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Review Article

Selenium Oxide Nanoparticles as a Novel Drug Delivery System: Synthesis, Biological Properties, Therapeutic Applications, Challenges, and Future Perspectives

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Abstract

Due to their distinctive physicochemical features, high surface to volume ratio, variable surface chemistry and versatile biological functions, selenium oxide nanoparticles (SeO₂ NPs) have recently gained much interest as novel drug carriers and therapeutics. This mini-review provides a comprehensive overview of recent advancements regarding the synthesis, biological properties, applications in therapy, drawbacks and future perspectives of SeO₂ NPs. Different methods for the synthesis of SeO₂ NPs such as physical, chemical and biological approaches are elaborated upon along with their pros and cons and effect on the morphological features and biological performance of these nanoparticles. Moreover, the mechanisms associated with the antioxidative, anticancer, antibacterial, antifungal, anti-inflammatory and immunomodulatory actions of SeO₂ NPs such as regulation of the reactive oxygen species (ROS), apoptosis induction, modulation of the signaling pathways and targeted action towards diseased cells are explored in detail. Furthermore, the possible utilization of SeO₂ NPs as potential drug carriers, tissue engineering, biosensing, diagnostic imaging and environmental nanomaterials is highlighted. Nevertheless, certain drawbacks still exist that may hamper their clinical applicability, including dose dependent toxicity, lack of sufficient safety information, physicochemical instability, variability in the synthesis process, poor targeting efficacy, regulatory issues and lack of clinical trials. Future research should prioritize the development of standardized and scalable synthesis protocols, advanced surface functionalization strategies, stimulus-responsive and targeted delivery systems, comprehensive pharmacokinetic and toxicological investigations, and well-designed clinical trials. Overall, selenium oxide nanoparticles represent a versatile and innovative nanoplatform with significant potential to advance precision medicine and nanotherapeutics, provided that the existing scientific, manufacturing, and regulatory challenges are effectively addressed.

Keywords: Selenium oxide nanoparticles; Drug delivery system; Nanomedicine; Targeted drug delivery; Cancer therapy; Biomedical applications

1. Introduction

Selenium (Se) is an essential trace element with a significant impact on the body's normal functioning and human health. The element is involved in the functioning of antioxidant enzymes, the immune system, the endocrine system, reproduction, and regulation of cell death. Selenium is found in nature in inorganic forms – selenite and selenate, and organic – selenomethionine and selenocysteine. In turn, selenocysteine is part of enzymes known as selenoproteins, which protect cells from oxidative stress. Thus, this trace element is essential for the human body and has positive effects on health¹. However, an excess or deficit of selenium has a negative effect on human health. In addition, a lack of selenium can lead to the development of various diseases, such as those affecting the thyroid and cardiovascular system, weakened

immunity, and diabetes. On the other hand, excess selenium has a toxic effect on the body, leading to the development of selenosis a disease characterized by brittle nails, hair loss, coordination problems, liver and kidney dysfunction and other symptoms. Therefore, selenium must be present in the human body in optimal amounts to avoid the negative consequences of its deficiency or excess². Because of the importance of selenium for the human body and the challenges of conventional selenium compounds, there is a growing interest in developing new selenium-containing nanomaterials with enhanced physicochemical and biological properties. Nanotechnology is a promising tool for improving the therapeutic efficacy of many drugs. The use of nanomaterials in medicine allows to increase the bioavailability of drugs, increase the efficiency of their delivery to target cells and reduce side effects. It is important to note that nanomaterials are

characterized by a high surface area, increased surface activity, and unique physicochemical properties that are not inherent to conventional selenium compounds. These properties allow the use of selenium oxide nanoparticles in various fields, including biology and medicine³. Selenium oxide nanoparticles (SeO₂ nps) are considered one of the perspective nanomaterials that have found their application in the medical field. At the same time, there is still a need to study and improve the properties of SeO₂ nps. Such nanoparticles are promising tools in cancer therapy. They can inhibit tumor growth by causing cell death and have a targeted and dose-dependent effect on cancer cells by regulating the level of reactive oxygen species (ROS). Moreover, SeO₂ NPs can serve as nanocarriers for targeted drug delivery. Thus, these nanoparticles are of great interest in cancer therapy due to their ability to suppress tumor growth and as carriers of various anticancer drugs. In addition, they have antioxidant, antibacterial, antifungal, anti-inflammatory, and immunomodulatory properties and can be used in various fields of medicine, such as cosmetics, dentistry, and surgery⁴. Recently, nanotechnology has opened new horizons in cancer therapy and has become a powerful tool to fight cancer. Researchers are focusing on studying and developing new ways to use selenium oxide nanoparticles in anticancer therapy and other areas of medicine. However, there is a need for extensive preclinical and clinical trials to clarify the benefits and safety of these nanoparticles for the human body⁵. Therefore, SeO₂ NP is a multifunctional and promising nanomaterial that has found its application in different areas of biology and medicine. The current study aims to analyze the synthesis methods and properties of SeO₂ NPs, investigate their anticancer mechanisms, and evaluate their applications for drug delivery, as well as current challenges and opportunities of these nanoparticles in biomedical research⁶.

2. Selenium Oxide Nanoparticles (SeO₂ NPs)

Selenium oxide nanoparticles (SeO₂ NPs) are nanosized particles of selenium oxide that have a diameter of 1 – 100 nm. Due to their small size and high surface-to-volume ratio, SeO₂ NPs exhibit unique physicochemical properties. In recent years, there has been a growing interest in SeO₂ NPs due to their potential use in pharmaceutical and medical fields. Thus, SeO₂ NPs seem to be promising multifunctional nanomaterials for drug delivery and other biomedical applications⁷. SeO₂ NPs have many advantages and advantages over traditional selenium compounds, such as reduced toxicity and higher therapeutic efficiency with prolonged exposure. The surface of these nanoparticles can be modified to obtain targeted nanostructures with enhanced bioavailability and improved targeting properties. Such modifications allow SeO₂ NPs to specifically deliver therapeutics to tumor tissue and other target sites, while minimizing the damage to healthy cells. Another important advantage of SeO₂ NPs is their ability to regulate the level of reactive oxygen species (ROS). It is known that high levels of ROS are toxic to cells, cause oxidative stress and damage to biomolecules. At the same time, selenium oxide nanoparticles can reduce

oxidative stress and serve as antioxidant agents. Thus, SeO₂ NPs can be used as effective and safe nanomedicines that regulate the level of ROS, reduce cellular oxidative stress and protect cells from application⁸. In addition, it was found that SeO₂ NPs are promising nanomaterials in the fight against cancer. Indeed, selenium oxide nanoparticles can accumulate in tumor tissue, leading to tumor cell death. Moreover, SeO₂ NPs show the ability to induce programmed cell death mechanisms, such as apoptosis and necrosis. Targeted targeting of cancer cells by selenium oxide nanoparticles allows selective inhibition of tumor growth. At the same time, SeO₂ NPs have a selective effect on cancer cells due to the ability of these nanoparticles to control the level of ROS. The use of SeO₂ NPs is not limited to cancer therapy: these nanoparticles exhibit antioxidant, antimicrobial, antifungal, anti-inflammatory and immunomodulatory properties and can be used in cosmetics, dentistry, surgery and other branches of medicine. At the same time, the biological activity of SeO₂ NPs depends on their optical, electrical, magnetic and surface properties, which are determined by the method of preparation. Therefore, the choice of a particular method for obtaining SeO₂ NPs is of great importance for obtaining the desired morphological and structural characteristics with the corresponding properties and applications⁹.

3. Synthesis of Selenium Oxide Nanoparticles

The most commonly used methods for synthesizing selenium oxide nanoparticles can be conditionally divided into three main groups: chemical, physical, and biological (green). Each method has its advantages and disadvantages in terms of preparing nanoparticles with specific properties and morphology. Thus, choosing the right method is a key step in obtaining high-quality selenium oxide nanoparticles¹⁰. Chemical methods are the most commonly used methods for preparing SeO₂ NPs. A distinctive feature of the chemical synthesis of nanoparticles is the use of reducing and stabilizing agents to obtain the desired size and structure of particles. While allowing the targeted design of nanosized materials, such agents may be associated with additional toxicity. Physical methods allow to produce nanoparticles with high purity and specific morphology without the use of chemical additives, but they require special and expensive equipment. However, physical methods are usually more energy-intensive and complex. Green synthesis is one of the most promising ways to obtain SeO₂ NPs. Unlike classical chemical methods, green synthesis allows to obtain nanoparticles using natural reducing and stabilizing agents contained in plant extracts, bacteria and other microorganisms. The advantage of the described method is ecological safety and cost-effectiveness. Moreover, green synthesis makes it possible to reduce the toxicity of the nanoparticles obtained. Thus, the choice of the method of synthesis directly affects the properties of the nanoparticles¹¹. In this regard, an in-depth understanding of the intricacies of each of the methods is of great importance for researchers who want to obtain nanomaterials with the desired performance characteristics. Therefore, the description of various

conventional and innovative ways of preparing selenium oxide nanoparticles was given in great detail in the current study¹². Moreover, many of the reviewed methods are characterized by high energy consumption, complex and expensive equipment, and the use of toxic substances. Thus, there is a need to search for new techniques that will provide a cost-effective, reliable and safe way to produce nanomaterials¹³.

3.1 Physical Methods of Synthesis of Selenium Oxide Nanoparticles

3.1.1 Laser Ablation Method

Laser ablation is a physical technique used for the production of selenium oxide nanoparticles (SeO₂ NPs). The process involves directing a laser beam on a target of selenium in a liquid medium. The resulting plasma, formed on the target surface by the laser beam, evaporates and condenses forming nano-sized particles. The particle size is determined by laser density, wavelength, pulse duration and irradiation time. Laser ablation is a fast and simple method and does not require adding any reagents or surfactants to the reaction medium. The process is highly efficient and produces high-quality nanoparticles with good morphology. However, it has a disadvantage of requiring an expensive installation and is not suitable for large-scale production of SeO₂ NPs¹⁴.

3.1.2 Hydrothermal Method

Hydrothermal synthesis is used for the preparation of high purity crystalline selenium oxide nanoparticles. The method is based on heating water solution of Se precursors in an explosion-proof vessel made of stainless-steel and lined with Teflon. During the reaction, the solution is heated under a high pressure to a temperature at which the desired nanoparticles form. The reaction time varies from 5 minutes up to several hours depending on a number of factors including the desired particle size. The obtained nanoparticles are isolated by filtration and dried. This method allows for obtaining a high crystalline material with good particle size distribution. However, since the synthesis is performed in a special high-pressure vessel, it is regarded as less eco-friendly and complicated in terms of apparatus design¹⁵.

3.1.3 Solvothermal Method

The solvothermal method is similar to the hydrothermal one but it uses organic solvents instead of water. In this method, a raw material solution is heated in a reaction vessel under pressure so high that the solvent becomes able to dissolve minerals, oxides and salts. Since solvents like ethanol or ethylene glycol have a lower boiling point compared to water, the reaction mixture should be heated to a higher temperature so that evaporation does not occur. Using organic solvents improves the possibility to obtain materials with desired properties. The solvothermal method is more environmentally friendly compared to hydrothermal one and allows for producing nanoparticles with high crystallinity. However, the method is expensive and associated with the necessity to use high pressures¹⁶.

3.1.4 Photocatalytic Synthesis Method

This method uses light for the synthesis of SeO₂ NPs. A solution of Se ions is illuminated by UV or VIS radiation in order to provide photo-catalytic reactions necessary for the reduction of Se 6+ to Se 4+ or elemental selenium. The process is initiated by light-induced electron-hole pairs, which promotes reduction and oxidation reactions. Photocatalytic reduction is an easy and environmentally friendly method because it does not require adding reducing agents to the reaction mixture. Additionally, the reaction conditions are easily adjustable. On the other hand, the reaction rate is lower compared to chemical methods and it may require special equipment for irradiation¹⁷.

3.1.5 Physical Vapor Deposition

This method is a type of physical synthesis of SeO₂ NPs and nanoparticles in general. In this approach, the raw material (Se or SeO₂) is vaporized by heating in vacuum. The vapor phase then condenses forming nanoparticles or a thin film of the material. PVD method is used for the preparation of SeO₂ NP coatings and thin films. It has some advantages over other approaches because it allows for obtaining high purity materials with good morphology. The method is easy to control and has found its application in electronics, sensor industry and optoelectronics. At the same time, it is not suitable for biomedical purposes because it requires expensive equipment and has low productivity¹⁸.

3.2 Chemical Methods of Synthesis of Selenium Oxide Nanoparticles

3.2.1 Chemical Reduction Method

Chemical reduction is the most common method for the preparation of selenium oxide nanoparticles due to its simplicity and possibility to obtain materials with well-defined morphology and particle size. In this approach, Se precursor is reduced in an aqueous solution with the help of a reducing agent. The solution typically contains sodium selenite or sodium selenate. The most common reducing agents include sodium borohydride, ascorbic acid, hydrazine hydrate and glucose. To prevent nanoparticle aggregation, different stabilizing agents can be used, including PVP, PEG, or polyvinyl alcohol. The reduction of Se ions can be achieved by simply mixing sodium selenite solution with a reducing agent. The synthesis parameters including pH, temperature and concentrations of reagents can be varied in order to reach the desired particle size and morphology. The obtained colloidal solution is then subjected to centrifugal separation, washing and drying. Chemical reduction is an easy and fast method allowing for obtaining colloidal suspensions of SeO₂ NPs in aqueous media. However, the nanoparticles obtained by this method generally have to be purified from excess reducing agents and stabilizers¹⁹.

3.2.2 Sol-gel Method

The sol-gel method is a type of chemical synthesis of nanoparticles which is based on the formation of colloidal solution (sol) of nanoparticles. The sol is obtained by dissolution of a metal salt in water or an

organic solvent. The solution is then heated in order to obtain a gel-like consistency. The gel is finally dried and calcined in order to remove organic components resulting in the formation of SeO₂ NPs. The sol-gel method is effective in terms of producing highly crystalline and monodisperse particles with desired properties. The method requires optimization of reaction conditions, which may make it time-consuming. Nevertheless, it is applicable for the synthesis of a wide range of nanomaterials including SeO₂ NPs²⁰.

3.2.3 Co-precipitation Method

Co-precipitation is a simple, cost-effective and scalable method for the synthesis of SeO₂ NPs that does not require complex equipment. It is based on the principle of precipitation of particles from a solution. In this method, selenium salts are dissolved in water with continuous stirring. Then, a precipitating agent is added to the resulting solution in order to bring the pH to the required value. As a result, Se ions are precipitated in the form of SeO₂ NPs. The obtained precipitate is filtered and washed several times in order to remove any unwanted ions. After that, the material is dried and calcined. Co-precipitation is an easily scalable method allowing for obtaining particles with desired composition. However, the morphology of nanoparticles obtained by this method may be less controlled²¹.

3.2.4 Micro emulsion Method

The micro emulsion method makes use of micro-scaled water-in-oil or oil-in-water emulsions as nano-reactors for the synthesis of SeO₂ NPs. The method is based on the formation of Se nanocrystals within the confined environment of micelles, which are spherical aggregates formed by surfactants and co-surfactants. Micro emulsion allows for obtaining monodisperse particles with narrow size distribution. The method generally requires surfactants, making purification of resulting nanoparticles more difficult and time-consuming. However, the produced nanoparticles have good crystallinity and are suitable for biomedical applications. Micro emulsion is a promising technique for the production of high-quality SeO₂ NPs²².

3.2.5 Polyol Method

Polyol method is based on the reduction of selenium in polyhydric alcohols (ethylene glycol or diethylene glycol) acting as a solvent for the synthesis. The method is characterized by high viscosity of the medium, which decreases the possibility of nanoparticle aggregation. It allows for obtaining colloidal solutions of spherical SeO₂ NPs with good crystallinity. Synthesis in polyol is generally easier and faster compared to other chemical methods and does not require the use of additional reducing agents²³.

3.2.6 Thermal Decomposition Method

In the thermal decomposition method, Se precursor is decomposed at a relatively high temperature in order to obtain SeO₂ NPs. The thermal decomposition procedure can be performed either in solution or in the solid state. The method allows for producing high crystalline particles. However, the process is associated with the

need for high-temperature treatment thus being energy-consuming. It is less commonly used than some other methods for the production of SeO₂ NPs²⁴.

3.3 Biological (Green) Methods of Synthesis of Selenium Oxide Nanoparticles

Biological synthesis of SeO₂ NPs is a promising alternative to conventional methods. It is based on the use of biological resources such as plants, bacteria, fungi and algae as reducing and stabilizing agents. The method is regarded as more eco-friendly and cost-effective compared to conventional approaches. Different natural biomaterials such as leaves, barks and roots of plants as well as bacteria, yeasts and algae are capable of reducing and oxidizing selenium, converting its ions to nanoparticles and causing their crystallization. The use of natural resources such as plants is helpful in terms of the availability and low cost of raw materials. Additionally, plant extracts or bacterial cultures provide the possibility to obtain SeO₂NPs with good biocompatibility. The application of biologically synthesized nanoparticles is more promising in terms of pharmaceutical and biomedical development²⁵.

3.3.1 Plant-Mediated Synthesis

Plant-mediated synthesis is the most promising method among all existing approaches to SeO₂ NP production. It is based on the use of various parts of medicinal plants (leaves, stems, roots, flowers, fruits, seeds etc.) as reducing and stabilizing agents. The synthesis process usually requires extracting of active compounds from ground plant material using water or other solvents. The resultant extract is then mixed with selenium ions or a selenium salt solution so that the reduction of selenium and the formation of nanoparticles occur. Active constituents such as flavonoids, phenolics, proteids, enzymes, alkaloids, polysaccharides, and terpenoids reduce Se 6+ to lower oxidation states of selenium and stabilize the resulting nanoparticles. This method is simple, safe and suitable for large-scale production of SeO₂ NPs. Numerous plant species were found to be effective in the production of selenium nanoparticles. Among these are *Allium sativum* L., *Terminalia arjuna*, *Camellia sinensis*, *Clausena dentata* and others²⁶.

3.3.2 Bacteria-Mediated Synthesis

Bacteria are capable of reducing and oxidizing different heavy metals including selenium. Thus, it is possible to use different bacterial species for the conversion of selenium ions into elemental selenium or SeO₂ NPs. Bacteria play the role of reducing agents while their enzymes and proteins stabilize the formed nanoparticles. *Bacillus megaterium*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Ralstonia eutropha* are among the bacterial species capable of reducing Se. Bacterial-mediated synthesis of SeO₂ NPs is a promising approach but it requires specific cultivation conditions and optimization of the process²⁶.

3.3.3 Fungal-Mediated Synthesis

Fungi are regarded as effective biocatalysts for the reduction of Se ions into SeO₂ NPs. Fungal cell wall enzymes actively participate in the reduction of Se 6+ to

Se 4+ while intracellular enzymes contribute to the stabilization of nanoparticles. Fungal-mediated synthesis is a promising approach but it is associated with the necessity to culture fungi under strict conditions. Different fungal species including *Aspergillus*, *Penicillium*, *Fusarium*, *Trichoderma*, were found to be able to reduce selenium²⁷.

3.3.4 Algae-Mediated Synthesis

Marine and freshwater algae were found to have a great potential in the synthesis of SeO₂ NPs. These microorganisms contain a number of active constituents including proteins, carbohydrates, enzymes and antioxidants. Their extracts are able to reduce Se in solution and act as stabilizing agents. The synthesis of SeO₂ NPs with the help of algae is an eco-friendly approach which makes the nanoparticles more biocompatible²⁸.

3.3.5 Yeast-Mediated Synthesis

Yeast cells are able to reduce Se 6+ to elemental selenium with the production of SeO₂ NPs. Selenium interacts with yeast cell wall proteins and polysaccharides thus influencing the shape and size of nanoparticles. Yeast-mediated synthesis is a promising but less explored method which allows for producing stable SeO₂ NPs with a narrow particle size distribution. This method can be considered as a viable alternative to chemical and plant-mediated methods²⁶.

3.3.5.1 Advantages and Limitations of Biological Synthesis

1. Biological synthesis offers a number of advantages compared to conventional methods.

2. The production of SeO₂ NPs is simple and does not require expensive apparatus or additional chemical reagents.

3. The method is safe and eco-friendly and can be used for the large-scale production of nanoparticles.

4. Biologically synthesized SeO₂ NPs have good biocompatibility which makes them suitable for biomedical and pharmaceutical development.

5. The synthesis process may be time-consuming. Moreover, biological synthesis may not provide the necessary control over the physicochemical properties of nanoparticles.

However, given the numerous advantages over other methods, biological synthesis presents a great opportunity for the development of SeO₂ NPs as an effective drug delivery vehicle and tool in cancer therapy^{28,29}.

4. Mechanism of Selenium Oxide Nanoparticles

4.1 Mechanism of Antioxidant Activity of Selenium Oxide Nanoparticles

Selenium oxide nanoparticles are potent antioxidants that modulate cellular redox homeostasis and protect cells from oxidative damage. Oxidative stress is a condition that occurs due to an imbalance between the production of reactive oxygen species (ROS) and antioxidant defense system leading to cellular damage. High levels of ROS cause damage to lipids, proteins, DNA, and mitochondria resulting in cellular malfunction and death. The antioxidant effect of selenium oxide nanoparticles is achieved through the regulation of endogenous antioxidant enzymes such as glutathione peroxidase and thioredoxin reductase, scavenging of free radicals and reactive oxygen species, regulation of lipid peroxidation and maintenance of mitochondrial membrane potential, and restoration of glutathione levels. This review highlights the antioxidant action of selenium oxide nanoparticles and their therapeutic applications^{30,34}.

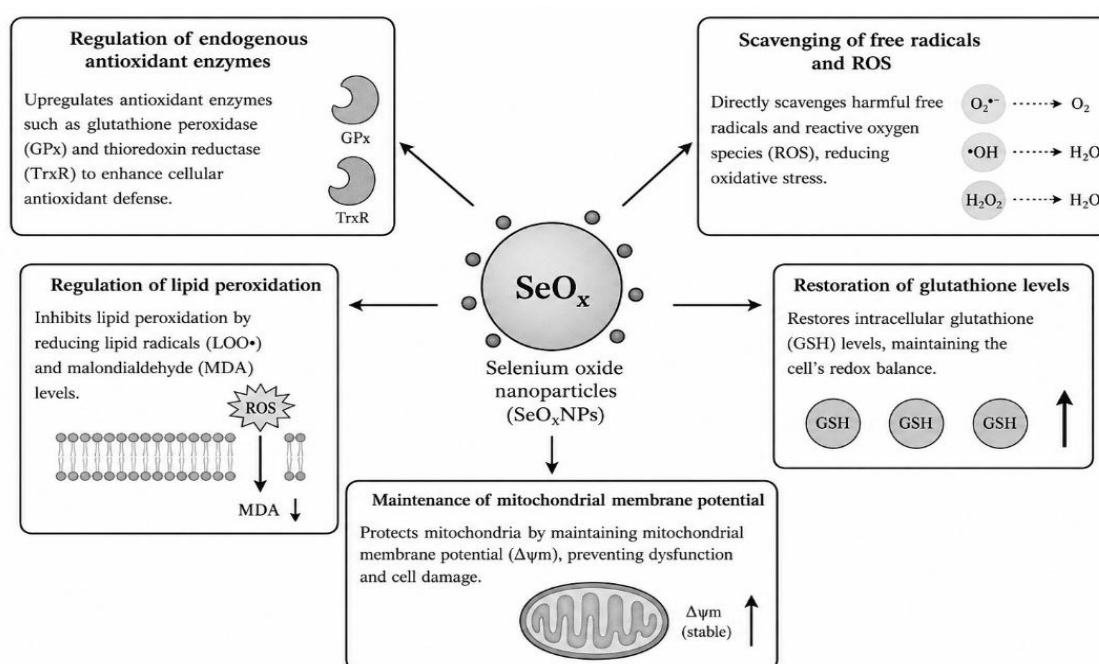


Figure 1: Antioxidant Mechanisms of Selenium Oxide Nanoparticles

4.2 Mechanism of Anticancer Activity of Selenium Oxide Nanoparticles

Selenium oxide nanoparticles have demonstrated significant anticancer effects. The mechanism of their anticancer activity is multifaceted and includes inducing oxidative stress by generating reactive oxygen species (ROS), causing mitochondrial dysfunction, regulating cell cycle progression, inhibiting tumor angiogenesis, promoting apoptosis, suppressing metastasis, modulating p53, Akt, and MAPK signaling pathways, and targeting cancerous cells with minimal damage to normal cells. Therefore, selenium oxide nanoparticles can be used to combat oxidative stress in patients with cancer, neurodegenerative diseases, diabetes, cardiovascular diseases, and other pathological conditions³¹.

4.2.1 Applications of Selenium Oxide Nanoparticles (SeO₂ NPs)

1. Selenium oxide nanoparticles have become an emerging class of nanomaterials with unique physicochemical properties.
2. The unique structural characteristics and biological activity of selenium oxide nanoparticles have triggered extensive research on their biomedical applications.
3. Selenium oxide nanoparticles have the potential to serve diverse pharmaceutical, medical, agrochemical, environmental, and electronic applications^{32,33}.

4.3 Antimicrobial Activity of Selenium Oxide Nanoparticles

Selenium Oxide nanoparticles demonstrate remarkable antimicrobial activities against a wide range of Gram-positive and Gram-negative bacteria. As such, they can be utilized as antimicrobial agents to manage bacterial infections in human health, animal husbandry, and agriculture. Moreover, their antimicrobial activity can be applied in drug formulation, food packaging, medical devices, and water purification technology^{34,35}.

4.4 Anti-fungal Activity of Selenium Oxide Nanoparticles

Selenium Oxide nanoparticles possess outstanding anti-fungal activities against dermatophytes and *Candida* species. Therefore, they can be utilized in the

management of superficial fungal infections such as athlete's foot and oral thrush among other conditions³⁶.

4.5 Anti-inflammatory Activity of Selenium Oxide Nanoparticles

Selenium oxide nanoparticles possess anti-inflammatory properties that inhibit the production of pro-inflammatory cytokines and reduce the production of reactive oxygen species (ROS). Hence, they can be used in the management of various inflammatory conditions and diseases³⁷.

4.6 Immunomodulatory Activity of Selenium Oxide Nanoparticles

Selenium is an essential trace element with powerful antioxidant properties that play a significant role in the proper functioning of the human immune system. Selenium oxide nanoparticles modulate the immune response by enhancing the activity of immune cells, improving the production of antibodies, and boosting the production of certain antioxidant enzymes. Thus, they can be used in managing numerous immunological disorders³⁸.

5. Application of Selenium Oxide Nanoparticles

5.1 Application in Biosensors and Diagnostic Imaging

These nanoparticles possess outstanding optical properties and can be conjugated with biomolecules and fluorescent tags for use in biosensing, imaging, and diagnostics. Their small size, large surface-area-to-volume ratio, biocompatibility, and unique optical properties make them ideal diagnostic imaging agents³⁹.

5.2 Application in Tissue Engineering

Selenium oxide nanoparticles can be used in tissue engineering and regenerative medicine to repair damaged tissues and organs. They possess antioxidant, antimicrobial, and anti-inflammatory activity that accelerates the tissue repair process⁴⁰.

5.3 Photocatalytic Degradation of Organic Pollutants

Selenium oxide nanoparticles are capable of photocatalytic degradation of organic pollutants, including dyes, due to their unique optical properties and semiconducting nature. Therefore, they can be used to remove organic pollutants from waste^{38,41}.

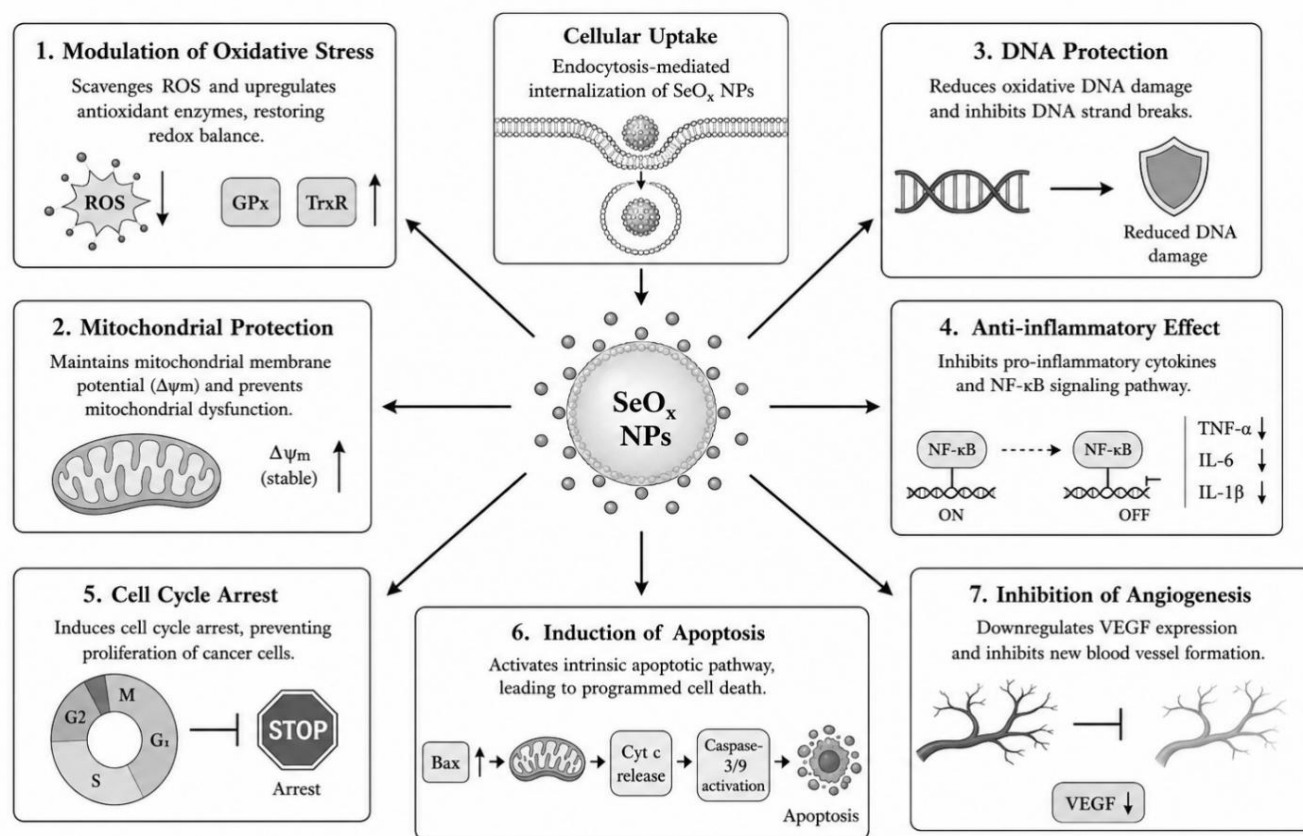


Figure 2: Mechanism of Action of Selenium Oxide Nanoparticles

5.4 Enhanced Bioavailability

Selenium oxide nanoparticles possess high surface-area-to-volume ratio and hence exhibit outstanding bioavailability and biocompatibility. This offers several advantages over selenium compounds with low surface-area-to-volume ratio³⁸.

5.5 Reduced Toxicity Compared to Inorganic Selenium Compounds

Selenium oxide nanoparticles possess reduced toxicity compared to inorganic selenium compounds. Their application allows lower doses to achieve the desired therapeutic effect while reducing adverse effects⁴².

5.6 Efficient Drug Delivery Carrier With High Drug Carrying Capacity

Selenium oxide nanoparticles have a large surface area that can be functionalized with ligands for better targeting effect. They can also be used as delivery carriers for numerous biomolecules, genes, and protein therapeutics⁴³.

5.7 Excellent Biocompatibility

Selenium oxide nanoparticles possess excellent biocompatibility and hence they are safe for human use. The modifications of their surfaces with specific ligands can enhance their targeting function as well as their effectiveness⁴⁴.

5.8 Increased Cellular Uptake and Targeting Effect

Selenium Oxide nanoparticles are of small size and hence have increased cellular uptake ability. Their tiny size enables the nanoparticles to penetrate the innermost tissues and cells to maximize their effectiveness^{44,45}.

5.9 Combination of Multiple Therapeutic Activity

Selenium oxide nanoparticles possess a wide range of therapeutic applications as they can be applied in drug delivery, tissue engineering, antioxidant, anti-inflammatory, antimicrobial, and immunomodulatory effects²⁶.

5.10 Surface Modification Potential to Increase Targeting Ability

The surface of selenium oxide nanoparticles can be modified by several other ligands and molecules to increase their targeting ability while minimizing side effects²⁶.

5.11 Wide Range of Pharmaceutical, Medical, Agriculture, and Environmental Applications

Selenium oxide nanoparticles have a wide application potential in the pharmaceutical, medical, agrochemical, and environmental sectors. Several studies are currently underway regarding the application of selenium oxide nanoparticles in clinical therapeutics, drug delivery, diagnostics, photonic devices, and semiconductors^{46,47}.

Advantages of Selenium Oxide Nanoparticles (SeO₂ NPs)

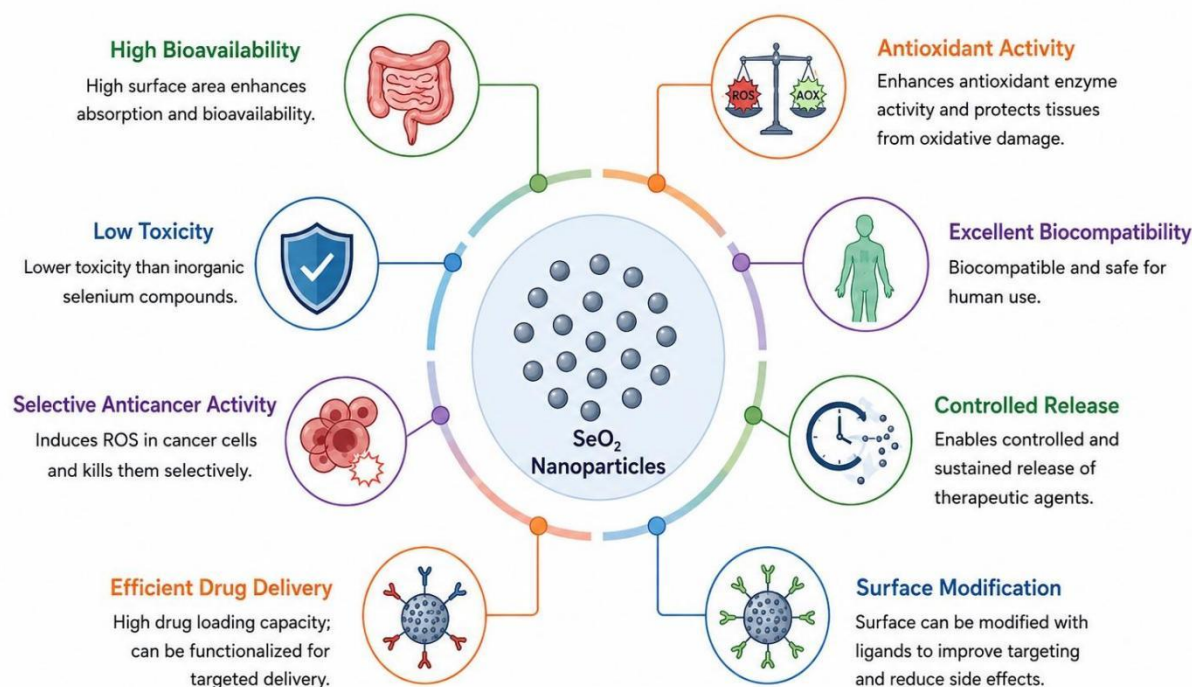


Figure 3: Advantages of Selenium Oxide Nanoparticles

Selenium Oxide Nanoparticles as a Novel Drug Delivery System

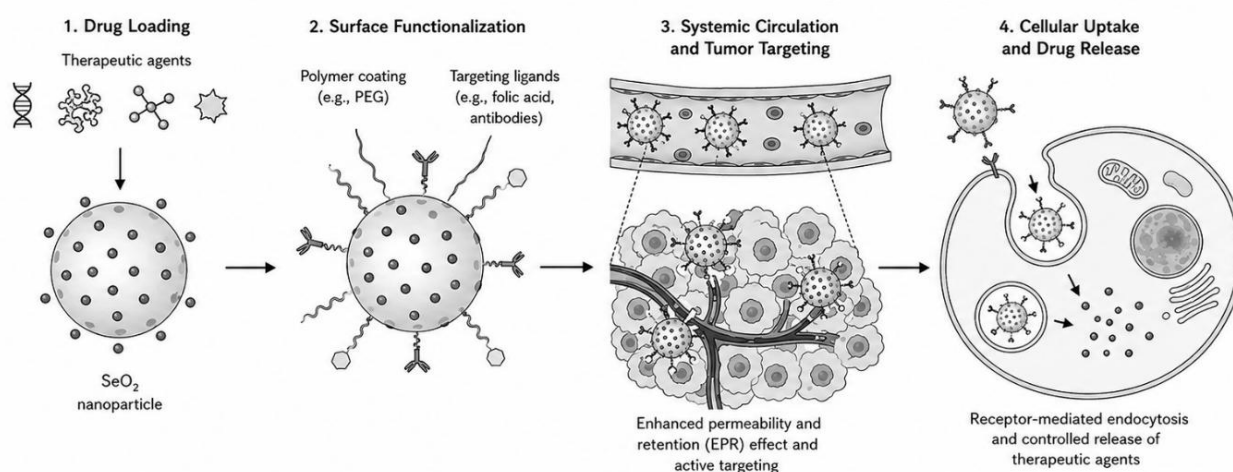


Figure 4: Selenium Oxide Nanoparticles as a Novel Drug Delivery System

6. Limitations of Selenium Oxide Nanoparticles

Despite the significant therapeutic potential of selenium oxide nanoparticles (SeO_x NPs), several limitations hinder their successful clinical translation and large-scale pharmaceutical application. Addressing these challenges is essential to ensure their safety, efficacy, and reproducibility. One of the primary concerns associated with selenium oxide nanoparticles is their **narrow therapeutic window**. Selenium is an essential trace element; however, the margin between its beneficial and toxic doses is relatively small. Excessive exposure to selenium oxide nanoparticles can induce oxidative stress, mitochondrial dysfunction, DNA damage, inflammation, and apoptosis in normal cells,

thereby limiting their therapeutic application. Consequently, careful optimization of dosage and treatment duration is necessary to maximize therapeutic efficacy while minimizing toxicity⁴⁸. Another important limitation is the **limited understanding of long-term biosafety**. Although numerous in vitro and animal studies have demonstrated promising antioxidant, antimicrobial, and anticancer activities, comprehensive investigations on chronic toxicity, immunogenicity, reproductive toxicity, and long-term organ accumulation remain scarce. Furthermore, the pharmacokinetic profile of selenium oxide nanoparticles, including their absorption, biodistribution, metabolism, and excretion, has not been

fully elucidated, making clinical dose prediction challenging⁴⁹. The **physicochemical stability** of selenium oxide nanoparticles also remains a concern. Nanoparticles are prone to aggregation during storage and upon exposure to physiological fluids because of their high surface energy. Aggregation can alter particle size, reduce colloidal stability, decrease cellular uptake, and ultimately diminish biological activity. Surface modification using polymers or biomolecules may improve stability; however, standardized stabilization strategies are still lacking⁵⁰. **Reproducibility of nanoparticle synthesis** presents another significant challenge. The biological activity of selenium oxide nanoparticles is strongly influenced by their size, morphology, crystallinity, surface charge, and oxidation state. Variations in synthesis methods often result in batch-to-batch inconsistencies, affecting therapeutic performance and limiting reproducibility across different studies. Therefore, the development of standardized, scalable, and reproducible synthesis protocols remains an important research priority⁵¹. Although selenium oxide nanoparticles exhibit selective cytotoxicity toward various cancer cells, **off-target toxicity** cannot be completely eliminated. At elevated concentrations or prolonged exposure, these nanoparticles may also affect healthy tissues, particularly the liver, kidneys, and nervous system. This limitation highlights the need for targeted drug delivery strategies capable of enhancing selective accumulation at diseased sites while minimizing systemic exposure⁵². Another challenge is the **lack of efficient targeting capability**. Native selenium oxide nanoparticles generally distribute non-specifically after systemic administration, resulting in limited accumulation at the target tissue. Functionalization with antibodies, peptides, aptamers, or other targeting ligands has shown promise in improving tissue specificity, but these approaches remain largely at the experimental stage⁵³. The **regulatory landscape** for selenium oxide nanoparticle-based therapeutics is also underdeveloped. There are currently no universally accepted guidelines governing nanoparticle characterization, toxicity assessment, manufacturing quality, or clinical evaluation. Regulatory uncertainty significantly delays the translation of laboratory findings into approved pharmaceutical products⁴⁸.

Finally, **clinical evidence remains limited**. The majority of available studies are confined to in vitro experiments and animal models, with only limited clinical investigations assessing the safety and therapeutic efficacy of selenium-based nanomaterials. Large-scale, well-designed clinical trials are therefore required before selenium oxide nanoparticles can be routinely incorporated into clinical practice⁵⁴. Overall, while selenium oxide nanoparticles demonstrate considerable promise as multifunctional nanotherapeutics, several critical challenges—including dose-dependent toxicity, limited long-term safety data, physicochemical instability, synthesis variability, off-target effects, inadequate targeting efficiency, manufacturing constraints, regulatory uncertainties, and the lack of clinical validation—must be addressed.

Future research should focus on developing stable and reproducible formulations, improving targeted delivery systems, conducting comprehensive pharmacokinetic and toxicological evaluations, and establishing standardized regulatory frameworks to facilitate the successful clinical translation of selenium oxide nanoparticles.

7. Future Directions of Selenium Oxide Nanoparticles

The application prospects of selenium oxide nanoparticles (SeO₂NPs) in nanomedicine are indeed promising, although they require further preclinical and clinical investigation. First, it is critical to perform in-depth studies to fully explore their therapeutic potential and optimize the design for each specific disease. To make these nanomaterials more effective and reduce their harmful effects on the body, they must be modified with targeting ligands, such as antibodies or peptides, to specifically recognize and bind to tumor cells. Moreover, smart SeO₂NPs capable of triggered release of their content can potentially be created by introducing specific stimuli-responsive elements on their surface. Furthermore, there is great potential in combining different treatment modalities, such as radiotherapy, photothermal, immunotherapy, gene therapy, and chemotherapy, with SeO₂NPs as nanocarriers to synergistically fight cancer and overcome multidrug resistance. One of the promising research directions includes the development and application of SeO₂NPs-based theranostic nanoplatforms that can simultaneously deliver therapeutics and monitor the treatment process. In the future, it is of paramount importance to evaluate the toxicity, biodistribution, pharmacokinetics, and overall safety profile of SeO₂NPs through extensive preclinical trials and carefully designed clinical investigations. Moreover, attention should be drawn to their technological development; therefore, optimizing the preparation protocols and making the manufacturing process cost-effective and scalable are crucial steps for translating research results into clinical practice. Finally, the applications of SeO₂NPs should not be limited to cancer treatment but should also include other diseases, such as infections, neurodegenerative disorders, cardiovascular diseases, and many others.

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