects involving membrane destabilization, oxidative stress induction, and intracellular macromolecular disruption, thereby reducing susceptibility to conventional resistance mechanisms. Concurrent suppression of NF-κB signaling and activation of Nrf2 pathways further confer anti-inflammatory and immunomodulatory benefits. These biological responses are intrinsically governed by physicochemical attributes—including particle size, crystallinity, surface charge, and functionalization—which determine cellular uptake, interfacial redox reactivity, biodistribution, and kinetic selenium release. Despite promising preclinical evidence in antioxidant, anticancer, antimicrobial, and anti-inflammatory applications, translational advancement remains constrained by selenium's narrow therapeutic window, incomplete pharmacokinetic characterization, long-term toxicity uncertainties, and variability in synthesis and characterization protocols. Future development of SeNP-based nanomedicines will require rigorous correlation of structural design with mechanistic endpoints, standardized safety evaluation frameworks, and scalable, reproducible manufacturing strategies to balance therapeutic efficacy with controlled redox liability.

Keywords: anti-inflammatory, anticancer, antimicrobial, antioxidant, selenium nanoparticles

1. INTRODUCTION

Selenium is an essential trace element that plays a central role in redox homeostasis, immune regulation, and cellular metabolism through its incorporation into selenoproteins, including glutathione peroxidases (GPXs), thioredoxin reductases, and iodothyronine deiodinases [1]-[3]. The unique nucleophilicity and redox reactivity of selenocysteine residues confer catalytic efficiency in the detoxification of hydrogen peroxide and lipid hydroperoxides, thereby safeguarding cellular macromolecules from oxidative damage. However, selenium exhibits a narrow therapeutic window, as both deficiency and excess can disrupt physiological equilibrium. Conventional selenium forms, such as sodium selenite and selenomethionine, are characterized by rapid systemic distribution, non-specific redox cycling, and dose-dependent toxicity, which limit their safe and effective clinical utilization [4]. These constraints have motivated the exploration of nanoscale selenium formulations capable of modulating bioavailability and redox behavior in a more controlled manner.

Selenium nanoparticles (SeNPs) represent a distinct physicochemical form of elemental selenium (Se^0) that integrates material tunability with biological functionality [5]. Unlike soluble selenium salts, SeNPs provide a reservoir-based release profile and surface-mediated redox reactivity governed by nanoscale dimensions, crystallinity, morphology, and surface chemistry. Advances in chemical, hydrothermal, plant-mediated, and microbial synthesis have enabled precise regulation of particle size distribution, zeta potential, and interfacial functionalization, thereby influencing colloidal stability and biological interactions [6]-[8]. The high surface-to-volume ratio of SeNPs enhances interfacial electron transfer processes, while surface coatings—ranging from

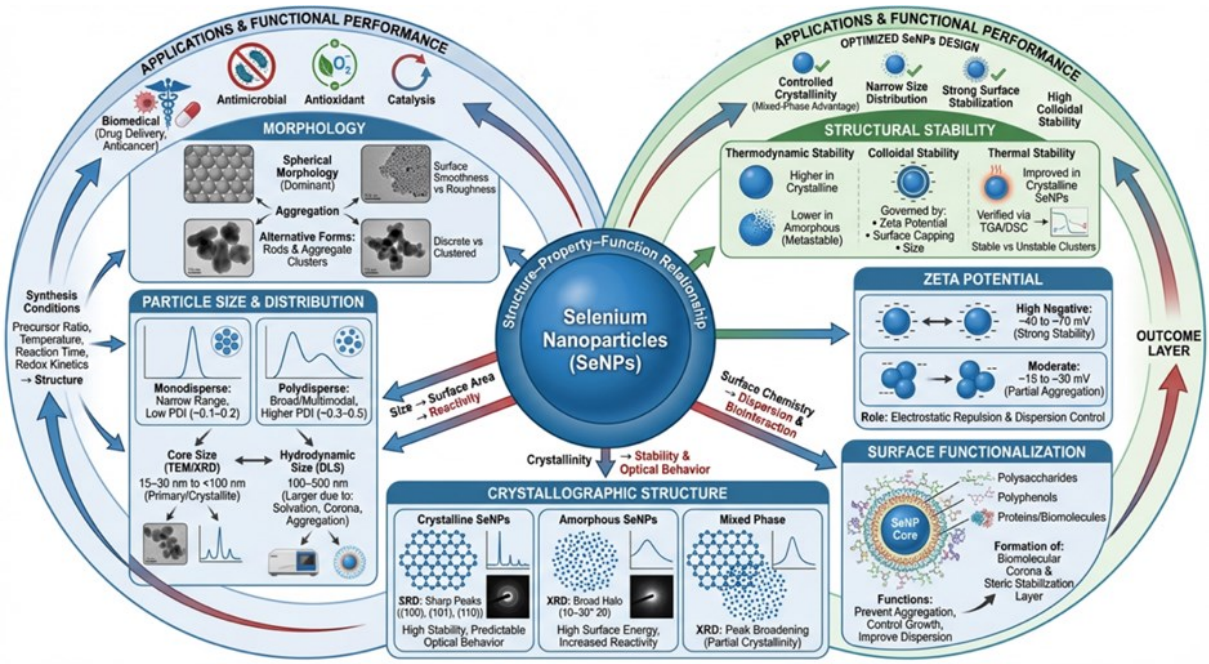

Figure 1. Illustrating the structural engineering of selenium nanoparticles (SeNPs) and its impact on stability, reactivity, and application-specific functionality.

polysaccharides and proteins to synthetic polymers and targeting ligands—modulate dispersion stability, cellular uptake, and tissue specificity. Consequently, SeNPs exhibit physicochemical characteristics fundamentally distinct from molecular selenium species, positioning them as nanoengineered platforms rather than simple micronutrient carriers.

Emerging evidence demonstrates that the biological activities of SeNPs are mechanistically unified by redox modulation. At physiological concentrations, SeNPs enhance endogenous antioxidant systems through upregulation of GPX isoforms and activation of Nrf2-dependent transcriptional programs, thereby restoring oxidative balance in stressed tissues [9]-[11]. Conversely, in pathological contexts such as cancer, SeNPs can amplify intracellular ROS beyond cytoprotective thresholds, triggering mitochondrial membrane depolarization, cytochrome c release, caspase cascade activation, and cell cycle arrest [12]-[14]. This bidirectional redox plasticity underlies their capacity to function as both antioxidant protectants and pro-oxidant cytotoxic agents depending on microenvironmental conditions. In microbial systems, analogous ROS-mediated mechanisms combine with direct membrane destabilization and oxidative damage to proteins and nucleic acids, producing broad-spectrum antibacterial, antifungal, and antibiofilm effects [15]-[17]. Additionally, modulation of NF-κB and Nrf2 signaling pathways extends SeNP functionality into anti-inflammatory and immunomodulatory domains, where cytokine suppression and macrophage polarization are regulated through redox-sensitive signaling networks.

These mechanistic properties have stimulated intensive investigation of SeNPs in diverse therapeutic applications. In oncology, SeNPs have demonstrated tumor-selective cytotoxicity, synergy with chemotherapeutic agents, and microenvironment-responsive redox modulation [18][19]. In infectious disease contexts, their multitarget antimicrobial activity offers a strategy to mitigate resistance development and disrupt biofilm -associated persistence. Anti-inflammatory and organ-protective effects further support potential utility in conditions characterized by oxidative and inflammatory dysregulation, including renal injury, colitis, and viral infection models [20]-[22]. Importantly, surface engineering strategies—such as ligand-mediated targeting, pH- or glutathione-responsive coatings, and nanozyme integration—have expanded the functional repertoire of SeNPs toward precision nanomedicine and combination

therapy paradigms .

Despite these advances, significant safety and translational challenges remain. The dose-dependent dual antioxidant–prooxidant behavior of SeNPs reflects selenium's intrinsic redox liability, necessitating precise control over exposure thresholds to avoid off-target oxidative injury. Variability in synthesis protocols, incomplete standardization of physicochemical characterization, and limited long-term toxicokinetic data impede cross-study comparability and regulatory progression. Furthermore, correlations between structural parameters and biological endpoints remain insufficiently quantified, constraining predictive nano–bio interaction modeling. These gaps underscore the need for an integrative assessment of molecular mechanisms, therapeutic potential, and safety considerations. Accordingly, this review critically examines the biological activities of selenium nanoparticles within a unified mechanistic framework, emphasizing how physicochemical design governs biological performance and delineating the strategic directions required to balance efficacy with safety in future biomedical development.

2. PHYSICOCHEMICAL PROPERTIES OF SELENIUM NANOPARTICLES

2.1. Structural Characteristics

Recent studies underscore that the structural state of selenium nanoparticles (SeNPs)—amorphous, crystalline, or mixed—critically governs their physicochemical behavior and application performance. Well-defined crystalline SeNPs are typically evidenced by sharp XRD reflections corresponding to trigonal or hexagonal phases, such as the (100), (101), and (110) planes, in agreement with standard reference patterns, confirming long-range lattice ordering and moderate-to-high crystallinity [23]-[25]. High-resolution TEM and SAED further corroborate these findings through visible lattice fringes and discrete diffraction rings, indicative of coherent crystalline domains [24][26]. In contrast, amorphous SeNPs are characterized by broad XRD halos within 10–30° (2θ) and the absence of distinct Bragg peaks, reflecting short-range disorder and structural metastability [26][27]. Notably, several green-synthesized systems exhibit coexistence of amorphous and crystalline domains, where peak broadening and diffuse scattering suggest partial crystallinity modulated by particle size and biogenic capping layers [26][27]. From a comparative standpoint, crystalline SeNPs generally demonstrate enhanced phase stability, more predictable optical responses (e.g., defined SPR or UV–Vis features), and improved thermal resistance, as supported by TGA/DSC analyses [23][24][28]. Conversely, amorphous fractions contribute higher surface energy and reactivity, potentially facilitating ROS modulation or catalytic interactions but at the expense of thermodynamic stability [26][27]. Importantly, polysaccharide or biomolecule-mediated synthesis does not necessarily induce amorphization; rather, it can regulate crystallinity while improving dispersion and preventing aggregation, as confirmed by homogeneous spherical morphology in TEM images [23][28]. Collectively, the emerging evidence suggests that controlled crystallinity—rather than purely amorphous or fully crystalline extremes—offers an optimal balance between structural stability and surface reactivity, thereby tailoring SeNPs for biomedical, antioxidant, antimicrobial, and catalytic applications [23]-[28].

Recent studies on selenium nanoparticles (SeNPs) consistently demonstrate that particle size and distribution are highly dependent on the biological or chemical synthesis platform, with reported dimensions ranging from ultrasmall primary cores (~15–30 nm) to broader hydrodynamic populations exceeding 150 nm. Transmission electron microscopy (TEM) frequently reveals primary spherical particles below 100 nm, such as 23.6 ± 6.9 nm [29], 20–30 nm [30], and 15–18 nm [31], reflecting direct visualization of the inorganic core. In contrast, dynamic light scattering (DLS) often reports substantially larger mean hydrodynamic diameters—e.g., 116.5 nm [32], 151 ± 42 nm [31], or multimodal distributions spanning 100–500 nm [33] —highlighting the contribution of solvation shells, biomolecular coronas, and soft aggregation. Systems such as TFGE-SeNPs (62.8 nm) [34] and BBP-SeNPs (54–64 nm, PDI 0.14–0.21) [35] exemplify relatively narrow distributions, whereas yeast-derived SeNPs exhibit pronounced heterogeneity with multiple size

fractions [33]. XRD-derived crystallite sizes (e.g., ~28–76 nm [30][31]) often differ from TEM values, implying polycrystallinity or clustering during drying. Collectively, these discrepancies underscore that particle size must be interpreted in the context of technique-specific sensitivity to core structure versus colloidal state.

Polydispersity and distribution profiles further differentiate synthesis strategies. Biogenic systems commonly exhibit moderate to high polydispersity indices (e.g., PDI ≈ 0.40 in plant-mediated SeNPs [32]), reflecting biological variability in nucleation and growth kinetics. In contrast, polyphenol-templated approaches [35] and controlled phytochemical reductions [34] yield unimodal distributions with limited aggregation, suggesting more effective steric stabilization. Zeta potential values ranging from −14.9 mV [34] to −70.1 mV [36] reveal that electrostatic repulsion plays a decisive role in dispersion homogeneity; highly negative potentials correlate with narrow DLS peaks and reduced secondary aggregation. Conversely, moderate surface charges (−18 to −26 mV [32][33]) permit partial clustering, broadening hydrodynamic profiles. Reaction parameters—including precursor concentration, molar ratios (e.g., optimal Vc/Na_2SeO_3 at 4:1 [35]), temperature (30–80 °C [30][35]), reaction time, and controlled dropwise addition—govern nucleation–growth balance and Ostwald ripening. Insufficient capping or excessive precursor availability accelerates particle coalescence, whereas balanced reduction kinetics and biomolecule-mediated stabilization suppress uncontrolled growth, enabling reproducible nanoscale uniformity.

From a functional standpoint, size and dispersity directly modulate physicochemical stability, surface reactivity, and application performance. Sub-100 nm SeNPs, particularly those with narrow distributions (e.g., 54–64 nm [35] or 62.8 nm [34]), offer enhanced surface-to-volume ratios and improved cellular uptake, attributes critical for antimicrobial and anticancer applications. However, excessively small cores without adequate stabilization may undergo rapid aggregation in biological media, compromising reproducibility, as observed in systems where DLS values far exceed TEM dimensions [31][32]. Conversely, highly polydisperse populations extending beyond 300–400 nm [33] may exhibit reduced colloidal stability and heterogeneous bio-interactions. Notably, strong electrostatic stabilization (−70.1 mV [36]) supports homogeneous dispersion and predictable bioactivity, illustrating how tight size control translates into functional consistency. Thus, beyond achieving nanoscale dimensions, effective SeNP design requires harmonizing nucleation control, surface capping, and colloidal stabilization to minimize polydispersity. A critical comparison of reported systems indicates that synthesis strategies integrating controlled redox kinetics with robust steric or electrostatic stabilization most successfully deliver monodisperse, functionally reliable SeNPs, aligning particle size engineering with application-driven performance requirements. The graphical conceptual framework (Figure 1) summarizes the interrelated structural parameters governing selenium nanoparticles (SeNPs), highlighting how synthesis-controlled morphology, size distribution, crystallinity, surface chemistry, and zeta potential collectively determine physicochemical stability and functional performance.

The structural characteristics of selenium nanoparticles (SeNPs) emerge as a decisive determinant of their physicochemical behavior, and recent literature collectively indicates that these features are not intrinsic constants but tunable outcomes of synthesis design. Morphologically, SeNPs are predominantly spherical, yet subtle variations—from discrete monodisperse nanospheres to clustered or partially aggregated assemblies—reflect differences in nucleation–growth kinetics and biomolecule-mediated stabilization. Particle size analysis consistently reveals a distinction between primary core dimensions (typically <100 nm by TEM) and larger hydrodynamic diameters measured by DLS, underscoring the influence of solvation layers and surface-bound organic coronas. Polydispersity further differentiates synthesis platforms: controlled redox systems and optimized capping strategies yield narrow unimodal distributions, whereas biologically mediated routes often produce broader, multimodal profiles due to inherent variability in reduction dynamics. Crystallographically, SeNPs span amorphous, crystalline, and mixed-phase configurations, with sharp XRD reflections and SAED patterns indicating ordered trigonal or

Tabel 1. Comparative overview of plant-mediated and microbial synthesis of selenium nanoparticles (SeNPs).

Biological Source	Selenium Precursor	Main Reducing Mechanism	Particle Size (nm)	Morphology	Crystallinity	Ref.
Dahlia pinnata(tuber)	Na_2SeO_3 (1 mM)	Phenolic-mediated electron transfer	~17	Spherical	Trigonal	[61]
Ceropegia bulbosa	H_2SeO_3	Polyphenols & flavonoids	~56	Spherical	Hexagonal	[62]
Ficus hispida	Se(IV), 50 mM	Flavonoid/phenolic reduction	7–12 (TEM)	Spherical	Hexagonal	[63]
Multiple medicinal plants	Na_2SeO_3 (10 mM)	Redox-active phytochemicals	50–320	Spherical/heterogeneous	Mostly amorphous	[17]
Cassia javanica	Na_2SeO_3 (10 mM)	Phenolic-mediated reduction	35–100	Spherical/irregular	Hexagonal	[64]
Allium sativum	Na_2SeO_3 (10 mM)	Phenolics + sulfur compounds	n.r.	Spherical	n.r.	[65]
Melia azedarach	Na_2SeO_3 (10 mM)	Flavonoid/phenolic reduction	~74	Spherical	Hexagonal	[66]
S. cerevisiae, *C. utilis*, *Y. lipolytica*	SeO_3^{2-}	NADPH–GSH–thioredoxin pathway	20–200	Spherical/irregular	Mostly amorphous	[67]
Aspergillus carneus	Na_2SeO_3 (1 mM)	Nitrate reductase-mediated	20–77	Spherical	Crystalline	[69]
Citrobacter, *Providencia*, *Brucella*	SeO_3^{2-}	GSH + nitrate/sulfate reductase	210–222	Spherical	Amorphous	[71]
Bacillus cabrialesii	Se(VI)	Respiratory electron transfer	11–25	Intracellular	Amorphous	[72]
Limosilactobacillus fermentum	Na_2SeO_3 (5 mM)	NADH-dependent reductase	17–30	Rod-shaped	Hexagonal	[74]
Lysinibacillus odysseyi	Na_2SeO_3 (15 mM)	NADH/NADPH reductases	~86	Spherical	Partially crystalline	[36]
Escherichia coli	SeO_3^{2-}	GSH–Trx redox system	~100	Spherical	Amorphous	[70]

Abbreviations: n.r. = not reported.

hexagonal lattices, while diffuse halos signify short-range disorder. Importantly, partial crystallinity—often regulated by particle size and surface functionalization—appears to balance structural stability with surface reactivity. Surface chemistry, typically governed by polyphenols, proteins, or polysaccharides, modulates nucleation, suppresses aggregation, and alters effective hydrodynamic size, thereby linking nanoscale architecture to colloidal behavior. Zeta potential values further integrate structural and dispersion properties, as stronger electrostatic repulsion correlates with improved homogeneity and long-term stability. Collectively, these interconnected structural parameters define a dynamic framework in which morphology, size distribution, crystallinity, and surface functionalization synergistically dictate SeNP stability, reactivity, and application-specific performance.

2.2. Surface Properties

Zeta potential has emerged as a critical electrokinetic parameter governing the colloidal stability and interfacial behavior of selenium nanoparticles (SeNPs), with reported values ranging from moderately negative (−15 to −21 mV) to highly negative regimes exceeding −70 mV depending on synthesis strategy and surface chemistry. Green-synthesized SeNPs commonly exhibit ζ-potentials around −30 mV, as determined by electrophoretic light scattering using DLS-based instruments such as the Malvern Zetasizer Nano-ZS90, indicating sufficient electrostatic repulsion to maintain dispersion stability ($|\zeta| \geq 30$ mV) while preserving interfacial reactivity [37][38]. Surface modification can markedly alter this parameter: chitosan-coated Se nanocomposites display reduced negativity (−21.84 ± 4.7 mV) due to partial charge neutralization by protonated amine groups, yet retain adequate stability through combined electrostatic and steric (electrosteric) mechanisms [37]. Systems exhibiting ζ-values between −15 and −20 mV, including polysaccharide-stabilized SeNPs, depend more strongly on steric hindrance to suppress aggregation, highlighting that absolute ζ-thresholds must be interpreted in the context of surface functionalization and corona formation [39]. Conversely, exceptionally high negative potentials (−70.1 mV) are associated with dense biomolecular coronas that enhance electrostatic stabilization and narrow hydrodynamic size distributions, thereby minimizing van der Waals-driven clustering [36]. Comparative analysis thus indicates that synthesis-mediated adsorption of proteins, phenolics, or polysaccharides dictates surface charge density and double-layer structure, directly influencing aggregation kinetics, dispersion longevity, and interactions with negatively charged biological membranes. Importantly, while highly negative ζ-values reinforce colloidal robustness, moderately tuned surface potentials may optimize cellular compatibility and antiviral or antimicrobial efficacy by balancing electrostatic repulsion and membrane adhesion. Accordingly, zeta potential should be regarded not merely as a stability indicator but as an integrative structural parameter linking synthetic chemistry to dispersion behavior and functional biointeractions in SeNP-based nanoplatforms [36]-[41].

Surface charge engineering plays a central role in regulating the colloidal stability and interfacial dynamics of selenium nanoparticles (SeNPs), with reported zeta potential (ζ) values spanning from near-neutral (−2 to −3 mV) to highly charged systems exceeding ±60 mV depending on the stabilizing matrix and synthetic approach. Measurements obtained via electrophoretic light scattering (Malvern Zetasizer platforms) consistently show that alginate-coated SeNPs may exhibit strongly negative potentials (−37 to −39 mV), indicative of robust electrostatic repulsion and suppressed aggregation [42], whereas chitosan-stabilized systems can generate highly positive ζ-values (+64 mV), conferring exceptional dispersion stability through protonated amine functionalities [43]. In contrast, moderately charged formulations (−15 to −23 mV) rely predominantly on electrosteric stabilization, in which polymeric coronas such as β-cyclodextrin, TPGS, or Angelica sinensis polysaccharides provide steric shielding that compensates for limited electrostatic repulsion [44]-[46]. Importantly, surface charge magnitude alone does not fully predict colloidal behavior: near-neutral alginate systems (≈ −2 mV) are particularly susceptible to ionic strength–induced aggregation due to Ca^{2+}-mediated charge neutralization [47], whereas polysaccharide-coated SeNPs maintain dispersion even under NaCl concentrations up to

0.4 M through steric stabilization mechanisms [46]. Environmental parameters, especially pH and ionic strength, modulate electrical double-layer thickness and functional group ionization, thereby affecting aggregation kinetics and dispersion longevity. Collectively, these findings underscore that colloidal stability in SeNP systems arises from a synergistic interplay between electrostatic charge density and steric barriers, with surface functionalization dictating not only resistance to aggregation but also biological interactions, cellular uptake, and drug release behavior. Consequently, rational tuning of surface charge remains fundamental to optimizing SeNP performance across biomedical and environmental applications [42]-[47].

Recent advances demonstrate that functionalization of selenium nanoparticles (SeNPs) has progressed from simple colloidal stabilization toward integrative nanoarchitectural engineering aimed at synchronizing physicochemical control with biological performance. Multilayer biomimetic systems such as ACMLMSeP exemplify hierarchical strategies in which mesoporous Se cores are sequentially coated with lipid bilayers and tumor cell membranes, followed by EDC/NHS-mediated Angiopep-2 conjugation to achieve dual homologous and receptor-specific targeting; concomitant modulation of ζ-potential and preservation of membrane proteins (e.g., CD44, CD47) confirm successful interfacial reconstruction and enhanced tumor accumulation [48]. Similarly, folic acid–conjugated OSAS micelles integrate chemical amidation and in situ selenite reduction to produce core–shell FA-OSAS-SeNPs, where steric polysaccharide coronas improve dispersion stability while folate ligands confer receptor-mediated selectivity and amplified ROS-dependent cytotoxicity [49]. In contrast, one-step hydrothermal synthesis with chitosan embeds reduction and cationic coating within the nucleation process, yielding highly positive surfaces ($\zeta \approx +58$ mV) that enable both covalent and electrostatic cargo binding, expand redox responsiveness, and enhance antimicrobial efficacy under near-neutral pH conditions [50]. Post-synthetic adsorption approaches employing lecithin, PEG, or β-cyclodextrin further modulate hydrodynamic size and surface charge without altering the selenium core, thereby improving drug loading capacity, anti-inflammatory activity, and electrostatic stabilization through non-covalent corona formation [51]. Complementary evidence indicates that polymeric coatings (PVP, PLL, PAA) profoundly influence oxidative stress induction, cellular uptake, and genotoxicity despite comparable core dimensions, underscoring that surface chemistry—rather than selenium dissolution—primarily governs biological fate [52]. Collectively, these studies demonstrate that chemical coupling, biomembrane cloaking, and polymeric or supramolecular adsorption reconfigure SeNP interfacial energetics, dispersion behavior, and redox-mediated bioactivity, highlighting functionalization as a central determinant of translational efficacy and safety in SeNP-based nanotherapeutic systems.

2.3. Synthesis Methods

Chemical reduction remains one of the most versatile and controllable strategies for synthesizing selenium nanoparticles (SeNPs). This approach predominantly employs soluble Se(IV) precursors, such as sodium selenite (Na_2SeO_3) or selenious acid (H_2SeO_3), which are converted into elemental Se^0 through electron-donating reductants under well-defined aqueous conditions [53]-[57]. Among these reductants, L-ascorbic acid is frequently preferred due to its mild redox potential, biocompatibility, and ability to promote rapid yet controllable nucleation at ambient temperature and near-neutral pH, typically within minutes to hours [55]-[57]. In contrast, stronger reductants such as sodium borohydride or hydrazine induce instantaneous supersaturation, accelerating nucleation but often increasing the risk of polydispersity and uncontrolled aggregation. Mechanistically, electron transfer to SeO_3^{2-} generates transient Se^0 clusters that evolve through nucleation–growth equilibria governed by precursor concentration, reductant-to-precursor ratio, and stabilizer availability. Variations in precursor concentration can shift the balance between growth-dominated enlargement and burst nucleation-driven size reduction, as demonstrated in concentration-dependent systems [54][56]. To mitigate secondary aggregation, surface-active polymers or surfactants—such as chitosan, cellulose nanofibers, or Tween-80—are introduced during reduction to provide electrosteric

stabilization and regulate ζ-potential [55]-[57]. Temperature (typically 25–37 °C) and pH further modulate reduction kinetics and surface charge evolution, thereby influencing crystallinity and long-term dispersion stability. Compared with biological or physical routes, chemical reduction offers superior reproducibility, shorter reaction times, and scalable process control. Nevertheless, its effectiveness ultimately depends on precise kinetic regulation to balance nucleation and growth while minimizing aggregation.

In contrast to ambient chemical reduction, hydrothermal synthesis employs elevated temperature and autogenous pressure to provide thermodynamically regulated control over reduction and crystallization processes. Using similar Se(IV) precursors (Na_2SeO_3 or H_2SeO_3), reductants such as L-ascorbic acid or D-glucose mediate in situ conversion to Se^0 within sealed autoclave or microwave-assisted systems [58][59]. Under hydrothermal conditions (≈90–121 °C, autogenous pressure, 15–60 min), enhanced supersaturation accelerates nucleation, while sustained thermal input promotes crystal growth and phase stabilization, often yielding hexagonal selenium as confirmed by XRD (JCPDS 06-0362) [58]. However, the temperature–time profile must be carefully optimized: insufficient heating suppresses nucleation, whereas excessive thermal input promotes coalescence or precipitation, narrowing the kinetic window for uniform colloid formation [59]. Particle size, morphology, and ζ-potential are therefore highly sensitive to precursor concentration, pH, reductant addition rate, and stabilizer presence. Under optimized conditions, hydrothermally synthesized SeNPs typically exhibit narrower size distributions (~110–170 nm) and stronger negative surface charges (−45 to −65 mV), reflecting improved electrostatic stabilization and phase integrity compared with room-temperature chemical systems [59][60]. Thus, hydrothermal synthesis provides enhanced structural control and crystallinity while maintaining relatively mild chemical environments, although it requires stricter thermal regulation to prevent aggregation.

Moving from thermally regulated systems to biologically assisted strategies, plant-mediated synthesis represents a bioinspired alternative that integrates reduction and surface passivation within a single phytochemical matrix. Diverse botanical sources—including *Dahlia pinnata* tubers [61], *Ceropegia bulbosa* tubers [62], *Ficus hispida* fruits [63], *Cassia javanica* flowers [64], *Allium sativum* bulbs [65], *Melia azedarach* leaves [66], *Azadirachta indica*, *Moringa oleifera*, *Gliricidia sepium*, *Cissus quadrangularis*, *Aloe barbadensis*, *Kigelia Africana*, and *Bobgunnia madagascariensi* extracts [17] have demonstrated the ability to

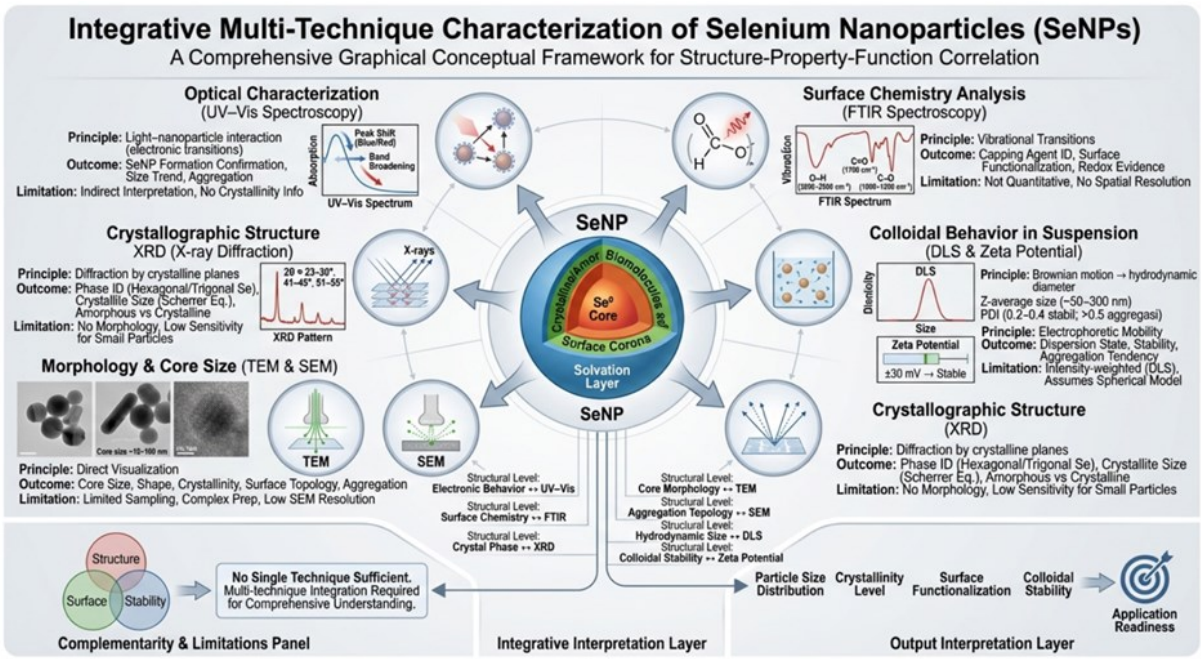

Figure 2. Multi-technique characterization framework for selenium nanoparticles (SeNPs).

reduce Se(IV) salts under mild aqueous conditions. Despite taxonomic variability, these systems consistently rely on extracts enriched in polyphenols, flavonoids, phenolic acids, terpenoids, reducing sugars, and sulfur-containing compounds. These phytochemicals donate electrons to Se(IV) while simultaneously adsorbing onto nascent nuclei through hydroxyl, carbonyl, amide, or carboxylate groups, forming a stabilizing organic corona confirmed by FTIR analysis [61]-[64][66]. As a result, nanoparticle formation is verified by characteristic UV–Vis absorption bands (≈260–300 nm) and XRD reflections corresponding to hexagonal or trigonal selenium phases. Importantly, reaction parameters—including pH, extract concentration, precursor-to-extract ratio, and temperature—govern supersaturation dynamics and nucleation kinetics, thereby influencing particle size (≈7–100 nm), crystallinity, and colloidal stability. While plant-mediated synthesis offers enhanced sustainability, safety, and intrinsic surface functionalization compared with conventional chemical routes, its reproducibility is often limited by phytochemical variability and less precise kinetic control.

Finally, microbial synthesis represents a metabolically driven extension of green synthesis, leveraging the intrinsic redox machinery of bacteria, yeasts, and fungi to convert soluble selenium oxyanions into Se^0 nanoparticles [36][40][67]-[74]. In yeasts, NADPH-dependent glutathione and thioredoxin systems mediate intracellular reduction, whereas in bacteria, NADH-dependent oxidoreductases, nitrate reductases, and thiol-based pathways frequently dominate [70]-[72]. Fungal systems similarly employ extracellular oxidoreductases and secreted proteins to facilitate reduction [69]. Depending on the organism and culture conditions, SeNPs may form intracellularly—with subsequent vesicle-mediated export—or extracellularly within enzyme-rich supernatants [70][74]. The resulting particles are naturally capped by proteins, polysaccharides, and other metabolites, generating electrosterically stabilized surfaces with ζ-potentials ranging from approximately −11 to −70 mV [36][69][74]. Culture parameters—including selenium concentration, pH (5.5–7.8), temperature (28–37 °C), aeration, and incubation time—critically influence nucleation kinetics and growth, yielding particle sizes from ~11 to >200 nm with predominantly amorphous or hexagonal phases [69][71][72]. Compared with chemical methods, microbial synthesis offers superior environmental compatibility and intrinsic biocompatibility; however, slower kinetics, biological variability, and challenges in purification and scale-up limit reproducibility and precise physicochemical control. A comparative summary of plant-mediated and microbial routes for SeNP synthesis, including biological sources, reduction mechanisms, and physicochemical characteristics, is presented in Table 1.

The synthesis of selenium nanoparticles (SeNPs) reflects a fundamental trade-off between physicochemical precision and biological sustainability. Chemically driven reduction methods provide the highest degree of control over nucleation kinetics, particle size distribution, and crystallinity through careful regulation of precursor concentration, reductant strength, pH, and stabilizer systems, thereby offering superior reproducibility and scalability for application-oriented design. Hydrothermal approaches further enhance structural order and phase purity by leveraging thermodynamically regulated temperature–pressure environments, although they require stringent optimization to prevent coalescence and aggregation. In contrast, plant-mediated and microbial syntheses prioritize environmental compatibility and intrinsic surface functionalization, as phytochemicals or enzymatic redox pathways simultaneously mediate reduction and stabilization under mild aqueous conditions. These biologically assisted routes often yield nanoparticles with enhanced colloidal stability and biocompatibility due to naturally formed organic coronas; however, they remain limited by metabolic variability, batch-to-batch inconsistency, and less precise control over crystallinity and monodispersity. Overall, no single synthesis strategy is universally optimal: chemically controlled systems excel in structural precision and industrial scalability, whereas green and microbial approaches offer sustainable platforms with built-in functional interfaces. Future progress in SeNP synthesis will likely depend on hybrid strategies that integrate kinetic control with biological stabilization, enabling reproducible, scalable

production of structurally defined yet functionally adaptable nanomaterials tailored for biomedical, environmental, and technological applications.

2.4. Characterization Techniques

UV–Vis spectroscopy is consistently applied as a rapid and preliminary technique to confirm the formation of selenium nanoparticles (SeNPs). The characteristic absorption band typically observed between ~250 and 300 nm originates from electronic transitions of Se^0 nanoclusters and size-dependent surface plasmon-like resonance phenomena, where incident photons interact with confined conduction-band electrons. Variations in peak position and bandwidth provide indirect information on particle size and aggregation state: blue shifts are generally associated with smaller particles and enhanced quantum confinement, whereas red shifts and spectral broadening indicate increased diameter, polydispersity, or interparticle coupling. Changes in absorbance intensity further enable semi-quantitative monitoring of reduction kinetics and nanoparticle concentration. However, UV–Vis lacks structural specificity and cannot independently determine crystallinity, morphology, or exact size distribution. Overlapping absorption from precursors or capping agents may also complicate interpretation. Therefore, while indispensable for monitoring nucleation and dispersion stability, UV–Vis requires complementary techniques for comprehensive structural analysis [13][[25][28]-[38][40][41][75].

Fourier Transform Infrared (FTIR) spectroscopy, plays a central role in elucidating the surface chemistry of SeNPs, particularly in plant-mediated and microbial systems. FTIR spectra commonly exhibit O–H stretching (~3200–3500 cm^{-1}), amide I/II (~1650 and 1540 cm^{-1}), C=O (~1700–1730 cm^{-1}), and C–O/C–O–C (~1000–1200 cm^{-1}) vibrations, confirming the adsorption of phenolics, proteins, and polysaccharides onto nanoparticle surfaces [17][63]-[68][76]. Shifts in band position or intensity relative to crude extracts indicate involvement of hydroxyl and carbonyl groups in Se (IV) reduction and subsequent surface passivation. In microbial systems, amide and carboxylate bands support formation of a proteinaceous corona that governs electrosteric stabilization. Despite its value in confirming functionalization and interfacial interactions, FTIR provides ensemble-averaged information and lacks spatial resolution, making it insufficient for determining ligand density, bonding configuration, or crystallinity without complementary analyses [36][40][69]-[74].

X-ray diffraction (XRD) is essential for identifying crystalline phases and evaluating structural order in SeNPs. Diffraction peaks at $2\theta \approx$ 23–30°, 41–45°, and 51–55° are typically indexed to trigonal/hexagonal Se (JCPDS 06-0362), confirming successful reduction to elemental Se^0. Peak broadening reflects nanoscale crystallite dimensions, commonly estimated using the Scherrer equation (≈10–40 nm), while diffuse halos indicate amorphous character in biogenic systems. Although XRD robustly confirms phase composition and average crystallite size, it cannot resolve morphology or surface chemistry and may exhibit weak intensity for ultrasmall or polymer-coated nanoparticles [42][43][45][46][48]-[54].

Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM) vprovide complementary morphological insights. TEM enables high-resolution visualization of individual particles, revealing core sizes typically between ~10 and 100 nm and, in HR-TEM mode, lattice fringes corresponding to hexagonal Se planes [54]-[59]. SEM, in contrast, offers broader surface topology information and highlights aggregation behavior at larger scales, often yielding larger apparent sizes due to drying-induced clustering. While TEM excels in resolving internal structure, it is limited by sample statistics; SEM provides macroscopic morphological context but lacks lattice-level detail. Together, these methods clarify morphology and aggregation state but cannot determine hydrodynamic behavior in suspension [60]-[63] [75].

Dynamic Light Scattering (DLS), complements electron microscopy by measuring hydrodynamic diameter and polydispersity in colloidal suspension [23]-[27]. Typical reported sizes range from ~50 to 300 nm, often exceeding TEM core diameters due to biomolecular coronas and solvation layers. Polydispersity index (PDI) values between 0.2 and 0.4 suggest moderate uniformity, whereas higher values indicate aggregation. Although DLS is indispensable for assessing colloidal stability and dispersion kinetics, it is intensity-weighted and

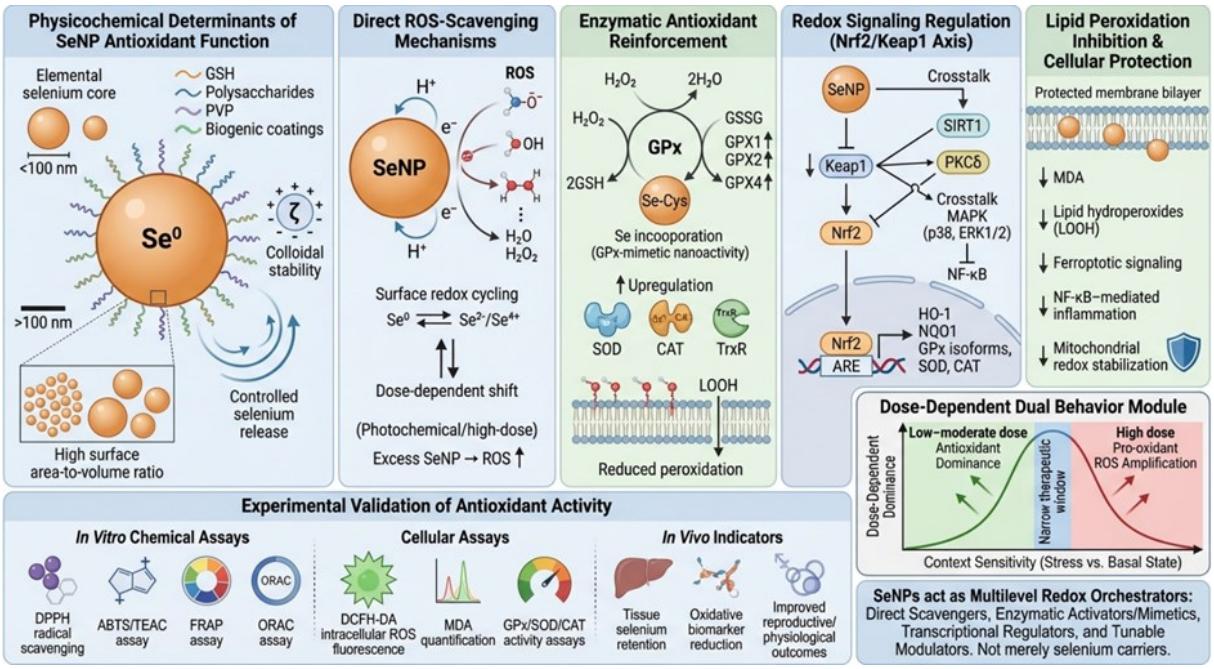

Figure 3. Mechanistic framework of selenium nanoparticle–mediated antioxidant activity: integration of ROS scavenging, enzymatic modulation, Nrf2/Keap1 signaling, and dose-dependent redox effects.

assumes spherical geometry, limiting accuracy for multimodal or anisotropic systems [13][28][29][33]-[36][75]. Consequently, DLS provides critical information on suspension stability but must be interpreted alongside microscopic and structural techniques for comprehensive characterization [30]-[32][37][38][40][41]. The comprehensive physicochemical characterization of selenium nanoparticles (SeNPs) requires the integration of complementary analytical techniques to elucidate their electronic behavior, crystallographic structure, surface chemistry, morphology, and colloidal stability, as schematically illustrated in Figure 2.

The rigorous physicochemical characterization of selenium nanoparticles (SeNPs) necessitates an integrated, multi-technique approach to accurately resolve their structural, optical, morphological, and interfacial properties. UV–Vis spectroscopy serves as a rapid diagnostic tool for monitoring nanoparticle formation and assessing size-dependent optical behavior, yet its interpretative power remains indirect without structural corroboration. FTIR spectroscopy elucidates surface functional groups and confirms interactions between SeNP cores and stabilizing biomolecules, providing critical insight into surface passivation and colloidal stabilization, although it lacks spatial and quantitative precision. X-ray diffraction establishes crystalline phase identity and enables estimation of crystallite dimensions, but cannot resolve particle morphology or surface chemistry. Electron microscopy techniques, particularly TEM and SEM, offer direct visualization of particle size, shape, aggregation state, and lattice structure, thereby validating crystallographic findings; however, they are limited by sampling constraints and preparation artifacts. Dynamic Light Scattering and zeta potential analysis extend structural interpretation into the colloidal domain, quantifying hydrodynamic size distribution and electrostatic stability in suspension, yet are inherently model-dependent and sensitive to aggregation bias. Collectively, no single technique provides a complete description of SeNP systems. Instead, reliable interpretation emerges only through cross-validation among complementary analytical methods. Such integrative characterization is essential to accurately correlate synthesis parameters with nanoparticle performance, ensuring reproducibility, stability, and application-specific functionality in advanced selenium-based nanomaterials.

3. ANTIOXIDANT ACTIVITY

The antioxidant efficacy of selenium

nanoparticles (SeNPs) is fundamentally linked to their capacity to modulate glutathione peroxidase (GPx) activity through both structural and regulatory mechanisms. Selenium, incorporated as selenocysteine at the catalytic center of GPx, confers exceptional nucleophilicity and redox reactivity, enabling efficient reduction of H_2O_2 and lipid hydroperoxides via GSH-dependent cycling. Several nanoformulations not only provide bioavailable selenium for selenoprotein biosynthesis but also display intrinsic GPx-mimetic activity, as illustrated by GSH-functionalized SeNPs exhibiting low Km values toward GSH and H_2O_2, indicative of high catalytic efficiency [77]. In cellular and in vivo models, SeNPs consistently restore or enhance GPx activity while reducing malondialdehyde (MDA) and other oxidative biomarkers, thereby integrating enzymatic reinforcement with attenuation of lipid peroxidation [78][79]. Notably, ultra-small or surface-modified SeNPs upregulate GPX isoforms (e.g., GPX1, GPX2, GPX4), frequently via Nrf2-dependent transcriptional activation, indicating that nanoparticle-mediated redox signaling amplifies endogenous antioxidant networks rather than acting solely as passive selenium donors [34][80][81]. Physicochemical parameters—including particle size, surface functionalization, and biogenic versus inorganic origin—critically determine bioavailability, tissue targeting, and redox kinetics, shaping whether SeNPs function predominantly as GPx activators, mimetics, or modulators of the glutathione cycle [79]-[81]. Nevertheless, antioxidant benefits remain dose- and context-dependent; supra-physiological concentrations may disturb redox equilibrium and provoke secondary oxidative stress, reflecting selenium's narrow therapeutic window [82][83]. Thus, SeNPs should be regarded not merely as micronutrient carriers but as tunable redox nanomodulators whose interaction with GPx represents a central mechanistic axis linking nanoparticle chemistry to biological antioxidant outcomes.

Selenium nanoparticles (SeNPs) act as redox-responsive modulators of the Nrf2/Keap1 signaling pathway rather than as passive radical scavengers, with mechanistic variability influenced by formulation and biological context. In renal toxicity models, SeNPs restore Nrf2 transcriptional competence through coordinated upregulation of SIRT1 and Nrf2 alongside suppression of Keap1, thereby enhancing HO-1 expression and attenuating lipid peroxidation and NF-κB–associated inflammation under chlorpyrifos challenge [10]. Biogenic SeNPs (BNSe), in contrast, activate Nrf2 predominantly through kinase-dependent phosphorylation (p38, ERK1/2, AKT), facilitating nuclear translocation without marked Keap1 downregulation and highlighting a Keap1-independent regulatory route [9]. Similarly, BRP-SeNPs and SeNPs-AOS recalibrate hepatic and systemic redox homeostasis by suppressing Keap1, stabilizing Nrf2, and inducing ARE-driven genes—including HO-1, NQO1, SOD, GPx isoforms, and other selenoproteins—while concurrently reducing CYP2E1-derived ROS or ferroptotic signaling cascades [9][84]. Functionalized PTR-SeNPs further demonstrate upstream integration with PKCδ-mediated phosphorylation and Keap1 repression; attenuation of these effects in Nrf2-deficient models confirms pathway specificity and causality [11]. Importantly, SeNPs generally display context-dependent activation, exerting minimal influence on basal Nrf2/Keap1 signaling in non-stressed systems [10], suggesting redox-threshold–sensitive modulation rather than indiscriminate amplification. Particle size, surface chemistry, and selenium bioavailability appear to influence intracellular uptake and kinase engagement, thereby shaping Nrf2 dynamics. However, given selenium's narrow therapeutic index and the adaptive consequences of sustained Nrf2 activation, prolonged or excessive stimulation may present paradoxical risks. Collectively, SeNPs orchestrate antioxidant defense through finely regulated reprogramming of Nrf2/Keap1 signaling, integrating nano-physicochemical attributes with transcriptional redox control.

Recent studies further indicate that reactive oxygen species (ROS) scavenging constitutes a central mechanistic axis of SeNP antioxidant activity, emerging from complex surface redox interactions rather than passive radical quenching. In chemical assays such as DPPH and ABTS, SeNPs demonstrate concentration-dependent radical neutralization, achieving scavenging efficiencies exceeding 65% at 100 μg mL^{-1}, consistent with efficient electron or hydrogen donation from

surface Se^0 sites [85]. Dextrin- or polysaccharide-stabilized SeNPs likewise exhibit enhanced elimination of superoxide ($O_2^{\bullet-}$), hydroxyl radicals (•OH), and H_2O_2 compared with ionic selenium, as verified by DPPH, TEAC, ORAC, and specific ROS assays [86]. These in vitro findings are supported by cellular data showing significant attenuation of DCFH-DA fluorescence in LPS-stimulated macrophages, reflecting intracellular ROS suppression partially associated with GPx4 induction [87]. Mechanistically, nanoscale dimensions (<100 nm), spherical morphology, and stabilized Se^0 surfaces increase specific surface area and facilitate interfacial electron transfer, while biomolecular capping agents (e.g., polysaccharides, PVP) enhance colloidal stability and prevent aggregation, preserving reactive sites [23][85][87]. However, the same redox-active surface capable of ROS neutralization may, under photochemical or high-dose conditions, participate in ROS generation—as evidenced by photocatalytic dye degradation approaching 90%—underscoring a context-dependent balance between antioxidant and pro-oxidant behavior [85]. Therefore, SeNP-mediated ROS interception reflects a size-, surface-, and dose-governed redox interplay that integrates physicochemical reactivity with biological environment, defining both therapeutic potential and safety boundaries.

Accumulating evidence consistently demonstrates that selenium nanoparticles (SeNPs) exhibit superior antioxidant efficiency compared with sodium selenite, attributable to fundamental differences in redox behavior, bioavailability, and cytotoxicity. In vitro assays show that nanoformulated Se^0 cores possess enhanced DPPH, ABTS, and superoxide radical scavenging activities relative to their ionic precursor, reflecting improved surface-mediated electron transfer and direct ROS interception [88][89]. In contrast, sodium selenite (Se^{4+}) primarily exerts antioxidant effects following intracellular reduction to selenide and subsequent incorporation into selenoproteins such as GPx, a process constrained by a narrow therapeutic margin and potential pro-oxidant intermediate formation [90]. Experimental findings in algal and plant systems reveal that elevated selenite concentrations increase oxidative stress markers and impair growth despite stimulating antioxidant enzymes, indicating stress-induced rather than protective redox activation [90][91]. Conversely, SeNPs enhance GPx, CAT, and related enzymatic defenses while maintaining improved physiological stability, likely owing to gradual selenium release and moderated redox reactivity [91][92]. In vivo evidence further supports higher selenium retention, improved reproductive performance, and lower toxicity profiles in SeNP-treated groups compared with sodium selenite [92]. Collectively, these observations indicate that SeNPs provide a more balanced antioxidant–prooxidant profile, integrating efficient ROS scavenging with improved safety margins. Nevertheless, dose-dependent effects remain critical, as excessive selenium—irrespective of its form—may disrupt cellular redox homeostasis and promote pro-oxidant signaling under specific biological conditions [88][90]. Mechanistic Framework of Selenium Nanoparticle–Mediated Antioxidant Activity: Integration of ROS Scavenging, Enzymatic Modulation, Nrf2/Keap1 Signaling, and Dose-Dependent Redox Effects shown in Figure 3.

Selenium nanoparticles (SeNPs) exhibit a dose-dependent dual redox behavior, functioning as antioxidants at physiological concentrations but shifting toward pro-oxidant activity when exposure exceeds cellular buffering capacity. At low-to-moderate doses (e.g., ≤0.4 mg kg^{-1} in vivo or ≤100 µg mL^{-1} in vitro), SeNPs enhance glutathione peroxidase (GPx) activity, activate Nrf2/ARE signaling, and reduce lipid peroxidation markers such as MDA, thereby reinforcing endogenous antioxidant networks and restoring redox homeostasis [10][77]-[79][92]. Mechanistically, controlled selenium release and surface-mediated redox cycling promote efficient H_2O_2 and lipid hydroperoxide detoxification while maintaining balanced kinase signaling (e.g., SIRT1/Nrf2 or PKCδ pathways) [9]-[11][20][84]. However, supra-physiological concentrations or specific environmental contexts (e.g., photochemical activation) can provoke excessive ROS generation, mitochondrial perturbation, or overstimulation of redox-sensitive pathways, resulting in secondary oxidative stress and potential cytotoxicity [82][83][85]. Comparative analyses with sodium selenite further suggest that although SeNPs possess a broader therapeutic window, both forms may

induce oxidative imbalance when dose thresholds are surpassed, partly due to redox cycling and pro-oxidant intermediate formation [88]-[91]. Notably, variability in particle size, surface functionalization, and biogenic origin influences this threshold, indicating that nano-physicochemical properties modulate the antioxidant–prooxidant transition. Despite overall consistency regarding dose sensitivity, precise concentration limits and long-term adaptive consequences remain insufficiently defined, highlighting a critical gap for translational toxicology and nanomedicine optimization.

4. ANTICANCER ACTIVITY

4.1. Cytotoxic Effects on Cancer Cell Lines

Selenium nanoparticles (SeNPs) have emerged as versatile nanotherapeutics exhibiting reproducible, dose-dependent cytotoxicity across multiple cancer cell line models, with mechanistic convergence around redox imbalance, mitochondrial dysfunction, and apoptosis induction. In breast cancer systems, including estrogen receptor–positive MCF-7 and triple-negative MDA-MB-231 and 4T1 cells, SeNPs consistently reduced viability in concentration- and time-dependent manners while demonstrating variable selectivity toward non-malignant counterparts. In MDA-MB-231 cells, ferulic acid–loaded formulations (Alg@FA-SeNPs and CS@FA-SeNPs) showed differential potency (IC_{50} 103.6 vs 178 µg/mL), engaging distinct pathways such as H2AX-associated genotoxic stress or Bcl-2–mediated mitochondrial apoptosis independent of global oxidative imbalance [47]. In MCF-7 models, biosynthesized and surface-modified SeNPs enhanced apoptotic fractions and mitochondrial perturbation relative to free agents, underscoring redox-mediated sensitization and improved intracellular delivery [12][14]. Notably, green-synthesized SeNPs frequently triggered ROS overproduction, lipid peroxidation, and G2/M arrest, yet exhibited higher IC_{50} values in normal fibroblasts or endothelial cells, suggesting a comparatively favorable therapeutic indeks [15][93][94]. In contrast, sodium selenite displayed broader cytotoxicity, highlighting the biocompatibility advantages conferred by nanoscale engineering [95].

Parallel redox-centered mechanisms are evident in colorectal cancer models. In HCT-116 and HT-29 cells, polysaccharide-stabilized SeNPs (LP-SeNPs) induced concentration-dependent reductions in viability (2.5–20 µg/mL), with greater sensitivity in HCT-116 and selective sparing of IEC -6 epithelial cells [96]. Mechanistically, ROS accumulation, mitochondrial membrane depolarization, cytochrome c release, Bax

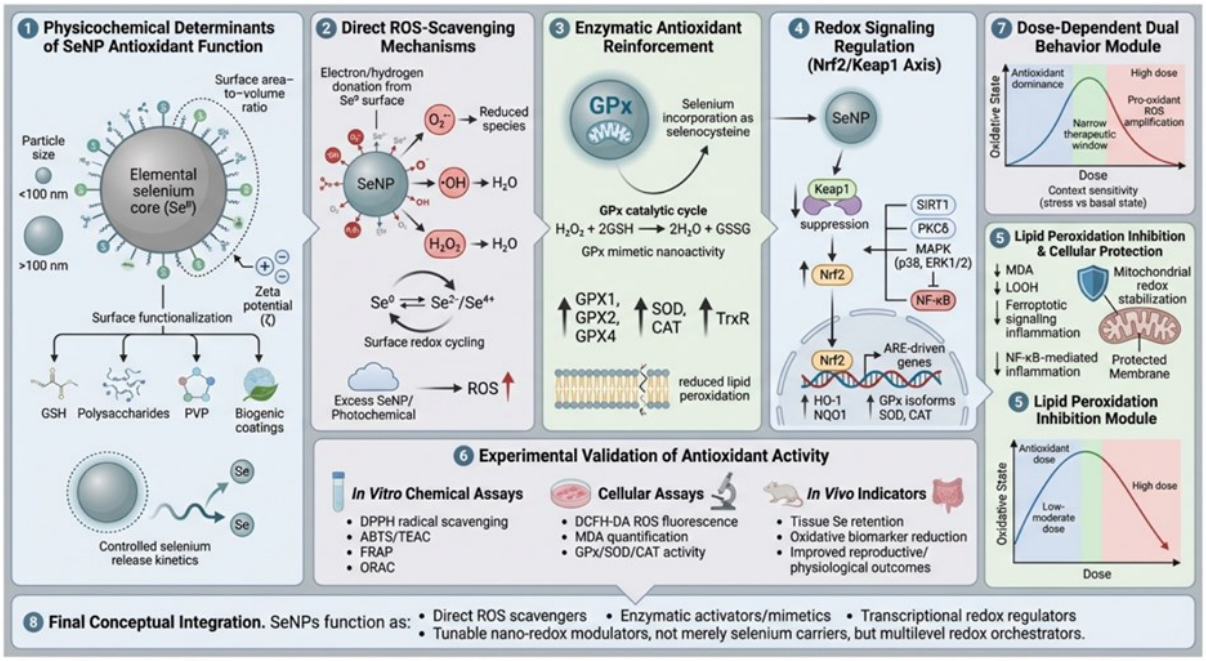

Figure 4. Selenium nanoparticles in cancer therapy mechanisms.

upregulation, Bcl-2 suppression, and caspase-3 activation collectively confirmed intrinsic apoptosis as the dominant pathway [96]. ORP-SeNPs further inhibited Caco-2 proliferation (IC_{50} ≈247.8 μg/mL) through S-phase arrest and apoptosis, outperforming sodium selenite in biocompatibility [22]. In vivo MC38 models revealed suppression of PI3K/mTOR/HIF-1α and STAT3 signaling alongside attenuation of EGFR, MMP-9, and inflammatory mediators, extending cytotoxic interpretation beyond apoptosis to include proliferative and angiogenic pathway repression [97][98]. Although biogenic SeNPs occasionally demonstrated lower acute potency than 5-fluorouracil, they exhibited reduced systemic toxicity and improved selectivity [22][96]. Hybrid photodynamic systems further illustrated that SeNPs amplify oxidative damage upon activation without intrinsic dark toxicity [99].

In hepatocellular carcinoma models, predominantly HepG2 cells, SeNPs consistently elicited redox-mediated mitochondrial apoptosis. β-glucan–stabilized SeNPs reduced viability (IC_{50} 6.5 ppm) with a selectivity index of 7.4 relative to fibroblasts, inducing Annexin V–positive apoptosis and sub-G1 accumulation [100]. Alginate-based nanocomposites further enhanced potency (IC_{50} 0.792 μg/mL) while sparing normal Vero cells, emphasizing the critical influence of surface chemistry [42]. Green-synthesized SeNPs displayed moderate cytotoxicity comparable to doxorubicin yet greater selectivity toward malignant hepatocytes [101]. Remarkably, berberine-loaded SeNPs achieved submicromolar IC_{50} values (0.04 μg/mL), surpassing cisplatin in HepG2 cells through Bax/Bcl-2 modulation, cytochrome c release, caspase-3 activation, ROS accumulation, and G1/G2–M arrest [102]. Complementary in vivo data from selenium–sorafenib nanocomplexes demonstrated inhibition of PI3K/AKT/mTOR and MAPK signaling while preserving non-tumoral liver architecture, implying functional selectivity [103]. Nonetheless, reliance on single hepatoma lines and limited validation in Huh-7 or primary hepatocytes constrain generalizability.

In non-small cell lung cancer (NSCLC) models, including A549, H1299, and H460 cells, SeNPs again exerted concentration-dependent cytotoxicity via oxidative stress amplification and mitochondrial apoptosis. Se–curcumin–PEG NPs reduced A549 viability (IC_{50} 50 μg mL^{-1}) and enhanced radiosensitivity (SER 2.5) through ROS-driven redox disruption [104]. TGTs-SeNPs induced S-phase arrest and robust apoptosis in H460 cells, outperforming 5-fluorouracil while sparing HFL1 fibroblasts [39]. Lentinan-modified SeNPs potentiated pemetrexed cytotoxicity in A549 and H1299 cells by activating the ATM/ATR–Chk2–p53 axis and promoting mitochondrial depolarization [105]. AZEPS-SeNPs displayed low IC_{50} values (1.724 μg mL^{-1}) and a therapeutic index >7 relative to WI38 fibroblasts, reflecting intrinsic apoptotic activation and S-phase blockade [18]. Although mechanistic coherence across models consistently implicates ROS-driven mitochondrial dysfunction and checkpoint signaling, most studies remain limited to in vitro systems with restricted cell-line panels and incomplete comparative analyses against standard chemotherapeutics.

SeNPs as mechanistically versatile, redox-active nanoplatforms capable of modulating apoptosis, cell-cycle progression, and oncogenic signaling across diverse cancer cell types. Surface functionalization critically influences potency, selectivity, and pathway engagement, reinforcing the notion that SeNPs are best conceptualized as adjunctive or combinatorial nanotherapeutics rather than stand-alone cytotoxics. Broader validation across heterogeneous tumor models and rigorous comparative studies remain essential to substantiate their translational superiority.

4.2. Molecular Mechanisms

The anticancer activity of selenium nanoparticles (SeNPs) is mechanistically anchored in controlled redox perturbation that propagates through mitochondrial dysfunction, checkpoint activation, and programmed cell death. A primary initiating event is dose-dependent ROS overproduction, consistently observed across breast, colon, liver, and lung cancer models, where escalating SeNP concentrations amplify lipid peroxidation and oxidative stress markers while depleting antioxidant defenses such as GSH and SOD [15][18][96][102]. ROS generation has been linked to disruption of electron transport chain integrity, modulation of NADPH oxidases (e.g., Nox1/Nox4), and interference with thioredoxin and glutathione

systems, collectively shifting redox homeostasis toward a pro-oxidant state [97][98]. This oxidative imbalance precipitates mitochondrial membrane depolarization (ΔΨm collapse), promoting permeability transition pore opening, cytochrome c release, and apoptosome formation, thereby activating initiator caspase-9 and executioner caspase-3 in concert with Bax upregulation and Bcl-2 suppression—hallmarks of intrinsic apoptosis [18][39][96][102]. In some systems, caspase-8 activation indicates extrinsic pathway engagement or cross-talk via Bid truncation, reinforcing apoptotic commitment [18][105].

Mitochondrial depolarization and ROS-mediated DNA damage further activate ATM/ATR–Chk2–p53 signaling, frequently resulting in S- or G2/M-phase arrest and suppression of cyclin–CDK complexes, thus coupling cell cycle blockade with apoptotic priming [18][102][105]. Downstream, caspase-3–dependent cleavage of ICAD releases CAD endonuclease, driving internucleosomal DNA fragmentation detectable by TUNEL assays, Annexin V/PI cytometry, sub-G1 analysis, and gel electrophoresis [15][100][105]. Importantly, the magnitude of DNA fragmentation and caspase activation correlates with intracellular ROS burden, supporting a redox-threshold model in which oxidative stress irreversibly commits cells to apoptosis [96][102].

Beyond apoptosis, SeNPs also modulate autophagic pathways. Alterations in Beclin-1 and LC3-II expression suggest context-dependent induction or restoration of autophagic flux, particularly in colorectal and hepatic models [98][102]. At moderate ROS levels, autophagy may function cytoprotectively to mitigate oxidative damage; however, higher SeNP doses appear to shift the balance toward autophagy-associated cell death or facilitate apoptosis via mitochondrial cross-talk.

Critically, physicochemical properties—including surface coatings (polysaccharide, alginate), drug conjugation (berberine, ferulic acid), and charge—govern the intensity and selectivity of these responses. Surface-functionalized SeNPs enhance tumor-selective ROS amplification and mitochondrial targeting while limiting nonspecific toxicity relative to inorganic selenium salts [22][42][95]. Moreover, certain formulations exhibit microenvironment-responsive redox modulation, attenuating oxidative injury in inflamed normal tissues yet promoting mitochondrial depolarization in tumor cells [21][103].

Collectively, SeNPs orchestrate a coordinated molecular cascade—from ROS overproduction to mitochondrial collapse, caspase activation, DNA fragmentation, cell cycle arrest, and autophagy modulation—that underpins their anticancer efficacy. However, the narrow therapeutic window between selective oxidative cytotoxicity and systemic toxicity underscores the necessity for precise dose optimization and rational nanoparticle engineering to maximize therapeutic benefit while minimizing off-target effects. Selenium nanoparticles orchestrate a coordinated molecular cascade encompassing ROS overproduction, mitochondrial membrane depolarization, caspase cascade activation, DNA fragmentation, cell cycle arrest, and modulation of redox-sensitive signaling pathways, collectively driving tumor-selective apoptosis and growth inhibition (Figure 4).

4.3. Synergistic Effects with Chemotherapeutic Agents

Selenium nanoparticles (SeNPs) have emerged as redox-active chemosensitizers that enhance the efficacy of conventional anticancer agents through coordinated modulation of oxidative stress, mitochondrial integrity, and apoptosis signaling. In non-small cell lung cancer (NSCLC) models, lentinan-modified SeNPs synergistically potentiated pemetrexed in A549 and H1299 cells, as evidenced by combination index values <1, indicating true pharmacological synergy rather than additive toxicity [105]. Mechanistically, co-treatment markedly amplified intracellular ROS, promoted mitochondrial membrane depolarization (ΔΨm collapse), activated caspase-9/-3, and reinforced the ATM/ATR–Chk2–p53 axis, culminating in enhanced DNA damage and S-phase arrest. These findings suggest that SeNPs lower the apoptotic threshold by destabilizing redox homeostasis and mitochondrial function, thereby allowing reduced doses of pemetrexed to achieve comparable or superior cytotoxicity. Similar ROS-driven sensitization has been reported in systems co-delivering doxorubicin, where SeNP incorporation intensified Bax upregulation, Bcl-2 suppression,

and cytochrome c release relative to free drug, indicating amplification of intrinsic apoptotic commitment [47][102].

Doxorubicin-based combination strategies further illustrate the translational promise of SeNP-enabled synergy. In osteosarcoma, hyaluronic acid–coated mesoporous silica nanoparticles co-encapsulating SeNPs and doxorubicin (SeMS^Dox-HA) significantly reduced IC_{50} values in Saos-2 and U2OS cells compared with monotherapies, while maintaining lower toxicity toward mesenchymal stem cells [106]. Selenium-mediated depletion of intracellular glutathione and NADPH augmented superoxide generation, thereby exceeding the oxidative tolerance of tumor cells and enhancing caspase-dependent apoptosis. Likewise, ZIF-8/SrSe@DOX systems integrated glutathione oxidase –like activity with pH-responsive drug release, intensifying ROS and lipid peroxidation while inducing both apoptosis and ferroptosis through SLC7A11–GPX4 axis inhibition and iron dysregulation [19]. These nanoengineered platforms not only improved intracellular accumulation and tumor-selective release but also mitigated systemic toxicity, as reflected in reduced cardiac and hepatic damage relative to free doxorubicin. Collectively, such evidence underscores that SeNP-based co-delivery systems extend beyond passive carriers, functioning as active redox modulators that reshape tumor bioenergetics and sensitize cells to DNA-damaging agents.

Combinations involving platinum agents further highlight the bidirectional redox functionality of SeNPs. While cisplatin (CDDP) exerts cytotoxicity via DNA crosslinking and oxidative injury, SeNP conjugates have demonstrated the capacity to attenuate CDDP-induced nephrotoxicity by restoring antioxidant enzymes (SOD, CAT, GPx) and suppressing NF-κB–mediated inflammation, without compromising anticancer activity [107]. This context-dependent modulation—pro-oxidant within tumor cells yet protective in normal tissues—reflects the microenvironment-responsive behavior reported for several SeNP formulations [96][103]. In hepatic and colorectal models, berberine- or ferulic acid–loaded SeNPs amplified apoptosis through PI3K/AKT/mTOR and STAT3 pathway suppression while simultaneously reducing proliferative and angiogenic signaling [97][98][102]. Such dual targeting of survival pathways and redox balance offers a mechanistic basis for overcoming drug resistance, particularly in tumors characterized by elevated antioxidant buffering capacity.

The magnitude of synergistic efficacy is critically influenced by nanoparticle physicochemical attributes, including size, surface charge, and functionalization. Polysaccharide-, chitosan-, and alginate-stabilized SeNPs exhibit improved dispersion, enhanced cellular uptake, and greater tumor selectivity compared with inorganic selenium salts, which often induce broader, less discriminating toxicity [22][42][95]. Surface ligands such as hyaluronic acid facilitate receptor-mediated uptake (e.g., CD44 targeting), while pH- or GSH-responsive matrices ensure controlled drug release within the acidic and reductive tumor microenvironment [19][106]. Moreover, metabolomic analyses of chitosan-stabilized SeNPs reveal ATP depletion and TCA cycle disruption in HepG2 cells, lowering the energetic threshold for apoptosis and sensitizing cells to ROS-generating chemotherapeutics [108]. Nevertheless, the therapeutic window remains narrow; excessive ROS amplification may risk off-target mitochondrial injury and genomic instability. Thus, precise dose optimization and rational surface engineering are essential to balance synergistic antitumor efficacy with systemic safety. Collectively, the integration of SeNPs with chemotherapeutic agents represents a strategically compelling approach to enhance cytotoxic potency, mitigate resistance, and expand therapeutic indices, warranting further in vivo validation and standardized comparative evaluation for clinical translation.

5. ANTIMICROBIAL ACTIVITY

Recent investigations consistently demonstrate that selenium nanoparticles (SeNPs) exhibit broad-spectrum yet species-dependent antimicrobial activity, encompassing Gram-positive and Gram-negative bacteria, filamentous fungi and yeasts, as well as biofilm-forming pathogens [16][109]-[117]. Collectively, the evidence indicates that SeNP efficacy is strongly dose-dependent and critically modulated by physicochemical attributes such as

Table 2. Comparative synthesis of antimicrobial activity of selenium nanoparticles (SeNPs) against Gram-positive, Gram-negative, and fungal pathogens.

Microorganism (Type)	Assay Methods	SeNPs Physicochemical Characteristics	Effective Concentration	Proposed Mechanisms	Main Findings / Comparative Effectiveness	Ref.
MRSA, *S. aureus* (Gram+)	MIC, MBC, SEM	Biogenic; spherical; <100 nm; bio-capped	MIC 0.5–1 µg/mL (MRSA)	Membrane disruption, ROS, mild protein synthesis interference	Highly potent vs MRSA; synergistic with imipenem; superior to chemically synthesized SeNPs	[40]
S. aureus, *B. subtilis* (Gram+)	Zone of inhibition	~50–100 nm; ζ ≈ −37 mV; plant-capped	100 µg/mL (18 mm zone)	Membrane damage, ROS	Moderate efficacy; lower than ciprofloxacin	[63]
MRSA, *E. faecalis* (Gram+)	MIC, biofilm assay	Biogenic; stable colloid	0.625–25 mg/mL	ROS, membrane depolarization, enzyme inhibition	Strain-dependent; moderate potency; synergistic/antagonistic interactions with antibiotics	[109]
S. aureus (Gram+)	Zone of inhibition	~23–30 nm; phytochemical surface	1–4 mg	ROS, membrane permeabilization	Surpassed erythromycin in selected strains	[110]
MRSA (Gram+)	MIC, gene expression	Myco-synthesized; nanospherical	0.125 mg/mL	ROS, mecA/blaZ suppression	Strong synergy with cefepime (8–32× MIC reduction)	[111]
P. aeruginosa, *K. pneumoniae*(Gram−)	Disc diffusion	~95 nm; ζ −15 to −17 mV	~100 µg/mL	Outer membrane disruption, ROS	Moderate inhibition; formulation-dependent	[112]
MDR *P. aeruginosa* (Gram−)	$MIC_{50/90}$, biofilm assay	15–18 nm; ζ −22 mV	MIC_{50} 60 µg/mL	Biofilm matrix disruption, QS interference	Anti-biofilm > antibacterial; no planktonic inhibition	[31]
E. coli, *A. baumannii* (Gram−)	Growth kinetics, antibiofilm	60–80 nm; ζ −18 mV	250–500 µg/mL	Membrane leakage, ROS	Strong biofilm inhibition; higher dose needed vs antibiotics	[32]
A. flavus, *A. niger* (Fungi)	Zone inhibition	16.7 nm; bio-capped	35–45 mm zone	Membrane damage, ROS	Strong antifungal; ineffective vs *F. oxysporum*	[16]
C. albicans(Fungi)	MIC, time–kill	50–100 nm; phytochemical-capped	100 µg/mL	Membrane leakage, oxidative stress	Competitive with antifungals in vitro; low toxicity in vivo model	[115]
C. albicans(Fungi)	CFU assay	Amorphous 72 nm; ζ −43 mV	0.025 µg/mL	ROS, thiol depletion	Amorphous > trigonal phase; strong structure–activity relationship	[117]
S. mutans, *P. aeruginosa*, *C. albicans* (Mixed)	Biofilm biomass, CFU	~20–30 nm; ζ −28 mV; PMMA-incorporated	250–1000 µg/mL	EPS disruption, ROS, contact-killing	>50% biomass reduction; long-term non-leaching antibiofilm material	[41]
MRSA, MDR *P. aeruginosa*	TCP biofilm assay	20–77 nm; ζ −25.7 mV	3.9–31 µg/mL	Membrane perturbation, ROS	Dose-dependent suppression; less potent than AgNPs	[69]
P. aeruginosa(Gram−)	Biofilm assay, qRT-PCR	32–42 nm; ζ +53.6 mV	41.65 µg/mL (sub-MIC)	EPS disruption, ROS (non-transcriptional)	48–87% biofilm inhibition; strong electrostatic interaction	[122]

particle size, surface charge, morphology, and surface functionalization, which together govern microbial interaction, oxidative stress generation, and membrane destabilization.

Against Gram-positive bacteria, SeNPs frequently display pronounced potency, particularly toward *Staphylococcus aureus* (including MRSA), *Bacillus subtilis*, *Bacillus megaterium*, *Streptococcus agalactiae*, and *Enterococcus faecalis* [114]–[118]. Biogenic SeNPs synthesized via *Lactiplantibacillus plantarum* demonstrated sub-microgram MIC values (0.5–1 µg/mL) against clinical MRSA isolates, surpassing conventional β-lactams and underscoring strain-dependent susceptibility [40]. Similarly, myco-synthesized SeNPs inhibited MRSA at 0.125 mg/mL and, when combined with antibiotics, reduced resistance gene expression (mecA, blaZ) with MIC reductions up to 32-fold, revealing marked synergistic potential [111]. Across these studies, antibacterial activity increased with concentration, reflected in expanded inhibition zones, reduced MIC/MBC values, and suppression of biofilm formation at sub-inhibitory levels [109][110]. Mechanistically, Gram-positive susceptibility is primarily attributed to disruption of cell wall and membrane integrity, intracellular leakage, and reactive oxygen species (ROS)-mediated oxidative damage to proteins, lipids, and nucleic acids, with proteomic analyses suggesting additional interference in enzymatic and metabolic pathways [40][109][111]. Importantly, smaller particle size alone does not guarantee enhanced activity; rather, biogenic capping agents, phytochemical composition, and surface charge (e.g., highly negative zeta potentials) modulate membrane affinity, ROS generation, and colloidal stability [63][110].

In contrast, antimicrobial activity against Gram-negative bacteria—including *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* is generally more variable and often requires higher concentrations [31][32][112]-[114]. This reduced susceptibility reflects the structural barrier imposed by the lipopolysaccharide-rich outer membrane. Nevertheless, dose-dependent improvements in inhibition zones and MIC values are consistently reported, as observed for mango peel–derived SeNPs (4–64 µg/mL) and Nyctanthes arbor-tristis–mediated formulations (notable effects at 250–500 µg/mL) [32][114]. Mechanistic analyses indicate that SeNPs compromise outer membrane permeability, induce ROS accumulation, damage intracellular proteins and DNA, and disrupt biofilm maturation [31][32][112]. Notably, chemically synthesized SeNPs preferentially suppressed biofilm architecture in multidrug-resistant P. aeruginosa without strong planktonic bactericidal effects, highlighting their anti-virulence potential [31]. Physicochemical parameters again play a decisive role: particles within the 15–60 nm range enhance membrane interaction, whereas moderately negative zeta potentials (−15 to −22 mV) promote colloidal stability but may reduce electrostatic attraction to negatively charged bacterial surfaces [31][112][113]. Surface functionalization by plant-derived polyphenols or peptides can partially overcome intrinsic Gram-negative resistance by amplifying ROS generation and membrane affinity [112][114]. Although SeNPs rarely surpass conventional antibiotics in direct bactericidal potency, their capacity to attenuate resistance-associated phenotypes and disrupt biofilms positions them as promising adjunct nanotherapeutics.

Beyond antibacterial activity, SeNPs demonstrate potent antifungal efficacy against clinically and agriculturally relevant species, including *C. albicans*, *A. niger*, *A. flavus*, *A. fumigatus*, *Fusarium solani*, and *Phytophthora capsici* [16][115]-[119]. Antifungal responses consistently exhibit concentration dependence, with progressive improvement in inhibition zones or MIC values and, in some cases, complete growth suppression at higher doses (e.g., 20–30 mM or ≥300 µg/mL) [116][118]. Remarkably, amorphous SeNPs achieved near-complete inhibition of *C. albicans* at sub-microgram concentrations, underscoring the importance of structural phase and surface energi [117]. Mechanistically, SeNPs disrupt membrane integrity, promote leakage of intracellular proteins, induce ROS-mediated oxidative damage, and impair hyphal development and biofilm formation [16][115][119]. In filamentous fungi, increased electrical conductivity and intracellular glycerol accumulation further implicate osmotic imbalance and cell envelope destabilization [116]. As observed in bacterial systems, smaller particle sizes (e.g., 16.7 nm) and

strongly negative zeta potentials (−43 to −52 mV) enhance colloidal stability, ROS generation, and bioavailability [16][116][117]. Surface functionalization by plant phenolics or microbial proteins not only stabilizes SeNPs but also augments redox reactivity and membrane interaction [115][118]. Compared with conventional antifungals, SeNPs frequently demonstrate comparable or superior in vitro inhibition, particularly against resistant or toxigenic strains, while offering potential advantages in reduced cytotoxicity and multimodal resistance suppression.

The antibiofilm potential of SeNPs further extends their antimicrobial relevance, particularly against Streptococcus mutans, MRSA, *P. aeruginosa*, and *C. albicans* [31][41][69][120]-[122]. Biofilm inhibition typically requires higher concentrations than planktonic MICs, reflecting the intrinsic resilience of sessile communities; inhibition thresholds range from tens of μg/mL in MRSA to several hundred μg/mL in *P. aeruginosa* and *C. albicans* biofilms [31][41][69]. Mechanistically, SeNPs disrupt extracellular polymeric substances (EPS), compromise membrane integrity, and induce intracellular ROS, thereby destabilizing matrix architecture and reducing cellular viability. In several models, reduced early adhesion, decreased EPS synthesis, and putative quorum sensing interference were observed, although transcriptional modulation was not consistently demonstrated, suggesting predominantly physicochemical disruption of biofilm integrity [120][122]. Particle size (<100 nm), spherical morphology, and optimized surface charge critically modulate matrix penetration and electrostatic interaction: moderately negative zeta potentials (−20 to −30 mV) favor stability and diffusion, whereas highly positive surfaces enhance adhesion to negatively charged biofilms [69][122]. Incorporation of SeNPs into polymeric matrices such as PMMA further enhances contact-killing activity and reduces surface roughness, limiting microbial colonization [41]. Compared with conventional antibiotics, which often fail to eradicate mature biofilms, SeNPs provide sustained virulence-targeting activity, though typically with incomplete eradication and lower potency than AgNP-based systems [69][121].

To provide a structured comparison of antimicrobial performance across microbial domains, the key findings summarized above are synthesized in Table 2. This comparative framework integrates Gram-positive, Gram-negative, fungal, and biofilm-associated data with nanoparticle physicochemical parameters and proposed mechanisms, thereby elucidating how SeNP engineering governs antimicrobial selectivity, potency, and translational applicability in the context of resistance mitigation and antimicrobial surface technologies.

Membrane disruption is consistently identified as a primary event that links the physicochemical properties of selenium nanoparticles (SeNPs) with microbial cell death. SeNPs adsorb onto microbial surfaces through electrostatic and hydrophobic interactions with phospholipid bilayers and membrane-associated proteins, followed by increased membrane permeability and depolarization. Microscopic observations and leakage assays demonstrate the release of intracellular proteins, nucleic acids, and ions, indicating irreversible structural damage [16][40][109][119]. This disruption is not merely mechanical; it is reinforced by localized reactive oxygen species (ROS) generation at the nanoparticle–membrane interface, promoting lipid peroxidation and oxidation of membrane proteins [111][115][117]. In Gram-positive bacteria, the absence of an outer membrane facilitates direct contact with the cytoplasmic membrane, generally resulting in lower effective concentrations for membrane destabilization. In contrast, the lipopolysaccharide layer of Gram-negative bacteria restricts nanoparticle access, necessitating higher doses or enhanced surface functionalization to achieve comparable disruption [31][32][112]-[114]. In fungi, although the chitin–β-glucan cell wall modulates initial penetration, plasma membrane damage remains a dominant downstream event once SeNPs traverse this barrier [16][115]-[119].

Oxidative stress induction represents a central and synergistic mechanism that amplifies membrane injury and extends intracellular damage. SeNPs promote excessive accumulation of ROS—including superoxide anions, hydrogen peroxide, and hydroxyl radicals—either through surface redox cycling or perturbation of electron transport

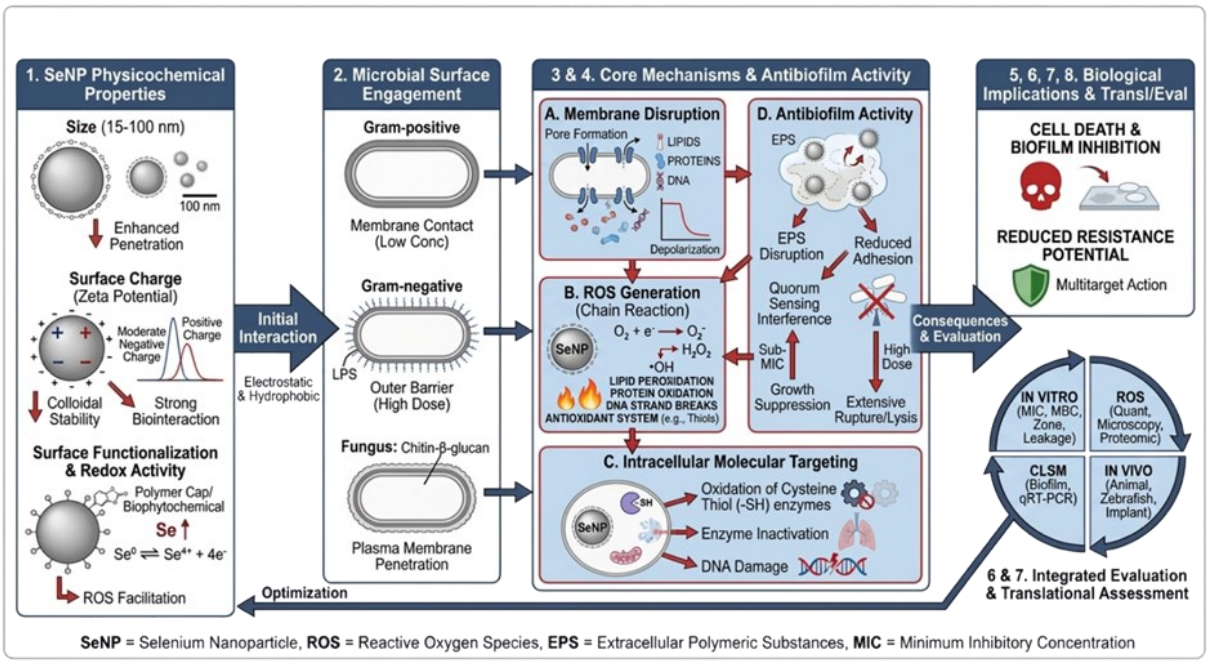

Figure 5. Antimicrobial mechanism of selenium nanoparticles.

processes [40][111][115]. Elevated ROS levels trigger lipid peroxidation within membranes, increasing permeability and reinforcing structural instability. Concurrently, ROS oxidize cytosolic proteins and inactivate essential metabolic enzymes, disrupting respiration and biosynthetic pathways [109][117]. Oxidative stress further targets nucleic acids, inducing strand breaks and base modifications that impair DNA replication and transcription [16][119]. Reports of intracellular thiol depletion and suppression of antioxidant defenses such as catalase and superoxide dismutase indicate that SeNPs overwhelm global redox homeostasis rather than acting on a single molecular target [69][117]. Dose-dependent effects are evident: sub-MIC levels may induce partial oxidative imbalance and growth suppression, whereas higher concentrations generate overwhelming ROS bursts culminating in irreversible cellular damage [32][116].

At the molecular level, interaction with microbial proteins and DNA consolidates the antimicrobial impact of SeNPs. Following membrane permeabilization or nanoparticle internalization, SeNPs and ROS interact with intracellular proteins, including respiratory enzymes and regulatory factors. Oxidation of cysteine thiol groups, conformational destabilization, and protein aggregation contribute to enzymatic inactivation and metabolic arrest [40][111][117]. Proteomic analyses in MRSA reveal interference with protein biosynthesis and energy metabolism, underscoring the systemic biochemical disruption induced by SeNP exposure [40]. Simultaneously, oxidative DNA damage compromises genomic stability, inhibiting replication fidelity and transcriptional efficiency [16][119]. Electrostatic interactions between charged nanoparticles and phosphate groups of DNA may further perturb helix stability. The intensity of these molecular interactions is strongly influenced by nanoparticle characteristics: smaller SeNPs (15–50 nm) exhibit greater surface-to-volume ratios and enhanced redox reactivity, facilitating intracellular penetration and biomolecular contact [16][117]. Surface charge modulates proximity and retention at microbial interfaces; moderately negative zeta potentials favor colloidal stability and diffusion, whereas positive charges enhance electrostatic adhesion to negatively charged membranes and biofilm matrices [69][122]. Increasing concentration proportionally augments ROS accumulation and macromolecular damage [32][69].

These interconnected mechanisms—membrane destabilization, oxidative stress, and macromolecular disruption—also underpin the antibiofilm activity of SeNPs [31][41][69][120]-[122]. Biofilm inhibition typically requires higher

concentrations than planktonic MICs, reflecting the protective extracellular polymeric substance (EPS) matrix and altered metabolic states within sessile communities. SeNPs compromise EPS integrity, enhance membrane damage within embedded cells, and induce ROS-mediated destabilization of biofilm architecture. Although transcriptional suppression of quorum sensing genes is not always evident, physicochemical interference with matrix cohesion and cellular adhesion is consistently observed [120] [122]. Particle size (<100 nm), spherical morphology, surface redox activity, and tailored functionalization—including phytochemical capping or polymer incorporation—further enhance matrix penetration and contact-mediated killing [41]. Compared with conventional antibiotics that target discrete biochemical pathways, SeNPs exert a multitarget effect that reduces the likelihood of resistance driven by single-gene mutation. Adaptation would require global reinforcement of membrane integrity and antioxidant capacity, a metabolically costly response. Nevertheless, the potent redox activity that underlies antimicrobial efficacy necessitates careful optimization of size, surface chemistry, and dosage to balance microbial selectivity with host cell safety. Collectively, the mechanistic versatility of SeNPs positions them as promising next-generation antimicrobial nanomaterials with broad-spectrum activity and reduced susceptibility to conventional resistance mechanisms. To facilitate conceptual integration of the mechanistic pathways discussed above, the principal antimicrobial mechanisms of selenium nanoparticles (SeNPs) are schematically summarized in Figure 5.

The Figure 5 provides a structured visualization of the interconnected processes linking SeNP physicochemical properties—such as particle size, surface charge, redox activity, and surface functionalization—with key biological outcomes, including membrane disruption, reactive oxygen species (ROS) induction, intracellular protein and DNA damage, and antibiofilm effects. Importantly, the schematic emphasizes that membrane destabilization represents an initiating event that is amplified by localized oxidative stress, which in turn drives enzymatic inactivation, genomic instability, and biofilm matrix disintegration. By integrating these pathways into a unified framework, Figure 5 illustrates the multitarget nature of SeNP-mediated antimicrobial action and clarifies how physicochemical tuning modulates microbial susceptibility across Gram-positive, Gram-negative, and fungal systems. This visual synthesis reinforces the mechanistic convergence underlying broad-spectrum activity while highlighting design-dependent variability in antimicrobial efficacy.

6. ANTI-INFLAMMATORY AND IMMUNOMODULATORY EFFECTS

Emerging evidence establishes selenium nanoparticles (SeNPs) as redox-responsive nanoplatforms with pronounced anti-inflammatory and immunomodulatory properties, largely mediated through coordinated regulation of NF-κB and Nrf2 signaling axes across diverse biological contexts [123]-[125]. At the molecular level, multiple SeNP formulations suppress phosphorylation and degradation of IκBα, thereby preventing nuclear translocation of the p65 subunit and limiting transcription of canonical NF-κB target genes, including TNF-α, IL-6, and IL-1β [124] [126]. In selected systems, SeNPs further interfere with NF-κB–dependent NLRP3 inflammasome priming and pyroptotic execution, attenuating inflammatory amplification loops at both transcriptional and post-translational levels [124]. A unifying mechanistic theme is redox modulation: by enhancing selenoprotein expression (e.g., GPX1–4, GPx4) and restoring GSH-dependent antioxidant defenses, SeNPs reduce intracellular ROS accumulation and disrupt the ROS–NF-κB feed-forward circuit that sustains chronic inflammation [125]-[129]. Concomitantly, normalization or activation of Nrf2-associated pathways reinforces endogenous antioxidant capacity, suggesting that cytokine suppression arises from restoration of redox homeostasis rather than indiscriminate immune inhibition [129][130].

These signaling effects translate into consistent downregulation of TNF-α, IL-6, and IL-1β in both in vitro and in vivo models, although magnitude and directionality remain formulation- and context-dependent [128][129][131]-[133]. Functionalized platforms, including silymarin-, melanin-, chitosan-, and polysaccharide-stabilized SeNPs, demonstrate

enhanced suppression of pro-inflammatory mediators via coordinated inhibition of PI3K/Akt/NF-κB signaling and attenuation of oxidative stress, with smaller particle sizes (≈30–100 nm) and stable negative surface charge correlating with improved cellular uptake and signaling interference [128][131][134]. Importantly, SeNPs also modulate macrophage plasticity: in autoimmune settings, they restrain pathological M1 polarization by reducing CD86, iNOS, and pro-inflammatory cytokines through redox-sensitive NF-κB inhibition [87], whereas engineered or targeted systems can promote M1-to-M2 reprogramming in colitis or selectively recalibrate pathogenic M2b subsets via GPX1-mediated suppression of JAK2/STAT1 signaling [135][136]. Conversely, in tumor microenvironments, ligand-functionalized SeNPs may repolarize immunosuppressive M2-like macrophages toward an M1 phenotype through TLR4/MyD88/NF-κB and STAT1 activation, enhancing antitumor immunity [137][138]. These divergent outcomes underscore that physicochemical parameters—particle size (≈30–190 nm), surface charge, and bioactive coatings—govern biodistribution, redox modulation, and pathway engagement, thereby dictating immunological consequences. As schematically illustrated in Figure 6, selenium nanoparticles (SeNPs) exert anti-inflammatory and immunomodulatory effects through integrated suppression of NF-κB signaling, activation of Nrf2-dependent antioxidant pathways, downregulation of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β), modulation of macrophage polarization dynamics, and coordinated responses observed across acute and chronic in vivo inflammatory models.

Evidence from acute and chronic in vivo inflammatory models further substantiates translational potential. In cisplatin-induced acute kidney injury, orally administered functionalized SeNPs (2–4 mg kg^{-1}) reduced serum creatinine and BUN, suppressed M1-like macrophage infiltration, and restored GSH/SOD levels while lowering MDA, linking SeNP biotransformation into selenocysteine with enhanced selenoenzyme activity and redox homeostasis [139]. In DSS-induced colitis, oral SeNPs (0.5–2 mg kg^{-1}) decreased TNF-α, IL-6, IL-1β, and MPO activity, improved colon architecture, and normalized oxidative stress markers through inhibition of NF-κB and reinforcement of Nrf2 signaling [130][134]. Similarly, topical or intranasal SeNP administration attenuated cytokine burden and inflammatory infiltration in infected wound and viral lung injury models by modulating NF-κB/STAT3 pathways and restoring tissue selenium levels [140][141]. Short-term safety assessments generally report minimal hemolysis and stable hepatic and renal biochemistry; however, therapeutic windows remain narrow, reflecting selenium's intrinsic redox reactivity and potential for immune perturbation at supraphysiological exposure.

Taken together, SeNPs emerge as rationally engineerable nanomodulators capable of attenuating inflammatory signaling, regulating cytokine expression, and recalibrating macrophage polarization through integrated NF-κB/Nrf2/redox pathways. Future advancement will require standardized in vivo protocols, comprehensive pharmacokinetic and long-term immunotoxicity evaluations, and systematic benchmarking against conventional selenium formulations to ensure that physicochemical optimization translates into durable clinical safety and efficacy in inflammatory and immune-mediated diseases.

7. CURRENT CHALLENGES AND FUTURE PERSPECTIVES

The advancement of selenium nanoparticles (SeNPs) toward clinically viable nanomedicine platforms is increasingly shaped by interrelated challenges in synthesis standardization, physicochemical stability, biological reproducibility, and translational validation. At the materials level, SeNP synthesis remains highly sensitive to precursor chemistry (e.g., Na_2SeO_3 vs. H_2SeO_3), reductant strength, pH, temperature, reaction time, and stabilizer concentration, all of which govern nucleation–growth kinetics and ultimately determine particle size, morphology, crystallinity, ζ-potential, and colloidal stability [25][54]-[57]. Minor deviations in stoichiometry or pH can shift controlled nucleation toward aggregation-dominated growth, generating inconsistent size distributions and variable bioactivity [28][54][56]. These issues are compounded by heterogeneous characterization practices—particularly inconsistent

DLS parameters, ζ-potential reporting, and limited cross-validation with TEM or XRD—which hinder cross-study comparability and meta-analytical assessment [23][24][26][27]. Green and microbial syntheses introduce additional variability due to batch-dependent phytochemical composition or metabolic fluctuations, limiting scalability and reproducibility [61]-[63]. The absence of harmonized reporting standards regarding reaction stoichiometry, purification protocols, and statistical size analysis further impedes regulatory alignment and industrial translation [33][34][53]. Accordingly, standardized synthesis guidelines, interlaboratory validation, and quality control frameworks integrating physicochemical benchmarks with biological performance metrics are urgently required [29][36].

Long-term stability and scalable production represent additional bottlenecks. Colloidal integrity is tightly coupled to surface chemistry and ζ-potential; aggregation, Ostwald ripening, or surface oxidation during storage or under physiological ionic strength can alter hydrodynamic size and functional performance [45][55]. Scaling laboratory protocols to industrial volumes challenges precise nucleation control and narrow size distribution maintenance, while reagent purity, mixing dynamics, solvent recovery, and cost efficiency influence manufacturability [56]-[58]. Regulatory translation will necessitate robust quality control metrics covering phase purity, size distribution, and defined storage stability conditions [33][36].

Biological variability further complicates translation. SeNP bioactivity is strongly dependent on physicochemical attributes, which influence protein corona formation, cellular uptake, redox modulation, and cytotoxic thresholds [55]-[57]. Inconsistent dosing regimens, animal models, and endpoint selection limit reproducibility and mechanistic clarity across in vivo studies [53]. Moreover, toxicological evaluation remains largely confined to acute models, with insufficient data on long-term biodistribution, organ accumulation, and subchronic exposure risks—particularly given selenium's narrow therapeutic window and dual antioxidant–pro-oxidant behavior [60][75].

Despite these limitations, smart functionalized SeNPs illustrate future opportunities. Rational surface engineering—including glutathione conjugation, polysaccharide or peptide stabilization, receptor-targeting ligands (e.g., mannose, hyaluronic acid), and pH- or redox-responsive coatings—enhances tissue selectivity, microenvironment-triggered release, and therapeutic precision [123]-[127]. Integration with drug-loaded or nanozyme-based systems supports combination therapy paradigms, enabling ROS amplification, pathway modulation (e.g., PI3K/Akt,

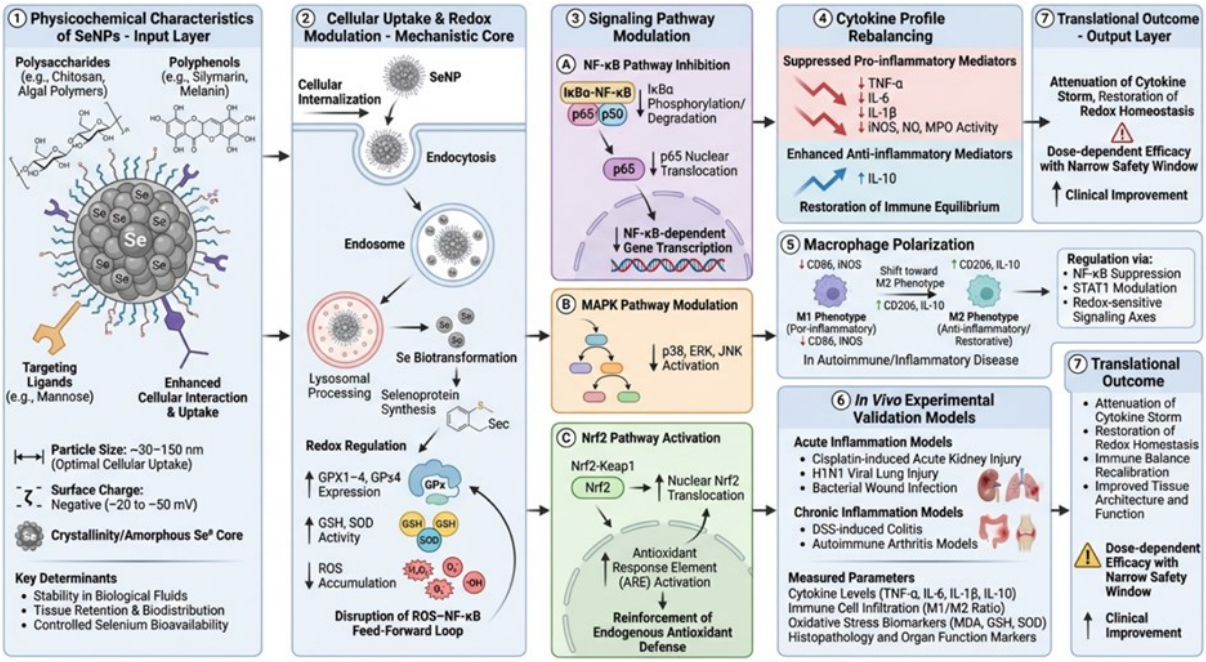

Figure 6. Anti-inflammatory and Immunomodulatory Effects of Selenium Nanoparticles (SeNPs).

MAPK, STAT3, NF-κB), and potential dose reduction in oncology or antimicrobial contexts [42][107][142][143]. Nonetheless, increased architectural complexity intensifies challenges in reproducibility, pharmacokinetics, and regulatory evaluation, particularly regarding nanoparticle-to-drug ratios, synchronized release kinetics, and cumulative oxidative toxicity [82][90]. Precision nanomedicine applications—incorporating receptor-mediated targeting and theranostic monitoring—offer promising personalization strategies, yet remain constrained by biological heterogeneity, unpredictable biodistribution, and insufficient long-term safety data [130][134][139]-[141].

Future progress will depend on harmonized synthesis protocols, scalable manufacturing platforms, standardized preclinical evaluation frameworks, and comprehensive toxicokinetic profiling. Only through integration of robust physicochemical control, reproducible biological validation, and regulatory-aligned characterization can SeNP-based technologies transition from experimental constructs to clinically reliable redox-adaptive nanomedicines.

8. CONCLUSIONS

Selenium nanoparticles (SeNPs) emerge as redox -adaptive nanomaterials whose biological activities are mechanistically unified by finely regulated modulation of oxidative homeostasis. At the molecular level, SeNPs operate through bidirectional control of reactive oxygen species (ROS), enhancing glutathione peroxidase activity and activating Nrf2-dependent antioxidant networks under physiological conditions, while inducing mitochondrial membrane depolarization, cytochrome c release, caspase activation, and cell cycle arrest when redox thresholds are exceeded in malignant cells. This context-dependent redox plasticity underlies their anticancer efficacy and capacity to sensitize tumors to chemotherapeutic agents. In microbial systems, SeNPs integrate membrane destabilization with ROS-mediated oxidation of proteins and nucleic acids, generating multitarget antimicrobial and antibiofilm effects that reduce susceptibility to conventional resistance mechanisms. Concurrently, suppression of NF-κB signaling and reinforcement of Nrf2-driven pathways confer anti-inflammatory and immunomodulatory benefits through recalibration of cytokine expression and macrophage polarization. These diverse biological outcomes are intrinsically governed by physicochemical attributes—including particle size, crystallinity, surface charge, and functionalization—which dictate cellular uptake, interfacial electron transfer, biodistribution, and kinetic selenium release. However, the same redox activity that underpins therapeutic efficacy also defines safety boundaries, as SeNPs exhibit dose-dependent dual antioxidant–prooxidant behavior within selenium's narrow therapeutic window. Limited long-term toxicological data, incomplete pharmacokinetic characterization, and variability in synthesis protocols remain significant barriers to clinical translation. Future biomedical development therefore requires rigorous correlation of structural parameters with mechanistic endpoints, standardized safety evaluation, and rational nanoengineering strategies that balance controlled pro-oxidant cytotoxicity with preservation of physiological redox equilibrium. Achieving this equilibrium between efficacy and safety will determine the successful integration of SeNPs into next-generation therapeutic platforms.

AUTHOR INFORMATION

Corresponding Author

Hanif Amrulloh — Department of Islamic Primary School Teacher Education, Universitas Ma'arif Lampung, Metro-34111 (Indonesia);
orcid.org/0000-0001-7458-9258
Email: amrulloh.h@umala.ac.id

Authors

Claudia Maria Simonescu — Department of Analytical Chemistry and Environmental Engineering, National University of Science and Technology POLITEHNICA Bucharest, Bucharest-060042 (Romania);
orcid.org/0000-0002-5308-7344

Oman Zuas — Research Centre for Testing Technology and Standard, Badan Riset dan Inovasi Nasional (BRIN), Tangerang Selatan-15314 (Indonesia);
orcid.org/0000-0002-0101-5277

Muhammad Saqib Khan — Department of Biological and Health Sciences, the Pak-Austria Fachhochschule Institute of Applied Sciences and Technology, Haripur-22600 (Pakistan);
orcid.org/0000-0002-0897-7436
Hamed Kioumarsi — Department of Animal Science Research, Gilan Agricultural and Natural Resources Research and Education Center, Rasht-41996 (Iran);
orcid.org/0000-0002-0783-0934

Author Contributions

Conceptualization, H. A., C. M. S., O. Z. and H. K.; investigation, H. A. and M. S. K.; writing—original draft preparation, H. A., O. Z. and H. K.; writing—review and editing, H. A., C. M. S., O. Z., M. S. K. and H. K. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

DECLARATION OF GENERATIVE AI

During the preparation of this manuscript, ChatGPT (OpenAI) was used solely to assist with language editing, improvement of clarity, and refinement of academic expression. In addition, limited assistance was obtained for drafting coding suggestions related to data analysis; however, all scripts were independently reviewed, validated, and executed by the authors. All figures, graphs, and visual materials included in this manuscript were generated by the authors using conventional scientific and statistical software based on original research data.

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