

Selenium Nanoparticles: Biomedical Application Advances and New Stomatology Pathways

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Abstract: Selenium nanomaterials, as current emerging materials, have garnered significant attention in the medical field due to their remarkable bio-compatibility, low toxicity, and environmental sustainability. Due to their facile synthetic accessibility and tunable physicochemical properties, they exhibit significant potential as novel adjuvant therapeutic strategies for treating inflammation, bacterial infections, and other pathological conditions. This review first systematically outlines three primary synthesis strategies for Selenium nanoparticles(SeNPs): physical, chemical, and biological approaches, highlighting their respective underlying mechanisms and unique advantages. Then it summarizes the properties of various SeNPs and the advantages and disadvantages of each method, assessing and providing a comprehensive comparison of the strengths and limitations associated with each synthesis method. Furthermore, this review introduces the molecular mechanisms underlying the anti-inflammatory, antioxidant, and antimicrobial activities of SeNPs, with a focus on the signaling pathways and enzymatic interactions through which SeNPs exert their therapeutic effects in vivo. Finally, this review summarizes recent advancements in the application of SeNPs in three critical areas: antimicrobial therapy, cancer treatment, and anti-inflammatory/antioxidant interventions, focusing on summarizing the current application of SeNPs and exploring the possibility of their application in the field of stomatology by elucidating their strengths and weaknesses, which provides a theoretical basis for SeNPs' application in the field of stomatology.

Keywords: selenium nanoparticles, synthesis, antibacterial, anti-inflammatory and antioxidant, anti-cancer, stomatology

Introduction

Selenium (Se) is an essential trace element in human physiology, playing a vital role in maintaining health and supporting normal physiological functions. As a key constituent of many selenoproteins and selenium-containing cysteine enzymes,^{1–3} Se deficiency disrupts the synthesis of various selenoproteins, leading to significant physiological consequences.⁴ The glutathione peroxidase (GPx) family, the first identified group of selenoproteins,⁵ is found in a wide range of organisms.⁶ It functions as a core enzyme responsible for scavenging reactive oxygen species (ROS) and alleviating oxidative stress.⁷ Through the catalytic activity of selenocysteine residues, GPx facilitates the decomposition of H₂O₂ to remove oxides, thereby conferring anti-inflammatory and antioxidant effects.^{8–10} Moreover, Se contributes to cancer prevention by serving as a catalytic center for enzymes such as GPx and as a precursor for anticancer metabolites, including hydrogen selenide (H₂Se),^{11–14} methylselenide,^{11,14} and selenocysteine.^{15–17} These diverse functionalities distinguish selenium-based materials among anti-inflammatory and antioxidant agents.

Among various selenium-containing materials, selenium nanoparticles (SeNPs) have attracted extensive interest in agriculture, food science, and medicine^{18–20} due to their distinctive physicochemical properties and multifunctional

advantages. Numerous studies have demonstrated that SeNPs possess higher biocompatibility,^{21,22} along with remarkable anti-inflammatory, antioxidant, and antibacterial activities.^{23–25} Meanwhile, they are also less toxic and exhibit superior performance in biological systems compared to active selenoproteins or other selenium-containing compounds.^{26,27} For example, in vitro studies have indicated that chitosan-stabilized SeNPs reduce cytotoxicity by 20–30% relative to sodium selenite and show selective anti-proliferative activity against cancer cells.²⁷ Currently, most reported SeNPs are stabilized with agents such as water-soluble *Ganoderma lucidum* polysaccharide derivatives,²⁸ SiO₂,²⁹ or chitosan,³⁰ which enhance their stability and bioactivity. This progress provides an important foundation for their potential applications in stomatology. The core mechanisms of current stabilizers lie in four pathways, including steric effects, potential regulation, chemical bonding and oxidation inhibition.³¹ For example, chitosan is a commonly used stabilizer for SeNPs. Hector Estevez et al have studied and shown that SeNPs modified by chitosan have a highly positive ζ -potential value of 62.5±5.2 mV that falls in the zone of colloidal stability. Furthermore, experiments have demonstrated that the steric effects of chitosan are also an important mechanism for stabilizing SeNPs. Therefore, chitosan mainly achieves the stability of SeNPs through three pathways: potential regulation, steric hindrance and oxidation inhibition.³² This indicates that a stabilizer achieves its stabilizing effect through multiple pathways rather than a single one.

Oral diseases, including periodontitis, dental caries, and oral mucosal infections, continue to pose significant public health challenges worldwide. Conventional treatments often face limitations such as antibiotic resistance, prolonged therapy duration, and risk of tissue damage.^{33,34} For instance, periodontitis, which is associated with pathogens like *Porphyromonas gingivalis* and *Enterococcus faecalis*,³⁵ frequently results in chronic inflammation and alveolar bone resorption.³⁶ Similarly, dental caries caused by *Streptococcus mutans* is complicated by biofilm resistance.³⁷ The antibacterial, anti-inflammatory, and antioxidant properties of SeNPs align well with the therapeutic requirements of these oral diseases. Despite their demonstrated efficacy in models of diabetes,^{38,39} Parkinson's disease,^{40,41} cancer,^{42,43} SeNPs are still in the stage of clinical development. There remains a scarcity of systematic research and application in the field of stomatology. Key unresolved issues include insufficient data on the stability of SeNPs in the oral microenvironment, unclear optimal dosing for oral conditions, and a lack of targeted studies supporting clinical translation for oral diseases. This review systematically summarizes the principal synthesis methods for SeNPs, including physical, chemical, and biological approaches, and evaluates their respective advantages and limitations. It further elaborates on the molecular mechanisms behind the antibacterial, anti-inflammatory, and antioxidant activities of SeNPs, with a particular emphasis on their potential to address oral health challenges. By integrating existing research progress and identifying current bottlenecks, this review aims to provide a theoretical foundation for the development and clinical translation of SeNPs in the field of stomatology.

The Synthesis of SeNPs

At present, there are three main methods of SeNPs synthesis: physical synthesis, chemical synthesis and biosynthesis.¹ Different methods lead to different characteristics of SeNPs.⁴⁴ Therefore, experimental personnel often select the corresponding synthesis method by evaluating the relevant characteristics of the required SeNPs (Figure 1).

Physical Synthesis

Physical synthesis utilizes various energy forms to produce elemental selenium (Se⁰), which is directly converted into SeNPs.⁴⁵ Currently, the main physical synthesis methods include electrochemical synthesis, microwave radiation, laser ablation, and laser irradiation.

Microwave radiation is one of the most commonly used physical synthesis methods. Compared to traditional heating methods, microwave radiation enables faster heating and cooling rates through more uniform particle size distribution, making it easier for materials to absorb energy. This process generates high thermal efficiency, resulting in green, energy-saving, and enhanced reaction selectivity.^{46–48} Kosar Sheikhlou et al mixed walnut extract with Se solution and subjected the mixture to microwave radiation with a fixed power of 800 W for 4 minutes, successfully obtaining SeNPs. Then the experimental results demonstrated the stability and excellent antibacterial properties of SeNPs.⁴⁹

In addition, laser ablation is also a commonly used green synthesis method at present. The nanoparticles (NPs), produced by pulsed laser ablation (PLAL), have the characteristics of uniformity, stability and ease of collection, which

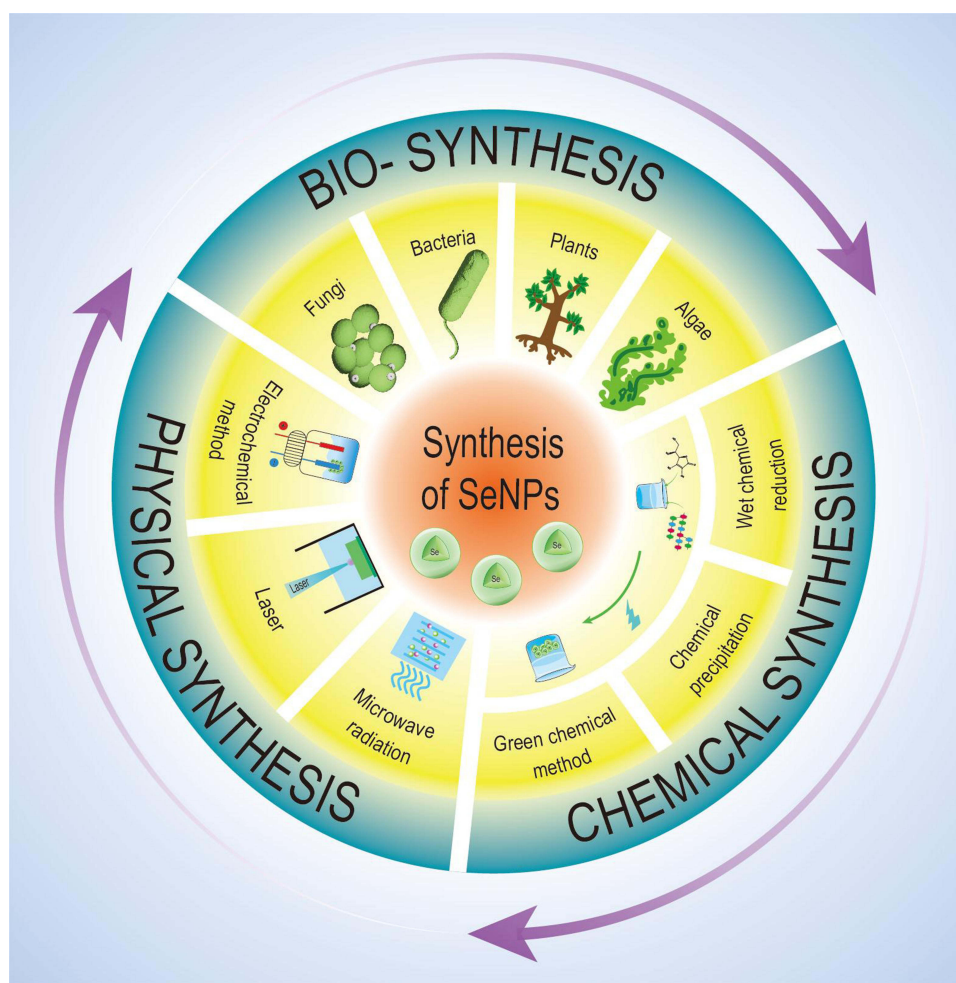


Figure 1 Synthesis methods of selenium nanoparticles.

meet the requirements of modern medicine for residue-free material surfaces.⁵⁰ At the same time, the PLAL method is environmentally, friendly and green, which can prevent adhesion during the generation of NPs, and has significantly promoted the application of SeNPs in the medical field.⁵¹ Grégory Guisbiers et al were the first to report the preparation of SeNPs using the PLAL method. Under conditions of 800nm infrared light, pulse duration less than 100 fs, and repetition frequency of 80 ± 1 MHz, they obtained SeNPs. Then SEM and TEM observations revealed that the surface of the SeNPs was smooth with no residue. Bacterial experiments also demonstrated the excellent antibacterial properties of the material.⁵²

While physical synthesis methods offer such core advantages as high product purity and environmental friendliness in SeNP synthesis. Notably (Table 1), the particle size and properties of SeNPs vary with different synthesis methods, and significant differences in SeNP properties are also observed when the same method is applied under different power conditions. In addition, compared with other synthesis approaches, physical synthesis methods are associated with the drawbacks of high energy consumption and excessive reliance on equipment.⁵⁰ For instance, pulsed laser ablation can efficiently produce SeNPs, but it remains challenging to achieve precise control over their properties. Meanwhile, pulsed laser ablation is overly reliant on laser generation equipment and constrained by economic considerations and scalability.^{53,54} Furthermore, in microwave-assisted synthesis, the failure to achieve uniform microwave irradiation may result in the thermal decomposition of some SeNPs due to overheating, whereas others lack sufficient energy for conversion.⁵⁵ Therefore, future efforts should focus on optimizing processes, upgrading energy-efficient equipment, and

Table 1 A Summary of Physical Synthesis Methods of SeNPs. The Table Mainly Summarizes Some of the New Common Methods

Methods	Structure and Morphology	Center Particle Size (nm)	Selenium Content	Energy Consumption	Reference
Laser ablation	Sphere (SEM)	43±20 (DLS)	40ppm (3000Hz)	YAG laser: 1×10^6 W; Optimal repetition rate: 3000 Hz	[51]
Microwave radiation	Sphere (SEM)	41.5 ± 1.7 (XRD)	Na	Optimal irradiation power: 788.6 W	[47]
Microwave radiation	Sphere (SEM), monoclinic crystalline phase (XRD)	10 (XRD), 1.03 (DLS)	Na	Optimal irradiation power: 1000 W	[56]
Electrochemical method	Sea urchin-like	Sucrose modified: 85 PVP modified: 43 SDS modified: 60	NA	Room temperature electrolysis (voltage-1.2 V)	[57]
Ultrasonic-assisted method	Sphere (TEM)	(DLS): 129.19 (0 min), 107.89 (20 min), 76.74 (40 min), 153.23 (60 min)	(ICP-MS): 13.6% (0 min), 16.8% (20 min), 18.9% (40 min), 11.9% (60 min)	Ultrasonic power: 250 W	[58]

improving pollution control and resource recovery systems to overcome the existing technical bottlenecks of physical synthesis methods, while achieving the low-carbon, clean, and sustainable production of SeNPs.

Chemical Synthesis

As the most widely adopted approach for SeNPs synthesis to date, chemical synthesis enables the formation of SeNPs through the reduction of Se ions in sodium selenite solution, facilitated by reducing agents and stabilizers.⁵⁹ Commonly used reducing agents include ascorbic acid, glutathione and sulfur dioxide.^{60,61} Besides, polysaccharides, glycoproteins, polyphenols, etc., are commonly used to modify SeNPs to improve their stability (Table 2).

It is noteworthy that different reaction parameters in the chemical synthesis system exert distinct effects on the properties of SeNPs. pH is a critical parameter requiring regulation during SeNPs synthesis. Daniela ˇ Stefankov´ et al found that a decrease in pH will significantly accelerate the reaction rate. And under acidic conditions (pH=3.16 or 2.5),

Table 2 A Summary of a Variety of New Chemical Synthesis Methods

researchers	Methods	Reductant	Materials	Products	Structure and Morphology
Vrundali Shinde et al ⁶²	Chemical precipitation	Ascorbic acid	Sodium selenite (Na_2SeO_3), L-methionine (Met) and Folic acid	Se-Met-Fa NPs	Nanospheres
Andrey V Blinov et al ⁶³	Wet chemical reduction	Ascorbic acid	Selenic acid and cocamidopropyl betaine (CAPB)	CAPB-Selenium NPs	Nanospheres
Anastasiya Blinova et al ⁶⁴	Wet chemical reduction	Ascorbic acid	Selenious acid and cetyltrimethylammonium chloride (CTAC)	CTAV-Selenium NPs	Nanospheres

(Continued)

Table 2 (Continued).

researchers	Methods	Reductant	Materials	Products	Structure and Morphology
Leilei Guo et al ⁶⁵	Wet chemical reduction	Glutathione	Sodium selenite (Na ₂ SeO ₃)	SeNPs	Amorphous (α-Se) selenium
Tianqi Nie et al ⁶⁶	Wet chemical reduction	Glucose	Sodium selenite (Na ₂ SeO ₃) and Glucose(Glu)	Glu-SeNPs	Crystal nanospheres
Qing Huang et al ⁶⁷	Wet chemical reduction	Cysteine and HCl	Sodium selenite (Na ₂ SeO ₃), Cysteine(Cys) and soybean polypeptides(SP)	SP-SeNPs	Nanospheres
Aleksandra Sentkowska et al ⁶⁸	Green chemical method	Ascorbic acid (AA) or gallic acid (GA) or Herbal Polyphenols	Sodium selenite (Na ₂ SeO ₃)	SeNPs (synthesized by 3 reductant)	All SeNPs are nanospheres

the reaction is almost instantaneous. But the particles will connect with each other to form a dense network structure, leading to severe agglomeration.⁶⁹ Besides, Meanwhile, product characteristics vary with the type of organic acid employed, primarily attributed to the stabilizing effect of organic acid anions, which modulate both the reducing capacity and the surface charge of the particles.^{70,71} Additionally, temperature exerts a notable impact on the properties of SeNPs. Several studies have demonstrated that low temperatures (25–40 °C) result in low Se atom mobility, typically leading to the formation of amorphous structures. In contrast, moderate to high temperatures (60–100 °C) enhance Se atom mobility and facilitate accelerated crystal growth, often yielding hexagonal or trigonal crystal systems with higher crystallinity.^{72,73} Thus, the selection and optimization of reaction parameters based on specific requirements represent a pivotal step in the chemical synthesis of SeNPs.

Although chemical synthesis is simple and economical, it often results in residues of chemical substances during the process, which may lead to the failure of treatments.⁷³ Meanwhile, variations in materials such as stabilizers also affect the chemical properties of SeNPs. Polysaccharides, for instance, may induce the aggregation of SeNPs in acidic environments, which in turn reduces the bioavailability of the material. This places stringent requirements on its purity, toxicity and performance in medical applications.⁷⁴ Furthermore, the selection or minor alterations of reaction parameters may induce uneven reactions of the material during synthesis, thereby leading to batch-to-batch variations. This may serve as a limitation to the widespread application of the chemical synthesis method.⁷⁵ But, some researches indicate that ascorbic acid, when used as a reducing agent in the synthesis of SeNPs, can significantly reduce surface chemical residues, thereby decreasing external toxicity while further enhancing the purity of SeNPs.^{76,77} Boroumand et al utilized ascorbic acid as the reducing agent and chitosan and polyvinyl alcohol as stabilizers to prepare SeNPs. Through SEM and TEM observations, along with absorbance measurements, they found that the SeNPs had a smooth surface and minimal chemical residues. Additionally, in ROS detection and bacterial experiments, these particles demonstrated excellent antioxidant and antibacterial properties.⁷⁶ Thus, the rational selection of reduction systems, stabilizers, and reaction parameters constitutes an urgent issue to be addressed for the efficient chemical synthesis of SeNPs.

Biosynthesis

Biosynthesis utilizes bionanotechnology, taking various biological systems as nanofactories to obtain corresponding extracts. These biological systems mainly include bacteria, fungi, plants, etc. The principle of this method is that Se salts, selenic acid, and Se dioxide are introduced into the so-called “bioreactor” as precursors for synthesizing SeNPs, and the production of SeNPs relies on the abundant precursors and reducing agents in biological resources. In these biological resources, due to the

presence of enzymes, proteins, lipids, carbohydrates, etc., the biological systems exhibit strong reducing capabilities towards Se ions.⁷⁸ The synthesis principle primarily involves the reduction of Se(IV) or Se(VI) to obtain SeNPs. The differences in the mechanisms of SeNPs synthesis among different biological systems mainly lie in the variations of reducing agents and enzymes involved in the process. According to current research findings, within bacterial systems, apart from non-enzymatic reduction pathways involving glutathione, sulfides, and siderophores, a variety of reductases including sulfite reductase, nitrite reductase, and glutathione reductase are also actively engaged in the reduction process.⁷⁹ Compared to bacteria, fungi are easier to cultivate and can survive and reproduce at higher concentrations. Meanwhile, fungi can not only release reducing proteins and enzymes into the extracellular medium, allowing these biomolecules to reduce Se ions and then precipitate to form SeNPs, but also perform reduction intracellularly.⁸⁰ For plant synthesis, SeNPs are mainly generated through proteins, amino acids, organic acids, vitamins, and some metabolites that act as reducing agents and stabilizers synthesized by plants. However, the products generated by plants are influenced by the plant parts and their functions.⁸¹ Additionally, other biological systems such as algae have also been confirmed to promote Se reduction and stabilization through various bioactive substances⁸² (Table 3).

Compared with physically and chemically synthesized SeNPs, biologically synthesized SeNPs have been reported to possess better bioactivity and lower toxicity.⁹² Moreover, due to the diversity of biosynthetic methods and relatively low synthesis costs, the biosynthesis of SeNPs shows promising prospects, yet there are also corresponding limitations tied to it. Firstly, the size of biologically synthesized SeNPs is not necessarily controllable. For instance, SeNPs synthesized by *Bacillus subtilis* have an average size of 536 nm with a wide particle size distribution range from 280 to 630 nm. Minor changes in selenate concentration and culture time can significantly affect particle morphology, resulting in poor batch-to-batch reproducibility.³ Furthermore, in large-scale production Helga Fernández-Llamas et al reported that although *Vibrio natriegens* can rapidly synthesize SeNPs the yield is limited by selenate concentration up to 15 mM and relies on complex medium

Table 3 Biomediated Synthesis of Selenium Nanoparticles

Researchers	Methods	Materials	Products	Structure and Morphology
Amr H. Hashem ⁸³	Reduction of sodium selenite	<i>Punica granatum</i> L.	SeNPs	The spheroidal forms with moderately mono-dispersed Se NPs.
Pallavee Srivastava ⁸⁴	Reduction of selenite	<i>H. salifodinae</i> BK18	SeNPs	Hexagonal selenium.
Hamida Y. Mostafa ⁸⁵	Extract <i>Orobanchae aegyptiaca</i>	<i>Orobanchae aegyptiaca</i>	Ag-Se NPs	The spherical nature and was ranged from 18.1 nm to 72.0 nm, and the average particle size is determined to be 30.58 nm.
Kawai TAM ⁸⁶	Reduction of sodium selenite	<i>Shewanella</i> sp. HN-41	SeNPs	The synthesized selenium nanoparticles were amorphous.
Tingting Wang ⁸⁷	Synthesis of Se/protein composites using <i>B. subtilis</i>	<i>Bacillus subtilis</i>	SeNPs	Semiconductor monoclinic Se nanoparticles, spherical shaped with diameters ranging from 50 to 400 nm.
Saeedeh Pouri ⁸⁸	Bacterial reduction of sodium selenite	<i>Bacillus cereus</i>	SeNPs	Spherical selenium nanoparticles with a mean diameter of 170 nm.
Fatemeh Shakeri ⁸⁹	Bacterial reduction of sodium selenite	<i>Pseudomonas aeruginosa</i>	SeNPs	Natural crystalline nature, spherical shape and the average particle size of SeNPs was 260 nm.
Nishant Srivastava ⁹⁰	Synthesis of SeNPs by bacteria	<i>Ralstonia</i>	SeNPs	Spherical in shape with size range of 40–120 nm. nanocrystalline selenium of pure hexagonal phase and The formation of actinomorphic trigonal selenium nanorods.
Yuting Wang ⁹¹	Isolated from the Gut of <i>Monochamus alternatus</i> (Coleoptera: Cerambycidae)	<i>Monochamus</i> larvae	SeNPs	Spherical electron-dense SeNPs with an average hydrodynamic diameter of 273.8 ± 16.9 nm, localized mainly in the extracellular space.

optimization, studies have indicated that when the selenate concentration exceeds 10 mM cell viability significantly decreases leading to a reduction in the release of nanoparticles, moreover the size of SeNPs produced by this method changes with time and concentration.⁹³ Additionally, although *Aspergillus oryzae* can efficiently accumulate Se at 8462 mg/kg dry weight, the Se reduction pathway involves both assimilatory and dissimilatory mechanisms involving the coordinated regulation of more than 20 genes. This complexity makes it difficult to conduct targeted optimization of the SeNPs synthesis process due to the unclear mechanism and metabolic complexity.⁹⁴ Moreover, SeNPs synthesized using plant extracts require multiple purification steps such as ultrafiltration and centrifugation. However, residual mixtures are difficult to completely remove. Studies have pointed out that the purification and separation process of this method is challenging and time-consuming, necessitating further process improvements.⁹⁵ In conclusion, although product stability and process complexity still pose significant challenges to its production, biosynthesis has certain advantages in terms of toxicity, biocompatibility, and cost.

Mechanism and Application of SeNPs' Activity

Infection

Antibacterial Activity of SeNPs in Biomedicine and Stomatology

The widespread misuse of antibiotics has led to the emergence of antimicrobial resistance in pathogenic microorganisms, posing a significant threat to global public health. Consequently, the development of novel antibacterial agents has become a critical focus in contemporary biomedical research. SeNPs exhibit considerable potential as antibacterial agents owing to their distinctive mechanochemical properties, biological activity, and intrinsic antimicrobial efficacy⁹⁶ (Table 4).

SeNPs demonstrate potent antimicrobial activity, with their mechanisms of action categorized into general and specific pathways. The general antibacterial mechanism of SeNPs involves multiple synergistic modes of action: electrostatic adsorption-mediated disruption of cellular membrane integrity and permeability; induction of reactive oxygen species (ROS) accumulation, resulting in oxidative stress; interference with energy metabolism through inhibition of ATP synthase activity; and suppression of essential biomolecule synthesis.¹⁰³ The surface negative charge characteristics of SeNPs result in significantly differential binding affinities to bacterial cells depending on their membrane charge properties.¹⁰⁴ The nanoscale dimensions and spherical architecture of SeNPs facilitate enhanced penetration through biofilm matrices.¹⁰⁵

In the specific antibacterial mechanism of bacteria, for Gram-positive bacteria (such as *Staphylococcus aureus*) and Gram-negative bacteria (such as *Porphyromonas gingivalis*), SeNPs disrupt ATPase activity by releasing Se^{2+} , consequently impairing cellular energy metabolism.^{106,107} Against drug-resistant strains (eg, MRSA, VRSA), SeNPs demonstrate three distinct mechanisms: (1) downregulation of antibiotic resistance-associated gene expression, (2) disruption of the thiol-based antioxidant defense system, and (3) potentiation of conventional antibiotic susceptibility.^{53,108–112} In the specific antibacterial mechanism of fungi, SeNPs can synergistically enhance nystatin to suppress the formation of fungal biofilm by selective interference with the RAS/cAMP/PKA signaling pathway against *Candida albicans* and other fungi.¹¹³ In addition, mechanism investigations showed that SeNPs disrupt the ergosterol biosynthesis pathway via modulation of the expression of key antifungal resistance genes ERG3, ERG11 and FKS1.¹¹⁴

Clinical studies in dental medicine have demonstrated that SeNPs exhibit broad-spectrum antimicrobial activity against major oral pathogens, including *Staphylococcus aureus* (*S. aureus*), *Streptococcus mutans* (*S. mutans*), *Porphyromonas gingivalis* (*P. gingivalis*), and *Enterococcus faecalis* (*E. faecalis*).^{115,116} In oral pathologies, these pathogens serve as primary etiological agents for oral mucosal infections, dental caries, periodontitis, and apical periodontitis. Their propensity for antimicrobial resistance development frequently complicates therapeutic interventions.^{117,118} Notably, methicillin-resistant *Staphylococcus aureus* (MRSA) and other multidrug-resistant (MDR) strains exhibit remarkable antibiotic resistance profiles. Importantly, clinical studies have demonstrated that SeNPs exert potent antibacterial activity against MRSA, highlighting their therapeutic potential for combating antimicrobial resistance. *S. mutans*, a primary etiological agent of human dental caries, colonizes biofilms on tooth surfaces. The antimicrobial mechanism of SeNPs involves membrane disruption and permeability alteration, resulting in biomacromolecule leakage and bacterial cell death - properties that suggest their therapeutic potential for caries prevention. Emerging evidence

Table 4 The Application of Anti-Bacteria. This Table Mainly Summarizes the Bacteria Used in Antimicrobial Experiments and the Corresponding Antibacterial Results

Researchers	Synthesis Methods	Materials	Shape and Size	Antibacterial Effect							
				Antibiofilm Activity	6.25% (ResSeNPs)	100µg/mL ResNPs	18.75µg/mL SeNPs				
Nina Tomić ⁹⁷	Physicochemical solvent–nonsolvent method	Trans-resveratrol (≥98%), selenite (Na ₂ SeO ₃), L-ascorbic acid(C ₆ H ₈ O ₆)	Optical microscopy: Interlaced nanobelt-like. FE-SEM: sphericity,70–100nm.								
				<i>P. aeruginosa</i>	55.15%	49.95%	69.81%				
Elizabeth G Wiita ⁹⁸	Droplet microfluidic strategy, chemical synthesis (SeNPs)	Silk-based microgels decorated with selenium nanoparticles	SeNPs: sphericity, 100–150 nm. Microgel: dense silk fibrillar network and spherical particles	Bacteria	Inhibition effect (50 µg/mL, 112 µg/mL, 250 µg/mL)						
				<i>B. subtilis</i>	Slight concentration dependence						
				<i>E. coli</i>	Complete inhibition of growth						
Luke D Geoffrion ⁵¹	Pulsed laser ablation in liquids (PLAL)	Bulk Se pellets	Nano-sphericity	Bacteria survival (0%):~25ppm	Luke D Geoffrion[–160]						
Hee-Won Han ⁹⁹	Chemical synthesis	Sodium selenite (Na ₂ SeO ₃), L-ascorbic acid(C ₆ H ₈ O ₆), D-(+) glucose (C ₆ H ₁₂ O ₆)	Nano-sphericity, 32.3 ± 5.6 nm	Bacteria	MIC (µg/mL)	Time(h)					
						Bactericidal activity			Bacteriostatic activity		
						1× MIC	2× MIC	4× MIC	1× MIC	2× MIC	4× MIC
				MSSA 6538	20	8	24	8	\	\	24
				MRSA 700699	80	8	8	8	\	24	24
VRSA 48	320	No bacteriostatic and bactericidal effects									
Mohsen M El-Sherbiny ²⁸	Biosynthesis	Chitosan nanoparticles (NCT), mucilage of cress seed (GCm), Sodium selenite (Na ₂ SeO ₃), L-ascorbic acid(C ₆ H ₈ O ₆)	Complicated structural physiognomies	Bacteria	T1 (mg/L) (ECT: GCm=2:1)			T3 (mg/L) (ECT: GCm=1:2)			
				<i>S. typhimurium</i>	15.0			27.5			
				<i>S. aureus</i>	17.5			32.5			

Pei Liu ¹⁰⁰	Biosynthesis	<i>Bacillus paramycoides</i> , Sodium selenite (Na ₂ SeO ₃)	Regular sphericity, average size:150nm	Bacteria	MIC (µg/mL)	MBC (µg/mL)
				S. aureus	400	600
				E. coli	600	800
Anastasiya Blinova ⁶⁴	Biosynthesis	Cetyltrimethylammonium chloride (CTAC), Sodium selenite (Na ₂ SeO ₃), L-ascorbic acid(C ₆ H ₈ O ₆)	Negative SeNPs: sphericity, 50–85nm. Positive SeNPs: sphericity, 20–50nm	Bacteria	MIC (mmol/L)	Inhibition zone(mm)
				E. coli	0.1940	15±2
				M. luteus	0.0194	20±2
				Mucor	0.1940	\
Wessam A Abd-Elraoof ¹⁰¹	Biosynthesis	Neptune grass extract (NG), chitosan, Sodium selenite (Na ₂ SeO ₃), L-ascorbic acid(C ₆ H ₈ O ₆)	Sphericity, 85.11–260.38nm (mean diameter:164.61nm)	Bacteria	MIC (µg/mL)	
				S. aureus	25.00	
				S. typhimurium	17.50	
				E. coli	20.00	
Mona Shaaban ¹⁰²	Biosynthesis	Spores of Streptomyces S12, SeO ₂	Nano-sphericity	Bacteria	MIC (µg/mL)	
				E. coli	197.5	
				K. pneumoniae	99	
				P. aeruginosa	395	
				MRSA	14.7-60	
				B. cereus	49	

supports this application, as demonstrated by Dhanraj et al, who fabricated SeNPs and evaluated their antibacterial efficacy against oral pathogens, including *S. mutans* and *S. aureus*. Their findings revealed potent growth inhibition of *S. mutans*, indicating potential applications in controlling cariogenic biofilms or incorporation into dental sealants for secondary caries prevention.¹¹⁹ In refractory apical periodontitis, *Enterococcus faecalis* (*E. faecalis*) establishes persistent biofilms within root canal systems, penetrates deep into dentin tubules, and induces sustained release of pro-inflammatory mediators, resulting in progressive destruction of periapical tissues. This pathogenic behavior constitutes a key determinant of treatment failure in refractory cases.³⁵ The distinctive physicochemical characteristics and inherent antimicrobial activity of SeNPs may offer novel therapeutic strategies for managing and preventing this pathological condition.

In addition, SeNPs exhibit broad-spectrum antimicrobial efficacy across diverse applications, underscoring their translational potential in dental medicine. They hold substantial promise in combination therapies, as adjuvants in combination therapies, and as functional additives in dental materials or nanocarriers or platform components for targeted delivery systems. A representative study by Samane Shahmoradi et al evaluated the synergistic effects of SeNPs with photodynamic therapy (PDT) against 24-hour-old planktonic cultures and biofilms of *Streptococcus viridans*. Through controlled experiments, they observed that SeNP-modified PDT achieved a significant reduction in colony-forming units (CFUs) of *S. mutans* biofilms. Notably, this combinatorial approach exhibited potent biofilm-disrupting activity against *S. viridans*.¹²⁰ In dental restorative applications, the inherent antimicrobial properties of SeNPs address critical requirements for oral restorative materials. As demonstrated by Iqra Saleem et al, SeNPs potentiate the antimicrobial efficacy of resin-based dental composites through the incorporation of Se-doped zinc oxide nanoparticles (Se/ZnO NPs) as antibacterial nanofillers. Comparative analysis revealed that composites containing 1% Se/ZnO NPs exhibited enhanced antibacterial activity, improved biocompatibility, and superior mechanical strength relative to those with 1% ZnO NPs alone, establishing Se/ZnO NPs as high-performance antibacterial additives effective at reduced concentrations.¹²¹ Therefore, SeNPs demonstrate significant clinical potential not only for managing prevalent oral diseases (dental caries and periodontitis) but also exhibit distinctive advantages in dental restoration and preventive applications.

Application and Mechanism of SeNPs Against Virus

SeNPs exert broad-spectrum antiviral activity through multiple synergistic mechanisms. As an essential trace element, Se participates in the biosynthesis of pivotal immunoregulatory enzymes, thereby potentiating host antiviral immunity. Current evidence demonstrates that Se enhances immune cell proliferation, promotes T-cell maturation and differentiation, augments cytotoxic activity, induces apoptosis of virus-infected cells, and stimulates interferon (IFN) and cytokine production.¹²² Additionally, SeNPs exhibit antiviral activity through modulation of host cell signaling pathways. Specifically, ribavirin-modified SeNPs (Se@RBV) demonstrate inhibitory effects against H1N1 influenza virus by targeting the caspase-3-dependent apoptotic pathway. Treatment with Se@RBV significantly downregulates expression of caspase-3-associated proteins, including cleaved poly-ADP-ribose polymerase (PARP), caspase-8, and Bax, while concurrently suppressing phosphorylation of p38, JNK and p53.¹²³ Furthermore, SeNPs mediate antiviral effects through dual mechanisms of ROS modulation: (1) inducing localized ROS generation to degrade viral nucleic acids and structural proteins, while (2) simultaneously suppressing excessive ROS accumulation to protect host cells from oxidative damage. This balanced redox modulation enables concurrent viral inactivation and host cytoprotection.¹²⁴ SeNPs exhibit potent antiviral activity through direct structural disruption of viral particles. Mechanistic studies demonstrate that SeNPs effectively inhibit influenza virus neuraminidase activity, thereby preventing viral progeny release.¹²⁵ However, the precise mechanisms underlying SeNP-virus structural interactions remain incompletely characterized. Drawing parallels from established nanoparticle-virus interaction paradigms, we hypothesize that SeNPs may similarly target viral envelope proteins and capsid components through analogous mechanisms.^{126,127} Furthermore, nanoparticles can block viral cellular entry by targeting surface antigens while simultaneously enhancing drug potency when utilized as antiviral nanocarriers.¹²⁸ Collectively, these findings establish a conceptual framework and mechanistic directions for advancing SeNP-based antiviral research.

Herpes simplex virus type 1 (HSV-1) serves as the principal etiological agent for oral pathologies, including herpetic stomatitis and labial herpes, with established associations to nasopharyngeal carcinoma. Recent studies demonstrate that

surface-modified SeNPs potently inhibit HSV-1 replication by targeting critical viral genes and structural proteins across multiple stages of the viral life cycle, effectively suppressing viral proliferation and assembly. These findings significantly advance understanding of SeNP-mediated antiviral mechanisms and their therapeutic potential for oral HSV-1 infections.¹²⁹ Despite their promise as antiviral agents, SeNPs remain underexplored in clinical applications. Their development could offer novel therapeutic strategies for viral infections in oral medicine.

Anti-Inflammatory and Antioxidant of SeNPs

Anti-Inflammatory Activity and Application of SeNPs

As a key component in histopathology, inflammation significantly influences pathological processes such as neurodegeneration, carcinogenesis, and immune system dysregulation.^{130–133} In the field of stomatology, periodontitis and gingivitis, as prevalent oral disorders, exhibit inflammatory processes that critically drive disease progression in oral ulcers and oral carcinomas.^{134–136} Therefore, timely treatment of inflammation is crucial for improving patients' quality of life and maintaining health. At present, antibiotic-based therapies present limitations including prolonged treatment courses, side effects, and oxidative stress-induced tissue damage from sustained activities of anti-inflammatory agents.^{33,34,137,138} Notably, SeNPs demonstrate remarkable anti-inflammatory activity with potential for alleviating and treating various oral diseases, including periodontitis and gingivitis.

The anti-inflammatory mechanisms of SeNPs primarily involve blocking inflammatory signaling pathways and suppressing pro-inflammatory factor expression. Current evidence indicates SeNPs mitigate inflammatory responses through inhibition of NF- κ B and MAPK pathways (Figure 2). Specifically, SeNPs can inhibit the NF- κ B pathway and subsequently suppress the expression of pro-inflammatory cytokine target genes, leading to reduced activity of inflammatory responses. Wang et al mixed the complex SPS-SeNPs with Raw 264.7 cells and found that SeNPs inhibited the activation of the NF- κ B pathway, thereby suppressing the production of NO and other anti-inflammatory factors,³⁰ which demonstrates the significant role of the NF- κ B signaling pathway in pro-inflammatory activation. In the classic NF- κ B pathway, SeNPs block the degradation of I κ -B to inhibit the activation of NF- κ B, thereby affecting the translocation of NF- κ B to the nucleus. Since NF- κ B is an activator of pro-inflammatory cytokines, it further inhibits the process of LPS-induced pro-inflammatory molecule iNOS and achieves the suppression of inflammatory responses.³⁰ In the alternative pathway of NF- κ B, the use of SeNPs also inhibits the phosphorylation of p65 protein induced by LPS, thus inhibiting the activation of the NF- κ B pathway.¹³⁹ In addition, SeNPs also interfere with MAPK signaling pathways by inhibiting the phosphorylation of JNK and p38 pathways, thereby inhibiting LPS-induced iNOS expression and subsequent NO and TNF- α production.³⁰ In this way, the expression of inflammatory cytokines such as IL-6, TNF- α , and IL-1 β is reduced, and the secretion of anti-inflammatory cytokines such as IL-12 is increased, so as to inhibit the inflammatory response.¹³⁹

Periodontitis patients frequently exhibit oral epithelial cell damage and gingival collagen degradation due to chronic inflammation.¹⁴⁰ This is also a key factor affecting supragingival scaling efficacy and prognosis. Therefore, how to more conveniently alleviate oral inflammation and reduce mucosal damage has become an urgent issue to address. Tritan et al prepared a kombucha dietary beverage rich in SeNPs and mixed it with gingival fibroblasts at different concentrations for culture. The detection of ROS generation rates showed that when the SeNPs concentration was 0.1 μ g/mL, the ROS generation rate decreased to 26.6%, and the cells exhibited good growth and proliferation status. Thus, the material demonstrated excellent anti-inflammatory capabilities and showed potential for promoting cell proliferation and repair.¹⁴¹ This makes it possible for patients to reduce periodontal inflammation and tissue damage by drinking dietary drinks on a daily basis. In addition, severe periodontitis can lead to inflammatory bone loss (alveolar bone resorption), which can lead to gum recession, tooth loosening and even tooth loss.³⁶ This is also the reason why the implant process is suspended due to periodontal inflammation caused by the restoration. At present, most of the treatment methods use bone powders and other materials to promote bone regeneration.^{142,143} However, the presence of periodontitis may lead to an imbalance between bone resorption and bone regeneration. The mechanisms of bone resorption mainly involve two aspects: on one hand, immune cells such as macrophages and T cells are stimulated, secreting large amounts of pro-inflammatory factors which activate osteoclasts and inhibit osteoblasts through the RANKL-RANK-OPG axis; on the other hand, precursor cells of macrophages can differentiate into osteoclasts under the influence of relevant factors, further intensifying bone resorption.^{144,145} Therefore, Huang et al adopted a macrophage polarization-targeting strategy

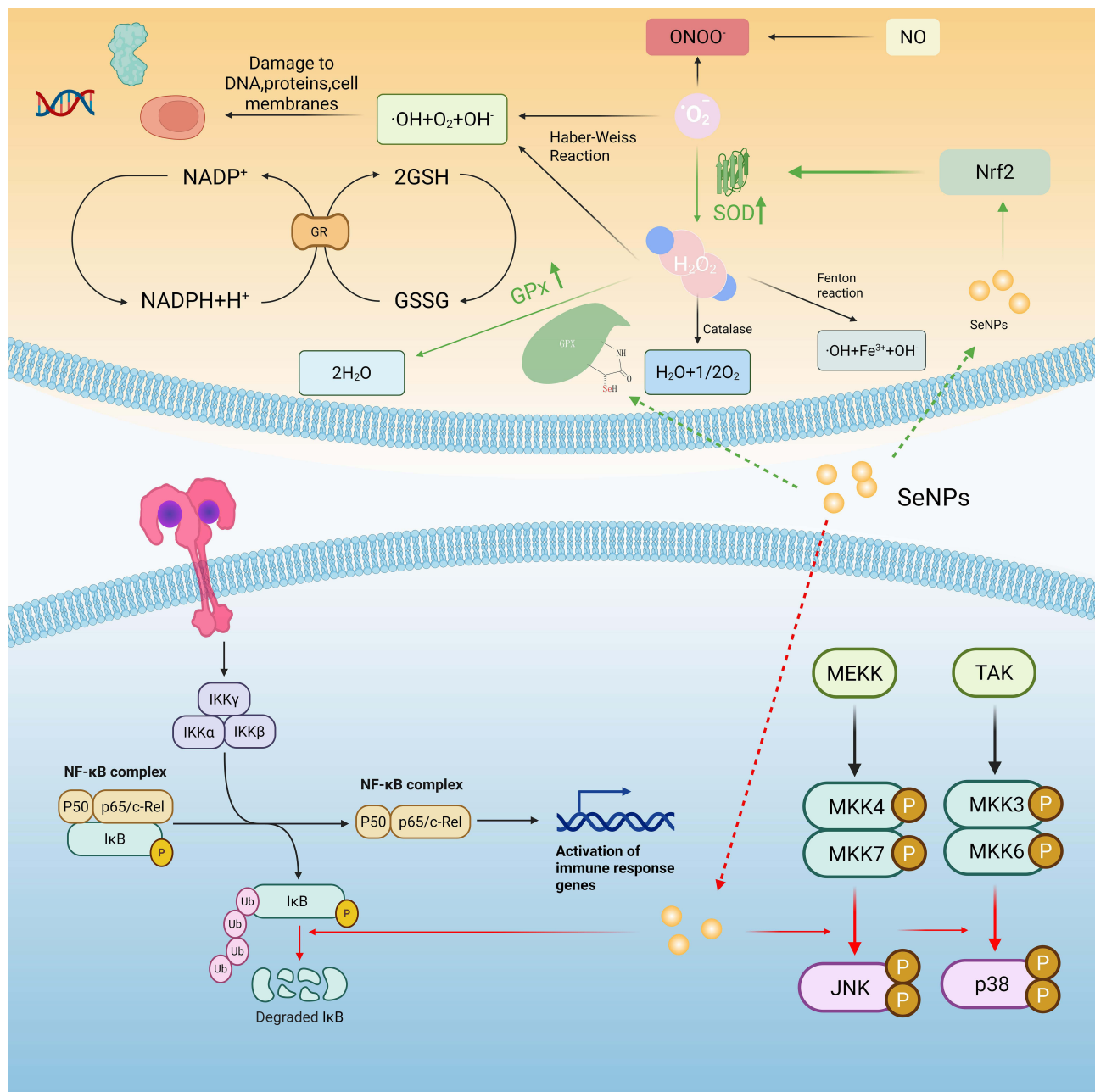


Figure 2 Anti-inflammatory and antioxidant mechanism of selenium nanoparticles.

Notes: Created in BioRender. Q, X (2025) <https://BioRender.com/g6ufr07>.

to address bone resorption, employing G3@SeHANs to scavenge circulating cell-free DNA (cfDNA). This approach concurrently promoted M2 macrophage polarization and suppressed production of pro-inflammatory mediators (TNF- β , IL-6).¹⁴⁶ In summary, compared with other materials, SeNPs provide new solutions for the two major challenges of inflammation suppression and tissue repair in the treatment of periodontal disease and gingivitis.¹⁴⁷ (Figure 3) At the same time, the advantages of simple application, rapid treatment and high efficiency of SeNPs can also reduce the pain in the treatment process of periodontitis patients and further improve the living standards of periodontitis patients for long-term treatment.

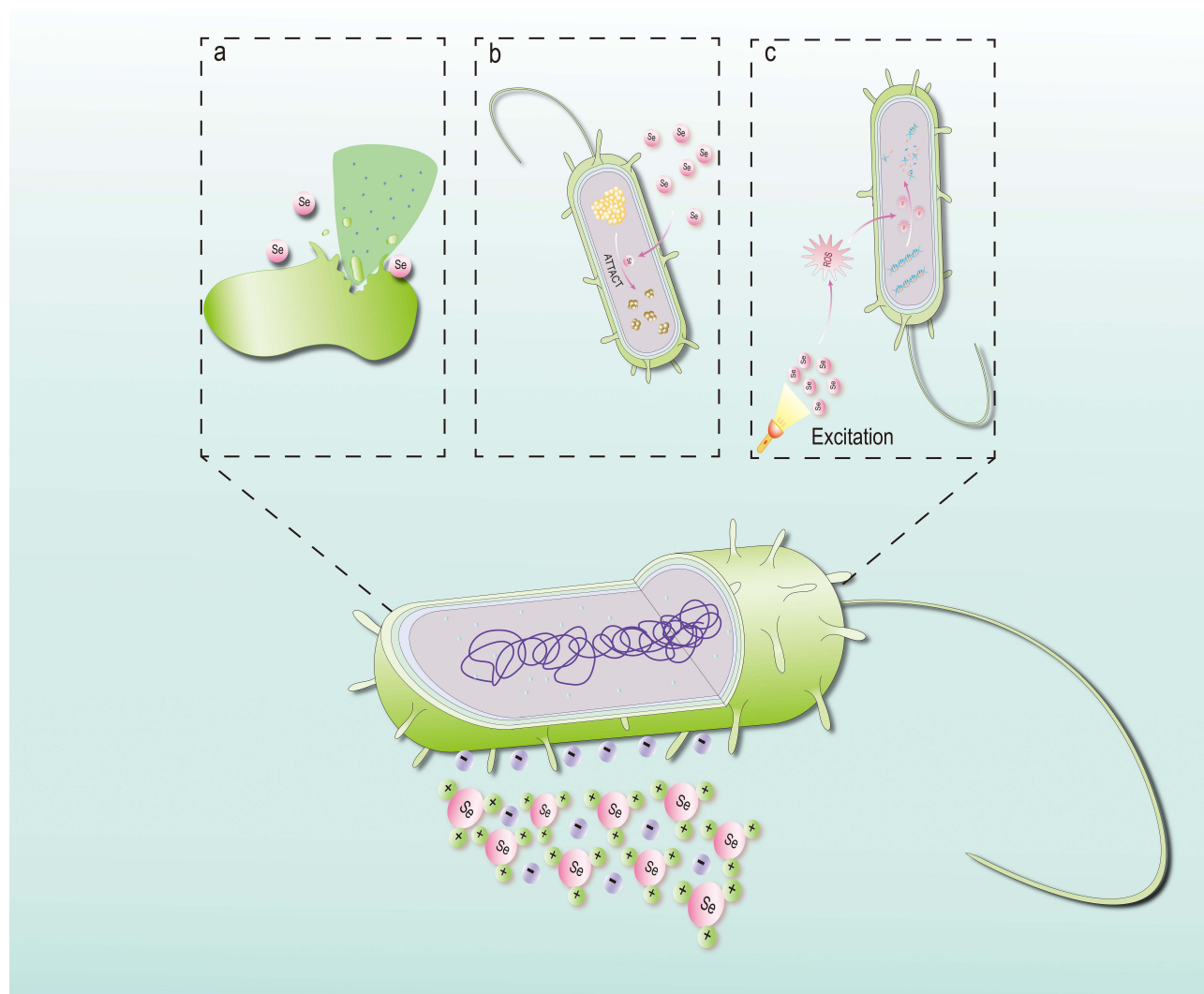


Figure 3 Antibacterial mechanism of selenium nanoparticles. (a) The bacterial cell membrane is broken and the contents are released, causing the bacteria to die. (b) SeNPs cleave and denature proteins in bacteria, killing the bacteria. (c) The SeNPs are excited by specific light and cleave the DNA which lead bacteria to die.

Antioxidant Activity and Application of SeNPs

Oxidative injury serves as a fundamental mechanism underlying numerous diseases, including inflammation and cancer. It mainly causes lipid peroxidation, protein denaturation and DNA damage, following cell death and tissue damage through the production of ROS in the body.¹⁴⁸ In a healthy body, oxidative damage and oxidative repair are in balanced states. However, when the body tissues are in pathological states (*eg*, cancer) or exposed to certain external influences (*eg*, radiation), the balance of the body will be disrupted due to oxidative stress, leading to excessive ROS accumulation and extensive tissue damage.^{149,150} This pathological process can further cause other diseases, such as diabetes, periodontitis, radiation jawbone osteomyelitis and so on. According to relevant studies, SeNPs have better antioxidant ability, which can significantly reduce the production and release of ROS, thereby offering a promising strategy for mitigating and repairing oxidative stress-induced damage.¹⁵¹

It is well known that selenoenzymes are the basis of redox homeostasis, and antioxidant enzymes such as glutathione peroxidase (GPx) and selenoprotein P are important enzymes in selenoproteins.¹⁵² SeNPs exert their antioxidative effects by leveraging the protective functions of selenoproteins, especially GPx.¹⁵³ Se increases the level of GPx protein, thereby enhancing GPx enzyme activity and increasing the oxidative process of GSH-GSSG, reducing the production of methyl-induced ROS within cells. Moreover, SeNPs can prevent lipid oxidation through GPx, thus protecting cell membranes.

Additionally, GPx protects biological systems by neutralizing peroxynitrite (ONOO⁻)-mediated oxidative damage.¹⁵³ Intracellular superoxide dismutase (SOD) is a specific oxygen radical scavenger, which can be enhanced by SeNPs. SOD catalyzes the disproportionation of superoxide anions into H₂O₂, which can subsequently be reduced by GPx to exert antioxidant function.¹⁵⁴

Diabetes mellitus (DM) represents a well-established risk factor for periodontitis.¹⁵⁵ Hyperglycemia in diabetic patients can induce oxidative stress and immune dysregulation, which will promote the process of periodontitis.¹⁵⁶ Conversely, periodontitis is also recognized to impact systemic inflammation, insulin resistance, lipid and glucose metabolism, thereby further influencing the development and progression of diabetes mellitus. Thus, diabetes and periodontitis exhibit a bidirectional relationship, with the core of their interaction lying in the exacerbation and dysregulation of inflammatory responses.¹⁵⁵ Current clinical interventions for periodontitis primarily involve mechanical debridement (*eg*, scaling and root planing) and antibiotic therapy to disrupt biofilms and inhibit bacterial growth.¹⁵⁷ However, because the incidence of this kind of periodontitis is multifactorial, the traditional treatment is always ineffective.¹⁵⁸ So, SeNPs have become a potential treatment option for alleviating diabetic periodontitis due to their powerful antioxidant properties. At present, several experiments have proved that SeNPs have strong antioxidant capacity.^{159,160} In the study by Biju Thomas et al, 150 subjects were divided into three groups, and their serum levels of glutathione, catalase, and Se were measured respectively. The results showed that compared with subjects with periodontitis but otherwise healthy and those without periodontitis, patients with type 2 diabetes and periodontitis had significantly reduced serum levels of glutathione, catalase, and Se. This indicates that in the inflammatory response induced by diabetes and periodontitis, the body can employ glutathione peroxidase and catalase to scavenge ROS for self-protection. Se, as a cofactor of glutathione peroxidase, plays a crucial role in this antioxidant defense process.¹⁶¹ In a separate study, they found that compared with periodontitis patients without other systemic diseases, those with concurrent diabetes had significantly lower serum Se levels. This highlights that Se may enhance the body's antioxidant defense by increasing glutathione peroxidase activity. Given the mechanisms underlying diabetes and periodontitis, this underscores the potential benefits of interventions targeting both conditions.¹⁶² And due to the similarity of the whole-body oxidation mechanism, SeNPs can achieve the reduction of the periodontal tissue damage caused by oxidative stress activated by diabetes, which especially improves the traditional therapy effect of periodontitis patients. Hence, SeNPs are expected to be used in the auxiliary treatment of diabetic patients with periodontitis.^{163,164} However, in current studies investigating the effects of Se supplementation on diabetes, relevant research indicates that Se supplementation may increase the prevalence of diabetes. When exploring the treatment of diabetic periodontitis, further evaluation of its potential implications for diabetes is thus required.¹⁶⁵ However, according to relevant literature analysis, a non-linear dose-response relationship exists between serum Se levels and type 2 diabetes mellitus (T2DM). The results indicate that in populations with relatively low serum Se levels (<97.5 µg/l) and those with relatively high serum Se levels (>132.5 µg/l), serum Se levels are positively correlated with T2DM. This suggests a potential U-shaped non-linear dose-response relationship between serum Se and T2DM.¹⁶⁶ Therefore, when considering the therapeutic application of SeNPs in diabetic periodontitis, a thorough evaluation of their safety profile is necessary. Although *in vitro* and animal studies have highlighted the potential of SeNPs, human trials are still insufficient. Meanwhile, it's still unknown whether the bioavailability and long-term safety of SeNPs are stable, which is an urgent problem to be solved in order to achieve clinical application.

With the development of medical technology, radiotherapy (RT) has become the primary treatment for head and neck cancer. However, prolonged RT exposure frequently leads to osteoradionecrosis of the jaws (ORN). As reported by Annu Singh et al, ORN typically manifests within two years of RT treatment, particularly in patients receiving doses exceeding 60 Gy, with a predilection for the mandible.¹⁶⁷ Despite technological advancements in RT, ORN remains the most severe complication within the treatment of head and neck cancer, reducing treatment efficacy and survival rates of patients.¹⁶⁸ The pathogenesis of ORN unfolds in three stages: endothelial injury, osteoclast apoptosis and sequestrum formation.¹⁶⁷ Prolonged RT induces oxidative stress of jawbone marrow, subsequently leading to accumulation of mass inflammatory factors and ROS, which culminates in marrow ischemia, osteocyte death, and bone necrosis.¹⁶⁹ Therefore, reducing the degree of oxidative stress in the body during RT and inhibiting the production of inflammatory factors and ROS provides a new direction for alleviating or even treating ORN. In an experiment evaluating the efficacy of Se replacement in preventing radiation-related toxicity, J. BÜNTZEL et al found that patients who received sodium selenite exhibited a significant reduction in dysphagia and taste loss compared with those who underwent irradiation without any Se

replacement. This indicates that Se replacement has a certain role in preventing radiation-related side effects. However, its effects on mucositis and xerostomia were not significantly affected, with limited efficacy and marginal effects. They attributed this to the fact that auxiliary detoxification is only one of the many pathways of excretion. Therefore, they suggested that in future studies investigating Se replacement for reducing radiation-related toxicity, it should be combined with other scavengers to further evaluate its efficacy.¹⁷⁰ In a randomized controlled trial involving post-operative patients with differentiated thyroid cancer, Tong, Huimin et al found that Se supplementation exerted a protective effect on the salivary glands during high-dose¹⁵⁵ I therapy. Furthermore, the combined administration of Se and vitamin C yielded superior outcomes. Specifically, antioxidant Se supplementation demonstrated significant protective effects on the excretory function of the parotid glands and the uptake and excretory functions of the submandibular glands.¹⁷¹ These experiments demonstrate that Se exhibits significant efficacy in scavenging ROS following radiotherapy. Furthermore, SeNPs can inhibit inflammation through multiple pathways and promote the production of GPx and SOD to clear ROS. Therefore, SeNPs may be an option for the treatment of ORN. However, due to the difficulty in simulating the osteomyelitis environment in vitro and the lack of clinical studies, further research is needed to determine whether SeNPs can achieve therapeutic effects on ORN (Figure 4).

Application of SeNPs in Cancer

Oral cancer is one of the most prevalent types of cancer. According to relevant data, there were 15,730 new cases and 9090 deaths from oral cancer in 2025, with the incidence rate increasing year by year,¹⁷² which poses a certain threat to people's life and health. Traditional treatment modalities involve surgical resection of tumors followed by chemotherapy and radiotherapy, which have side effects such as drug resistance and healthy cells damage.^{173,174} In recent years, emerging therapies including immunotherapy, gene therapy, and tumor treating fields (TTFields) have demonstrated promising advancements.^{174–176} Among them, nano-therapy has gained significant attention due to its high biocompatibility and low toxicity in cancer therapy, offering marvelous potential in anticancer applications¹⁷⁷ (Table 5).

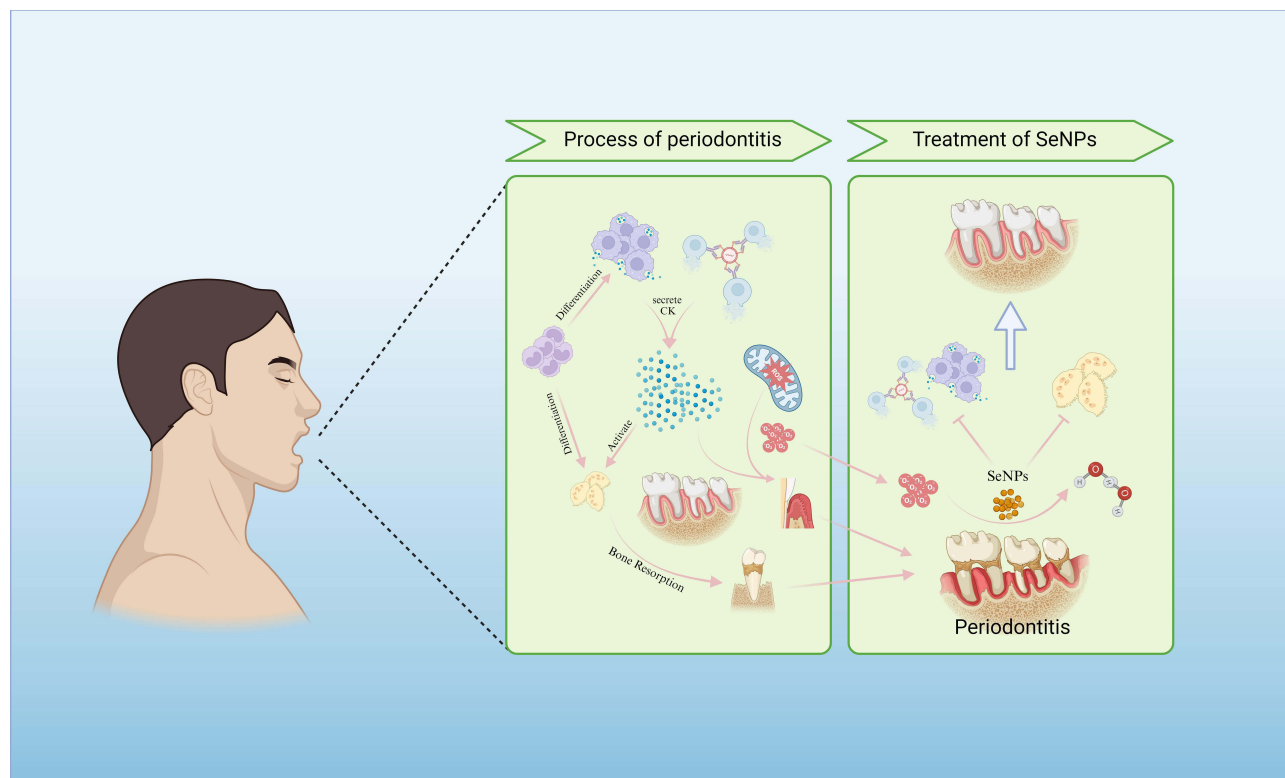


Figure 4 Pathogenesis of periodontitis and treatment of SeNPs particles.

Notes: Created in BioRender. Q. X (2025) <https://BioRender.com/f9sgtje>.

Table 5 The Application of Anti-Tumor. The Table Mainly Summarizes the Types of Tumor Cells Used in the Experiment and the Effect of the SeNPs

Researchers	Methods	Modifications	Tumor cell	Cell Kill Rate				
				Cell	125µg/mL (PVP3-I-SeNPs)	250µg/mL (PVP3-I-SeNPs)		
Shihai Zhang et al ¹⁷⁸	Chemical synthesis	Heteroxylan PVP3-I and R-PVP3-I	Pancreatic cancer cells (BxPC-3 and SWI990), normal human pancreatic duct cells (HPNE)	BxPC-3	50–60%	49.3%		
				SWI990	50–60%	49.6		
				HPNE	70–80%	77.2%		
				Cell				
Zehang Zhang et al ¹⁷⁹	Chemical synthesis	PTR-SeNPs	HCC1937 cancer cells	HCC1937	5µM (PTR-SeNPs) 20%	10µM (PTR-SeNPs) 30%	15µM (PTR-SeNPs) 35–40%	
				Cell				
Zifei Zhou et al ¹⁸⁰	Physical synthesis	Se-HA/CS	The human HCS-2/8 chondrosarcoma cells and Human SJSA osteosarcoma cells	HCS2/8	0.5% (Se-HA/CS) 18.6%	1.0% (Se-HA/CS) 21.9%	1.5% (Se-HA/CS) 22.8%	
				SJSA	21.6%	24.2%	30.4%	
				Cell				
Shuang Zhao et al ¹⁸¹	Chemical synthesis	MSe and HAS-MSe	MCF-7 human cells	MCF-7	1µM (HAS-MSe) 18%	10µM (HAS-MSe) 50%	20µM (HAS-MSe) 75%	
				Cell				
Pramod Kumar Gautam et al ¹⁸²	Chemical synthesis	SeNPs	Dalton's lymphoma (DL cells)	DL cells	5 ng/mL (SeNPs) 20%	20 ng/mL (SeNPs) 50%	40 ng/mL (SeNPs) 90%	
				Cell				
Karthik Rajkumar et al ¹⁸³	Biosynthesis	Biogenic SeNPs	HeLa cells	HeLa cells	1µg/mL (SeNPs) 30%	50µg/mL (SeNPs) 45%	100µg/mL (SeNPs) 50%	
				Cell				
Wanwen Chen et al ¹⁸⁴	Chemical synthesis	O-benzoylselenoglycolic chitosan	The human hepatocellular carcinoma cell line (HepG2) and human hepatic epithelial cell line (L-02)	HepG2	0.2µg/mL (O-benzoylselenoglycolic chitosan) 18%	0.6µg/mL (O-benzoylselenoglycolic chitosan) 55%	1.0µg/mL (O-benzoylselenoglycolic chitosan) 80%	
				L-02	5%	10%	15%	
				Cell				

Shuang Liu et al ¹⁸⁵	Chemical synthesis	SeASPs	The human lung adenocarcinoma cell line (A549), human non-small cell lung cancer cell line (H1975), human hepatocellular carcinoma cell line (HepG2)	Cell	100µg/mL (SeASP ₃)	200µg/mL (SeASP ₃)	400µg/mL (SeASP ₃)
				A549	10%	15%	17%
				H1975	20%	21%	30%
				HepG2	60%	66%	75%
Shaojie Zhang et al ¹⁸⁶	Chemical synthesis	EJP90-I-Se	Tumor cells (HepG2 or A549 cells)	Cell	50µg/mL (EJP90-I-Se)	100µg/mL (EJP90-I-Se)	200µg/mL (EJP90-I-Se)
				HepG2	8%	9%	33%

As an essential trace element in humans, Se is intimately associated with tumorigenesis. Hughes et al conducted a prospective cohort study to investigate the relationship between Se supplement intake and prostate cancer risk. Their results demonstrated an inverse association between Se intake and prostate cancer risk, with the highest intake group exhibiting a 32% lower risk (RR=0.68, 95% CI =0.54–0.85).¹⁸⁷ Furthermore, baseline Se concentration is closely correlated with cancer incidence. Fritz et al evaluated the association between baseline Se levels and cancer development via the Nutritional Prevention of Cancer (NPC) trial. They found that individuals with low baseline Se levels (serum<106ng/mL) who received Se supplementation experienced a 49% reduction in overall cancer risk and a hazard ratio (HR) of 0.42 for lung cancer (95% CI=0.18–0.96). Conversely, those with high baseline Se levels (serum≥121.6 ng/mL) showed an increased lung cancer risk (HR=1.25) subsequent to Se supplementation, alongside an elevated risk of diabetes (HR=2.70).¹⁸⁸ These observations provide empirical data and a theoretical framework for the application of SeNPs in cancer therapy.

SeNPs not only have anti-inflammatory and antioxidant effects, but can also inhibit the occurrence and metastasis of tumor cells through pathway activation, stimulation of immune cell proliferation and inhibition of inflammatory processes.^{189,190} The relevant studies indicate that high concentrations of SeNPs have weakened anti-inflammatory and antioxidant ability, which is mostly manifested as inhibition and killing of tumor cells.^{152,191} At the same time, the excessive accumulation of SeNPs in tumor cells can effectively kill tumor cells, and the ROS production rate is significantly higher than that of sodium selenite and other substances.¹⁹² Therefore, it is feasible for SeNPs to be used in the treatment of oral squamous cell carcinoma (OSCC) and head and neck tumors.¹⁹³ Chen et al developed a SeNP-indocyanine green (ICG) nanocomposite for combinatorial photothermal therapy. Using orthotopic oral squamous cell carcinoma (OSCC) murine models, they demonstrated 40% tumor growth inhibition via synergistic chemo-photothermal effects.¹⁹⁴ In addition, SeNPs can also be validated as targeted drug delivery carriers, which can increase the enrichment of drugs in tumor cells and improve the killing rate of tumors, as reported by Jia et al,¹⁹⁵ Xie et al.¹⁹⁶ Furthermore, multiple studies have demonstrated that adequate Se supplementation can enhance the efficacy of conventional radiotherapy (RT) and chemotherapy (CT). Zou et al divided PC3 prostate tumor-bearing mouse models into four groups: the experimental groups received SeNPs alone, RT alone, and combination therapy. The final results showed that the tumor volumes in the three monotherapy and control groups were 1.36 cm³, 1.11 cm³, and 0.97 cm³, while the tumor volume in the combination therapy group was significantly reduced to 0.32 cm³. Meanwhile, the body weights of the mice remained stable throughout the study, confirming the efficacy and safety of SeNPs combined with RT.¹⁹⁷ Besides, in a randomized, double-blind Phase II clinical trial for cervical cancer (NCT04815565), patients were randomly assigned to the control group (placebo plus chemoradiotherapy) and the experimental group (Se plus CRT). The results indicated that the incidence of grade 3 thrombocytopenia was significantly lower in the experimental group, accompanied by a more significant reduction in tumor volume. These findings further highlight the considerable potential of SeNPs in the field of cancer therapy.

Beyond their therapeutic potential, SeNPs also have significant advantages in cancer diagnosis. Traditional nanoimaging agents for cancer diagnosis and treatment often require coupling nanocarriers with photosensitizers or imaging agents.^{166–168} This hinders the release and transformation of materials, affecting the killing rate of cancer cells.^{169,170} Therefore, the label-free strategy has become a new direction for cancer diagnosis and treatment. Liu et al innovatively combined lentinan (LNT) and SeNPs, and used chemical exchange saturation transfer (CEST) MRI technology to detect and image a large number of free hydroxyl groups that exist in biomaterials within living organisms. Through fluorescence imaging, it was observed that LNT-SeNPs were extensively taken in by tumor cells with the assistance of TNF- α , achieving precise localization in CEST MRI images. Furthermore, continued cultivation of tumor cells demonstrated that LNT-SeNPs have excellent anticancer properties, with significant effects persisting even two weeks post-injection.

However, SeNPs do not exert exclusively positive therapeutic effects in cancer patients. Firstly, there is an overlap between their therapeutic and toxic doses, based on LD50 and NOAEL experiments in mice. Zhang et al categorized SeNPs doses into low (<200 μ g Se/kg/day), medium (200–750 μ g Se/kg/day), and high (>750 μ g Se/kg/day) groups. The results indicated that although the therapeutic effect of high doses is obvious, there is obvious toxicity. This suggests that the use of SeNPs should be considered when using them in cancer treatment.¹⁷⁹ Secondly, different tumor types exhibit

varying sensitivity to SeNPs. Elena V. Karpukhina et al compared their cytotoxic effects across four human cancer cell lines (glioblastoma, colorectal cancer, breast cancer, and prostate cancer) and found that 0.5 $\mu\text{g}/\text{mL}$ SeNPs significantly reduce glioblastoma cell viability, whereas the other three cell lines require 5 $\mu\text{g}/\text{mL}$ or higher to achieve comparable effects.¹⁹⁸ Furthermore, the intracellular redox environment is another key factor limiting the therapeutic efficacy of SeNPs. Xiong et al demonstrated that in tumor cells with a highly oxidative microenvironment, SeNPs are primarily converted into cytotoxic selenite (SeO_3^{2-}), triggering reactive oxygen species (ROS) bursts and apoptosis. But in normal cells or subsets of tumor cells in a low redox state, SeNPs are preferentially converted into non-toxic selenium-containing amino acids for selenoprotein synthesis, which may be an important factor in promoting tumor proliferation.¹⁹⁹ Additionally, due to the paucity of robust clinical research, translating SeNPs into clinical cancer therapy requires further research efforts, and continuous in-depth investigations are therefore warranted to design patient-specific SeNPs tailored to different tumor types and their distinct redox profiles, thereby facilitating the successful application of SeNPs in cancer diagnosis and treatment.

Summary and Outlook

Clinical Potential of SeNPs

With multiple advantages in antibacterial, anti-inflammatory and antioxidant, and tumor-targeted diagnosis and treatment, SeNPs have shown great potential to replace traditional therapies, especially for the early diagnosis of oral infections, inflammation, and tumors. (Figure 5) In terms of antibacterial, SeNPs can not only be used as an auxiliary sterilization method for periodontitis and other diseases, but also may achieve rapid sterilization of oral surgical instruments, which can avoid the disadvantages of traditional sterilization methods that are time-consuming and cumbersome to operate. In terms of anti-inflammatory and antioxidant properties, SeNPs may be used as adjunctive drugs to inhibit inflammation

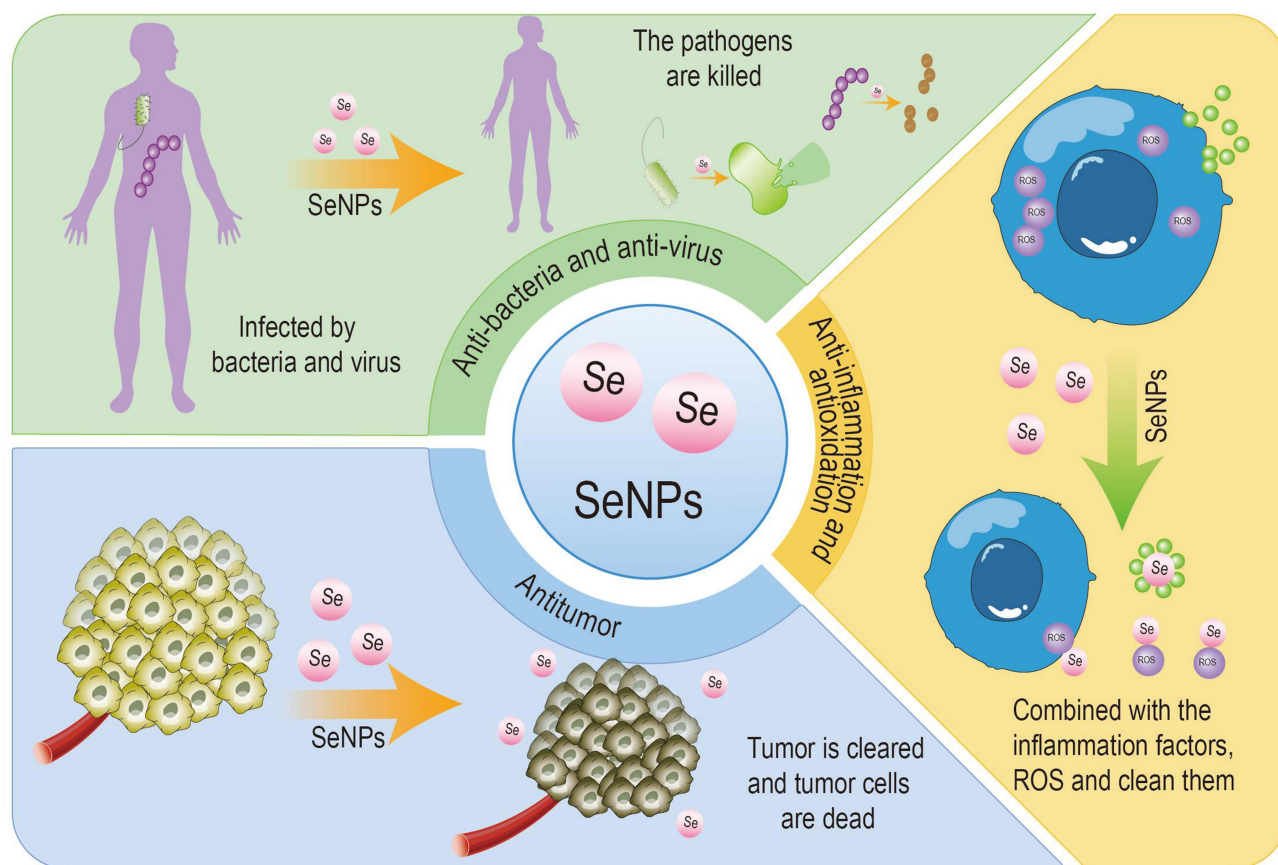


Figure 5 SeNPs have a potential application perspective in the field of antibacteria, antitumor and anti-inflammation, which may provide new directions of disease treatment.

and promote tissue repair. In addition, in the field of cancer, SeNPs are expected to become an important means of cancer diagnosis and treatment. However, most of the existing studies focus on in vitro experiments and short-term effect verification. And its insufficient stability, unclear pharmacokinetic laws, and lack of data support for long-term biocompatibility have become key obstacles restricting its use from basic research to clinical application.

Limitations on the Stability of SeNPs

At present, existing studies have obvious limitations in the stability verification of SeNPs. Most studies focus on a single environment in vitro and lack targeted consideration for practical clinical application scenarios. Due to the complex characteristics of the oral microenvironment, such as temperature fluctuations, dynamic changes in pH value, and salivary enzyme production, existing studies have not systematically verified the structural integrity and activity retention ability of SeNPs in this environment. Therefore, the complexity of the oral environment may become an important factor in the failure of SeNPs in the future. In addition, while numerous studies have employed surface modification strategies, including stabilizer coatings and inorganic encapsulation, to enhance nanoparticle stability, the majority of these investigations have focused solely on short-term efficacy, with insufficient evidence regarding long-term performance.²⁰⁰ Therefore, in practical applications, stabilizers may fail due to environmental variability, which will eventually lead to particle aggregation and settlement or even decomposition. Therefore, how to effectively improve the stability of SeNPs so that they can be better used for clinical treatment has become an urgent problem to be solved.

Limitations of SeNPs Metabolism and Biocompatibility

Drug metabolism and long-term compatibility are fundamental to the successful clinical application of therapeutics. Huang et al adopted a macrophage polarization-targeting strategy to address bone resorption studies indicate that after absorption via multiple routes, SeNPs primarily accumulate in the liver, kidneys, and spleen. Subsequently, SeNPs undergo partial conversion into Se compounds and are excreted in urine through renal metabolism. However, current pharmacokinetic research on SeNPs has predominantly focused on healthy individuals, with limited exploration in patients with oral diseases or other conditions.²⁰¹ Meanwhile, regarding concentration-dependent effects, existing studies have only confirmed the occurrence of phenomena without conducting in-depth analysis of regulatory mechanisms, action targets, or signaling pathways at different concentrations. Furthermore, biocompatibility assessments of SeNPs are mostly confined to short-term experiments, creating a significant gap in long-term safety data. Studies have demonstrated that prolonged use of SeNPs may lead to chronic inflammation and organ damage in patients, which remains the greatest obstacle to translating SeNPs from basic research to clinical practice.²⁰²

Future Research and Directions for SeNPs

Therefore, researchers must continue to advance pharmacokinetic studies on SeNPs, particularly focusing on critical clinical parameters such as optimal dosing regimens and dosing intervals, to establish a robust foundation for their clinical application in disease treatment. Additionally, the stability of SeNPs remains a pivotal factor for successful clinical translation. Researchers should deepen theoretical investigations into stabilizer mechanisms, identify the most suitable stabilizers for diverse application scenarios, and enhance the anti-degradation performance of SeNPs in complex biological environments. Concurrently, establishing a multi-scenario stability testing system is essential to systematically evaluate the long-term stability and biocompatibility of SeNPs across different conditions. Ultimately, through targeted research efforts, we aim to facilitate the transition of SeNPs from basic research to standardized clinical practice, offering safer and more effective innovative solutions for diagnosing and treating oral infections, inflammatory diseases, and tumors—thereby improving human health outcomes.

Abbreviations

SeNPs, selenium nanoparticles; NPs, nanoparticles; GPx, Glutathione peroxidase; ROS, reactive oxygen species; SeCys, selenocysteine; H₂Se, hydrogen selenide; Se⁰, elemental selenium; PLAL, pulsed laser ablation; TEM, transmission electron microscopy; SEM, scanning electron microscopy; DLS, dynamic light scattering; GSH, oxidation of glutathione; O²⁻, superoxide anions; H₂O₂, hydrogen peroxide, MSSA, *methicillin-sensitive Staphylococcus aureus*; MRSA,

methicillin-resistant Staphylococcus aureus; VRSA, *vancomycin-resistant Staphylococcus aureus*; PDT, photodynamic therapy; CFUs, colony-forming units.

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Disclosure

The authors declare that they have no competing interests in this work.

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