

Anticancer Properties Of Selenium: Mechanisms, Applications, And Future Perspectives

Anwesa Dutta¹, Pritha Pal^{2*}

¹M.Sc. student, Department of Biotechnology, School of Life Sciences, Swami Vivekananda University, Barrackpore, West Bengal, 700121

²Assistant Professor, Department of Microbiology, School of Life Sciences, Swami Vivekananda University, Barrackpore, West Bengal, 700121

*Corresponding author at: Department of Microbiology, School of Life Sciences, Swami Vivekananda University, Barrackpore, West Bengal, 700121. Corresponding Email: prithap@svu.ac.in

ABSTRACT

Selenium, a crucial trace element, has garnered attention for its potential to inhibit cancer. Its various biological effects, including redox regulation, immunological modulation, and selective cytotoxicity, render it a cancer preventive and therapeutic agent. Selenium compounds such as selenomethionine, selenite, and selenium nanoparticles have demonstrated the ability to induce apoptosis, suppress cell proliferation, and modify oxidative stress pathways in breast, prostate, and lung malignancies. Evidence indicates that selenium functions synergistically with selenoproteins, as these molecules support cellular homeostasis and inhibit tumor development, hence augmenting selenium's anticancer efficacy. Toxicity in a dose-dependent manner, inconsistent bioavailability, and varying clinical outcomes provide challenges that necessitate further exploration. This study elucidates the underlying mechanisms of action for the anticancer effects of Selenium, its clinical indications, and future prospects, particularly focusing on Selenium-based nanotherapeutics and their application in personalized medicine.

Keywords: *Selenium, Anticancer Properties, Chemoprevention, Redox Regulation, Selenoproteins, Apoptosis*

INTRODUCTION: Due to the challenges in monitoring and treating the disease, cancer remains one of the leading causes of mortality worldwide. Moreover, with surgical intervention, chemotherapy, radiation, and receptor modification therapy are commonly employed modalities for cancer treatment, despite their potential for significant adverse effects. The motivation generated by such constraints will be the pursuit of novel medicinal agents, particularly those derived from natural sources or dietary components, which are regrettably less hazardous. Selenium, a significant non-metal, has emerged as a possibility for cancer prevention and treatment among other substances. The incorporation of selenoproteins into specific selenoproteins, vital for antioxidant defense and immunological modulation, facilitates the maintenance of cellular homeostasis and redox buffering, with selenium serving this function. Population and cross-sectional studies have demonstrated a substantial connection between selenium concentration and cancer incidence rates, indicating its potential utility as an anticancer agent.

Selenium combats malignancies by mediating many activities, including oxidative stress, inducing apoptosis, and inhibiting cell proliferation. It possesses the distinctive capability of operating on a substantial tumor while preserving the adjacent healthy cells. Selenomethionine, sodium selenite, and selenium nanoparticles have demonstrated efficacy in both clinical and preclinical investigations and may be utilized in conjunction with several other cancer therapies. This review aims to elucidate the anticancer properties of selenium, focusing on its mode of action, applications in oncology, and inherent limits. It also examines selenium-based methodologies in personalized medicine and proposes potential applications for cancer treatment in the future.

Roles of Selenium in Cancer Prevention and Therapy		
Role	Mechanism/Function	Examples/Implications
Oxidative Stress Regulation	Neutralizes reactive oxygen species (ROS)	Prevents DNA damage and reduces tumor progression.

Redox Balance Maintenance	Incorporation into selenoproteins (e.g., GPxs, TrxRs)	Protects cells from oxidative damage and maintains cellular homeostasis.
Apoptosis Induction	Triggers programmed cell death in cancer cells	Selective targeting of tumor cells without harming normal cells.
Cell Proliferation Inhibition	Disrupts cell cycle and inhibits tumor growth	Effective against various cancers, including breast, prostate, and lung.
Immune Modulation	Enhances immune system activity	Promotes immune surveillance and destruction of cancer cells.
Anti-inflammatory Effects	Reduces inflammation-associated tumorigenesis	Limits tumor microenvironment conducive to cancer growth.
Gene Regulation	Influences DNA repair and gene expression	Reduces genetic instability and supports therapeutic outcomes.

Table. 1: Roles of Selenium in Cancer Prevention and Therapy**CHEMISTRY AND BIOLOGICAL ROLES OF SELENIUM:**

Selenium is essential for biological processes and exists in various chemical forms. The chemical considerations may encompass organic forms like selenomethionine and selenocysteine, in addition to inorganic forms including selenium nanoparticles and sodium selenite. These forms enhance bioavailability and biological activity across different physiological processes, demonstrating significant reactivity. The incorporation of this element into selenoproteins, including glutathione peroxidases (GPxs), thioredoxin reductases (TrxRs), and iodothyronine deiodinases, plays a crucial role in maintaining redox

homeostasis, supporting oxidative defense mechanisms, and regulating hormone metabolism within the body. Selenium encompasses a wide array of biological properties, including its roles in antioxidant activity and immune system modulation. This element of selenoproteins targets reactive oxygen species to maintain a stable redox state and aid in the repair of cells harmed by oxidative conditions and inflammation. In conjunction with these processes, Selenium modulates gene expression and the cell cycle, highlighting its significance in cellular stability. The significance of these properties is especially pronounced in the realm of cancer, where oxidative stress and redox dysregulation are pivotal factors in tumor progression. Selenium demonstrates its role as a preventive or mitigating agent by modifying these processes [Radomska et al. 2021].

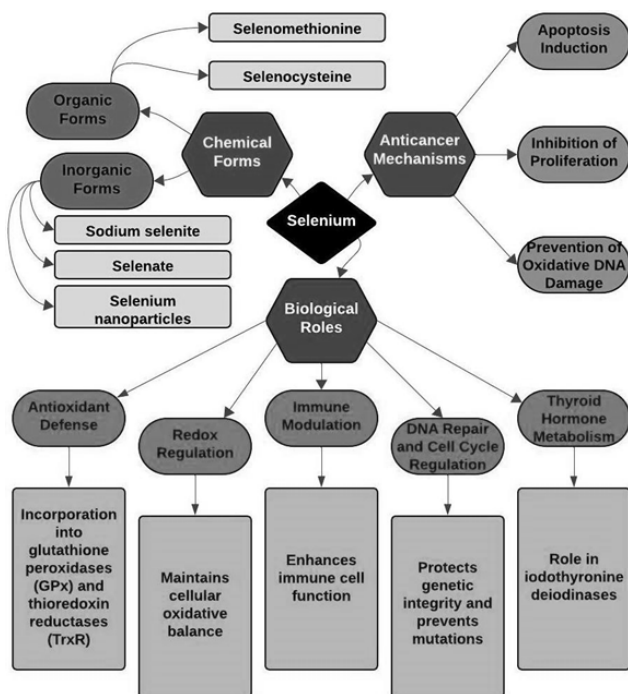


Figure 1. Chemistry and Biological Roles of Selenium

MECHANISMS OF ANTICANCER ACTIVITY:

Selenium demonstrates its anticancer properties via a variety of mechanisms, influencing several pathways that play a role in tumor development and progression.

Oxidative Stress Regulation: Selenium serves as an essential element of selenoproteins, including glutathione peroxidases (GPx) and thioredoxin reductases (TrxR), which are crucial in counteracting reactive oxygen species (ROS). Through the reduction of oxidative damage to DNA and cellular components, Selenium plays a crucial role in minimizing mutagenic events and inhibiting tumorigenesis. Furthermore, the selective cytotoxicity exhibited towards cancer cells is accomplished by restoring redox homeostasis. Selenium compounds demonstrate significant efficacy in inducing apoptosis within cancer cells. These compounds engage both intrinsic (mitochondrial) and extrinsic (death receptor-mediated) apoptotic pathways. This entails the modulation of apoptotic regulators, including the upregulation of pro-apoptotic proteins (e.g., Bax) and the downregulation of anti-apoptotic proteins (e.g., Bcl-2), resulting in programmed cell death. Selenium interferes with the growth of cancer cells by causing cell cycle arrest at critical checkpoints, including the G1/S and G2/M phases. The regulation of cyclin-dependent kinases (CDKs) and their inhibitors mediates this effect, which in turn prevents the replication of damaged DNA and restricts tumor growth.

DNA Repair and Genomic Stability: Selenium plays a crucial role in enhancing genomic stability by mitigating oxidative stress and supporting the function of DNA repair enzymes. This mechanism inhibits the buildup of mutations and chromosomal abnormalities, which are characteristic features of cancer advancement. Selenium demonstrates anti-angiogenic effects by reducing the levels of pro-angiogenic factors, including vascular endothelial growth factor (VEGF), thereby inhibiting tumor angiogenesis. The interruption in the formation of blood vessels restricts tumors from receiving vital nutrients and oxygen, consequently hindering their growth and spread.

Immunomodulation: Selenium boosts immune surveillance by elevating the activity of natural killer (NK) cells and T lymphocytes. This enhances the immune system's capacity to recognize and eradicate cancer cells. Additionally, Selenium's ability to combat inflammation contributes to the reduction of tumor-promoting inflammatory responses within the tumor microenvironment. Selenium plays a role in the expression of cancer-related genes by utilizing epigenetic mechanisms, including DNA methylation and histone modification. This approach reinstates the activity of dormant tumor-suppressor genes and inhibits oncogenes, effectively stopping the advancement of cancer. **The interaction with traditional treatments:** Selenium has shown potential in improving the effectiveness of chemotherapy and radiotherapy by making cancer cells more responsive to these treatments while safeguarding normal tissues from damage caused by therapy.

Selenium Nanoparticles (SeNPs): Recent findings indicate that Selenium nanoparticles may serve as promising targeted agents in cancer treatment. These nanoparticles exhibit enhanced bioavailability and reduced toxicity in comparison to traditional selenium compounds. They promote the highest levels of ROS production, leading to apoptosis and anti-proliferative effects in cancer cells.

The mechanisms highlighted here emphasize Selenium's promise as both a chemopreventive and therapeutic agent in the field of oncology. The capacity to selectively target cancer cells while maintaining normal cellular function positions it as a compelling subject for further exploration and potential clinical use [Kuršvietienė et al. 2020].

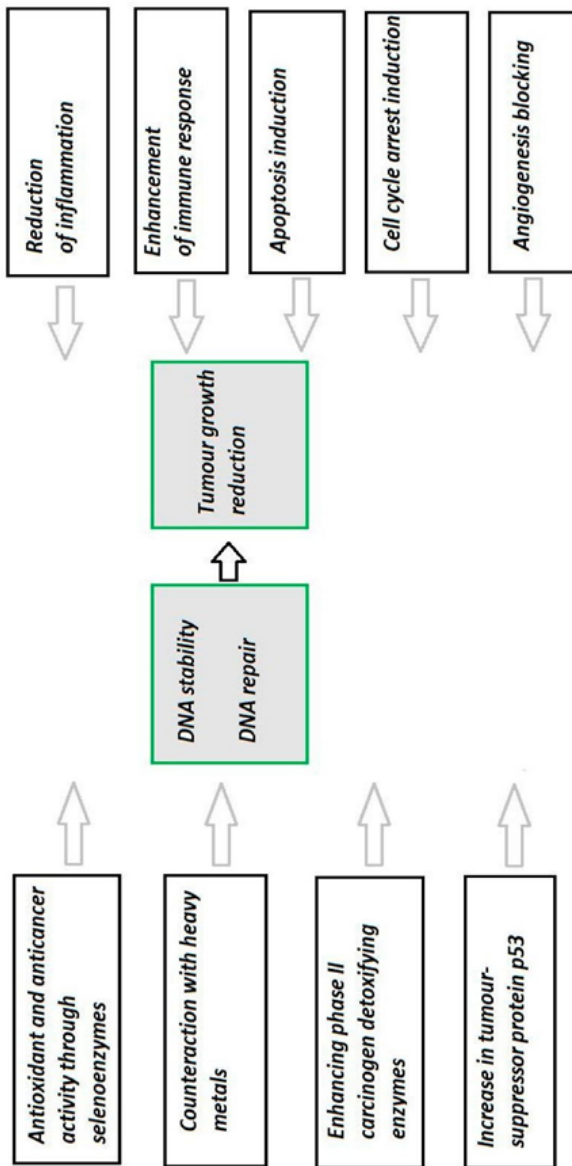


Figure 2. Anticancer effect of selenium may be asserted through various events and pathways in the cell. Data from studies [Wrobel et al. 2016, Chen et al. 2013].

SELENIUM COMPOUNDS IN CANCER TREATMENT:

Sodium selenite is frequently examined for its potential anticancer properties. The findings indicate a promising ability to induce apoptosis in cancer cells, inhibit tumor growth, and enhance the sensitivity of cancer cells to chemotherapy. Research indicates that it could improve the efficacy of standard therapies such as radiation and chemotherapy. Seleno-methylselenocysteine (SeMSC), a naturally occurring selenium compound, has been investigated for its potential to inhibit the growth of various cancer cell types, including those associated with prostate, colon, and breast cancers. The mechanism is thought to involve the modulation of antioxidant pathways, inhibition of DNA damage, and regulation of tumor suppressor genes. Methylseleninic Acid (MSA) represents a selenium-based compound that exhibits noteworthy anticancer properties. Evidence indicates that it can trigger cell cycle arrest, apoptosis, and autophagy in cancer cells. It has shown synergistic effects when used alongside other chemotherapeutic agents, boosting their anticancer activity [Gandin et al. 2018].

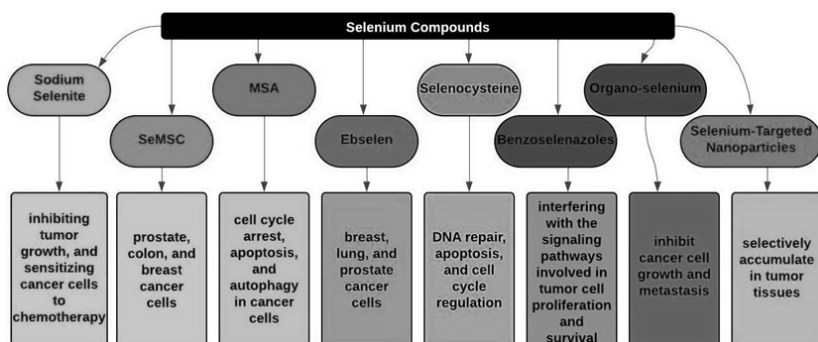


Figure 3. Selenium Compounds in Cancer Treatment

Ebselen is a synthetic organoselenium compound known for its anti-inflammatory, antioxidant, and anticancer properties. This has been examined for its potential to suppress tumor growth and trigger apoptosis in various

cancer cell lines, such as those from breast, lung, and prostate cancers. Selenocysteine (Sec), the amino acid variant of selenium, has been investigated for its possible applications in cancer treatment. This substance exhibits properties that combat oxidative stress and cancer, playing a crucial role in numerous cellular mechanisms, including the repair of DNA, programmed cell death, and the regulation of the cell cycle. Certain investigations indicate that it could be effective in focusing on cancer cells while preserving healthy cells. Benzoselenazoles represent a category of selenium-containing compounds that exhibit notable anticancer properties. These compounds are thought to disrupt the signaling pathways that play a role in the proliferation and survival of tumor cells. Organo-selenium compounds such as Selenium-containing Phenols and Thiophenols have been studied for their potential to inhibit the growth and spread of cancer cells. These compounds frequently function by triggering oxidative stress or influencing critical molecular targets that play a role in cancer advancement. Nanoparticles that incorporate selenium have surfaced as an innovative strategy for the targeted delivery of drugs in the treatment of cancer. The design of these selenium-based nanoparticles allows for selective accumulation in tumor tissues, which enhances the bioavailability of selenium and minimizes systemic toxicity [Shelar et al. 2021].

LIMITATIONS AND CHALLENGES:

Selenium Toxicity and Dose-Dependent Effects: Selenium compounds exhibit dose-dependent toxicity, with elevated dosages potentially resulting in selenosis, a manifestation of selenium poisoning characterized by symptoms including nausea, vomiting, alopecia, and neurological impairment. The distinction between therapeutic and hazardous levels is crucial, and precise dosing is essential to optimize efficacy while preventing unwanted effects. Prolonged consumption of selenium at elevated levels can result in toxicity, hence restricting its extended application as a therapeutic agent. This is a problem in formulating effective treatment protocols that reconcile anticancer advantages with potential hazards. At elevated quantities, selenium compounds are poisonous

and adversely affect organs including the kidneys, liver, and skin. A significant problem has been determining the correct dosage for clinical use without inducing toxicity.

Variability in Outcomes Due to Selenium Form, Dose, and Cancer Type:

The anticancer efficacy of selenium is contingent upon its chemical form. Organic selenium compounds, such as Selenomethylselenocysteine and Methylseleninic acid, may exhibit greater bioavailability and distinct effects relative to inorganic forms such as sodium selenite. This diversity influences their efficacy across various cancer types. The ideal selenium dosage for anticancer efficacy differs among individuals and is contingent upon the specific cancer type. The response of different cancer types to selenium may vary, and the required therapeutic dose for efficacy differs significantly, complicating the establishment of an optimal therapy plan. Various cancer types may exhibit differing levels of reactivity to selenium compounds. Selenium may exhibit a superior inhibitory impact on prostate cancer while demonstrating reduced efficacy in other cancer types, such as breast or lung cancer. This diversity hinders the advancement of broad-spectrum selenium-based cancer treatments. Variations in genetics, metabolism, and personal health circumstances may influence a patient's response to selenium-based therapies. This complicates the prediction of selenium therapy outcomes in various people, even with identical cancer types.

Gaps in Clinical Data and Translational Challenges:

Notwithstanding encouraging preclinical results, the clinical evidence endorsing the application of selenium compounds in cancer therapy remains insufficient. There is an absence of extensive, well conducted clinical trials that conclusively demonstrate the efficacy and safety of selenium-based treatments for cancer. Clinical investigations on selenium have frequently yielded inconclusive results, with certain studies indicating favorable effects, while others demonstrate no significant influence or even negative effects. This contradiction obstructs the broad practical implementation of selenium as a conventional anticancer treatment. Although

considerable knowledge exists regarding the anticancer characteristics of selenium compounds at the cellular level, the exact molecular processes via which selenium operates remain inadequately elucidated. Deficiencies in mechanistic comprehension hinder the optimization of treatment regimens and restrict the capacity to anticipate selenium’s behavior in a therapeutic context. Numerous preclinical studies have demonstrated encouraging outcomes with selenium in animal models; however, the application of these results to human cancer treatment has been difficult. The dose, absorption, and toxicity characteristics of selenium might vary considerably among species, complicating the straightforward application of animal studies to human therapy. The regulatory licensing process for selenium compounds in oncological therapy presents an additional barrier. As selenium is classified as a dietary supplement rather than a typical pharmaceutical, the process of obtaining regulatory approval for selenium-based medicines can be intricate and protracted [Garcia-Oliveira et al. 2021].

LIMITATIONS AND CHALLENGES	
Limitation/ Challenge	Description
Selenium Toxicity	High doses of selenium can lead to toxicity, including symptoms such as nausea, hair loss, and neurological damage. Toxicity risk increases with prolonged use.
Dose-Dependent Effects	Selenium has a narrow therapeutic window, making it difficult to identify the optimal dose for effective cancer treatment while avoiding adverse effects.
Variability in Selenium Forms	The effectiveness of selenium varies depending on its chemical form (organic vs. inorganic), affecting bioavailability and anticancer efficacy in different cancer types.
Cancer Type Specificity	Selenium compounds may show variable effectiveness across different cancer types, requiring personalized treatment strategies.

Patient-Specific Responses	Individual differences in genetics, metabolism, and overall health influence how patients respond to selenium-based therapies, complicating predictable outcomes.
Limited Clinical Data	There is a lack of large-scale, well-designed clinical trials to confirm the safety and efficacy of selenium compounds in cancer treatment.
Inconsistent Results in Clinical Trials	Clinical trials have yielded mixed results, with some showing benefits and others demonstrating no significant impact or adverse effects, making selenium a less reliable option.
Mechanistic Understanding	The precise molecular mechanisms by which selenium compounds exert anticancer effects are not fully understood, limiting treatment optimization.
Translation from Animal Models to Humans	Findings from animal studies may not be directly applicable to humans due to differences in metabolism, bioavailability, and toxicity profiles.
Regulatory Hurdles	Selenium is classified as a dietary supplement, not a conventional drug, complicating its regulatory approval process for cancer treatment.

Table 2. Limitations and Challenges

FUTURE DIRECTIONS:

The development of selenium nanoparticles presents a promising avenue for enhancing selenium-based therapies. These nanoparticles can be designed to specifically target tumor cells, improving the bioavailability of selenium in cancerous tissues while reducing systemic toxicity. Utilizing selenium nanoparticles for targeted delivery systems has the potential to enhance treatment effectiveness while minimizing side effects by focusing the therapeutic action directly at the tumor location. Current investigations focus on enhancing the dimensions, surface properties, and functional modifications of selenium nanoparticles to improve their efficacy in cancer targeting and

controlled release mechanisms. Progress in personalized medicine may result in selenium-based therapies that are specifically designed to align with the genetic makeup, cancer classification, and unique reactions of each patient. Investigating selenium supplementation may involve pinpointing biomarkers that can indicate the efficacy of selenium therapy in patients. By analyzing the distinct genetic and molecular traits of cancer cells, selenium supplementation can be tailored to enhance its efficacy, leading to better patient outcomes while reducing toxicity. Tailored dosing strategies and the choice between organic and inorganic forms of selenium may soon be integrated into routine clinical practice. The integration of selenium compounds with other innovative cancer therapies, including immunotherapy and gene therapy, presents a promising avenue for exploration. For instance, selenium might improve the immune response by increasing antioxidant levels or enhancing the effectiveness of immune checkpoint inhibitors. Furthermore, selenium may have a complementary effect when used alongside gene therapies designed to rectify genetic mutations or improve the body's capacity to target cancer cells. Investigating the integration of selenium with various therapeutic approaches could lead to more effective and comprehensive strategies for cancer treatment.

CONCLUSION:

Selenium compounds exhibit considerable potential as anticancer treatments; nonetheless, their clinical application encounters numerous hurdles, such as toxicity risks, dosage variability, and the necessity for more comprehensive clinical evidence. Ongoing research into new delivery technologies, such as selenium nanoparticles, and the potential for individualized treatment techniques based on individual genetic profiles present promising options for enhancing selenium's therapeutic efficacy. Furthermore, the incorporation of selenium with other medicines such as immunotherapy and gene therapy may improve therapeutic efficacy and offer a more holistic strategy for

cancer treatment. Ongoing research and development may render selenium-based therapies a significant element of individualized, targeted cancer treatment in the future.

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