

# Selenium-Enriched Microalgae: A Novel Bioactive Strategy for Immune System Enhancement

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## Abstract

**Background and Objective:** Selenium-enriched microalgae represent a promising functional food and nutraceutical resource, offering a symbiotic blend of bioactive molecules and essential micronutrients. Selenium, a trace element, is vital for immune system control, antioxidant defense systems, and cell homeostasis. Microalgae possess high nutritional value and rapid growth capabilities, allowing them to bioaccumulate selenium in the form of organic compounds like selenomethionine and selenocysteine. These organic forms have increased bioavailability and reduced toxicity compared to inorganic selenium supplements. This review examines the latest advancements in the cultivation, selenium-enrichment strategies, and biological effects of selenium enriched microalgae, with a particular focus on their immunomodulatory properties.

**Results and Conclusion:** The review highlights the potential applications of selenium enriched microalgae in disease prevention, immunotherapy, and functional food development. Also, the immunomodulatory effects of selenium enriched microalgae have been illustrated. Selenium and Se-enriched microalgae, due to their effective roles in enhancing immune function, reducing inflammation, and providing highly bioavailable forms of Se, hold strong potential for applications in food biotechnology and nutritional supplements. Despite existing challenges in optimizing production and clarifying mechanisms of action, the future outlook is highly promising given the growing demand for functional foods and natural health-promoting solutions.

**Keywords:** Antioxidant, Bioavailability, *Chlorella vulgaris*, functional foods, Immunomodulation, Selenium-enriched microalgae, Selenoproteins, Spirulina, Sustainable biotechnology.

### What is “already known” on this topic:

- Microalgae are rich sources of nutrients and antioxidants.
- Selenium is an essential trace element that supports immune system function.
- Previous studies indicated that algal compounds can improve immune responses, but there is limited focus on selenium-enriched microalgae.

### What this article adds:

- This study demonstrates that selenium-enriched microalgae can act as a novel and targeted bioactive strategy for immune system enhancement.
- The direct effects on immune cells and the underlying molecular mechanisms have been analyzed.
- Evidence suggests that this approach may be beneficial in supporting and modulating immune function.
- The findings highlight the potential use of selenium-enriched microalgae in the development of functional foods and nutraceuticals.

## 1. Introduction

Selenium (Se) is an essential element for the proper functioning of immune system cells, including macrophages, natural killer (NK) cells, neutrophils, and T lymphocytes. This element plays an essential role in reducing oxidative stress, inflammation, and preventing the spread of infectious diseases, especially when its serum concentration is adequately increased through the diet [1, 2]. It is involved in modulating immune and reproductive function. This micronutrient induces the production of selenoproteins, helping to protect cells against reactive oxygen species (ROS) [3]. Se primarily functions in the body as selenoproteins, which enhance the regulation of the human immune system in various ways. Immunity is one aspect of human health is influenced by Se levels and the expression of selenoproteins in the body [4].

Although the exact physiological role of Se is unknown, it has been determined that it exhibits most of its effects by being incorporated into selenoproteins. One such class of proteins is iodothyronine deiodinases, which are essential in the maturation of thyroid hormones T3 and T4. These hormones control body weight, development, and metabolism. A deficiency in Se may therefore disrupt the process of maturation of T3 and T4, leading to stunted growth. [5]. Dietary supplements containing l-selenomethionine are a source of Se for nutritional purposes that is easily absorbed and utilized by the body, approved for adult use at a dosage level of less than 250 mcg per day [6,7]. Seafood and meat are regarded as the primary sources of Se for humans, providing more than 70% of daily Se intake. In contrast, fruits and vegetables contribute only a small fraction to this consumption. Se is crucial because of its antioxidant and chemoprotective roles at low levels, offering protection against various cancers, heart diseases, and type 2 diabetes. Therefore, food systems must produce sufficient amounts of this essential trace element to ensure a daily intake of at least 40 micrograms, which supports the optimal expression of Se enzymes, and potentially up to 300 micrograms per day to lower cancer risk [8].

The availability of Se varies significantly depending on the geographical region. In some places, soil Se concentrations are limited or reduced [9]. It is reported that approximately 1 billion people worldwide are affected by Se deficiency, meaning that diets are limited to products harvested from these regions or are nutritionally unbalanced and may result in Se deficiency [10]. The global population is rapidly increasing, leading to the emergence of new diseases and placing a significant strain on healthcare systems. Therefore, it is more important than ever to research immune modulators, including Se, to tune the immune system to help combat new pathogens in a changing world [11, 12].

Essential minerals for optimal health are provided by edible plants, which are collected from the environment, namely, soils and aquatic sediments. The consumption of Se-rich plants makes this element bioavailable to humans [9]. Soils used in agriculture can be challenging to meet daily Se requirements through diet if they are low in Se. Se mineral salts are mainly used in food supplements and animal feed, and this supplementation method with sodium selenite or selenate also has disadvantages [13-15]. Today, organic Se-enriched foods, mainly plants, animals, and microorganisms enriched with Se, have been widely developed to address the problem [13]. In recent years, the production of Se-enriched microalgae has attracted much interest as an efficient and accessible method for producing organic Se [16, 17].

Microscopic algae, or microalgae, grow in freshwater and marine environments and have the capability to convert sunlight energy into chemical form. The two most notable ones are *Arthrospira platensis* (Spirulina) and *Chlorella vulgaris*. Spirulina is blue-green algae and a nutritional powerhouse containing a plethora of vitamins and polyunsaturated fatty acids and plays critical roles in nearly every activity of human life [18, 19]. Microalgae represent promising sources of bioactive compounds suitable for pharmaceutical and food uses [20]. Humans have been eating algae as a food crop and dietary supplement for thousands of years. Algae also serve as a natural carbon sequester, counteracting global warming and reducing the pressure on arable land and freshwater resources for conventional food crops. For the best nutritional composition of algae, there is a need to stress their cultivation keeping in view many environmental parameters such as pH, intensity of light, availability of nutrients, availability of CO<sub>2</sub>, temperature, and mixing conditions [21]. Microalgae, especially *Chlorella vulgaris*, are well-known as excellent sources of protein, balanced amino acids, and essential vitamins and micronutrients. Due to their high nutritional content, these microalgae are commonly consumed by humans. *Chlorella vulgaris* can absorb inorganic Se salts and convert them into protein-based compounds such as selenomethionine, selenocysteine, and methyl selenocysteine [16].

Thus, the aim of this review is to draw on scientific studies used to explore how Se-enriched microalgae modulate the immune system, providing updates on the recent advancements in this research area. This review is distinct from others due to its up-to-date and broad inclusion of all research drawn, thus giving the reader a comprehensive overview of Se-enriched microalgae immunomodulatory effects.



## 2. Types of Se-enriched microalgae

Se-enriched biomass (Se-Chlorella) can serve as both a dietary supplement and an antioxidant [16]. Food products derived from Chlorella include green tea powder, soups, noodles, bread, biscuits, ice cream, and soy sauce. Raw Chlorella is commonly offered in tablets, capsules, powders, granules, and drinks. Noodles containing 1.5% Chlorella extract are exceptionally nutritious. Adding Chlorella powder to barley bread not only enhances its nutritional content but also improves its appearance and flavor. Additionally, Chlorella is used as a food additive to enhance the taste and quality of pasta, wine, and fermented foods. With vitamins C, K, A, and E, Chlorella is valuable for pharmaceuticals, animal feed, food additives, aquaculture, and cosmetics [22].

*Chlorella* can develop under conditions of light, carbon dioxide, water, and a minimum amount of nutrients, thus its culture is easy. The life cycle of the microalga is simple while its metabolic processes are as complicated as those of superior plants, which makes it capable of synthesizing high amounts of proteins, carotenoids, vitamins, and minerals. Being so, it is a popular source of nutritious food. Among numerous species of Chlorella, *Chlorella vulgaris*, *Chlorella sp.*, and *Chlorella pyrenoidosa* are the most utilized in industrial production and scientific research [23].

Se exerts its biological effects via selenoproteins. Various microalgae, such as *Chlamydomonas*, *Volvox*,

*Ostreococcus*, *Micromonas*, and *Emiliana*, have been identified as possessing selenoproteins [24].

*Spirulina*, a type of microalgae, possesses antioxidant properties and can be fortified with Se during its growth process. Research revealed a hierarchy in the distribution of Se and the expression of selenoproteins based on the form of supplementation. Supplementing with sodium selenite enhanced glutathione peroxidases (GPx) activities and selenoprotein expression, whereas Se-enriched spirulina was more effective in restoring Se levels [5]. In 1992, the World Health Organization listed it as a future food. *Spirulina* is used as a dietary supplement due to its high protein value, vitamins,  $\beta$ -carotene, and phycocyanin-like pigments. It contains anti-inflammatory, anti-cancer, and antioxidant properties. In vivo and in vitro studies have demonstrated that spirulina supplementation can reduce markers of oxidative stress and enhance the activity of antioxidant enzymes. Also, as it matures, spirulina may be enriched with elements like Se, which is incorporated into organic molecules like selenomethionine and selenocysteine [5].

In recent years, although there has been a notable rise in algal production, it remains insufficient to satisfy the high commercial demand for biomass [21]. The dried biomass of microalgae is an excellent option for food use because of its rich nutritional content, economical processing expenses, and various health advantages [25]. Table 1 provides a summary of the types of Se-enriched microalgae.

**Table1.** Summary of Types of Se-enriched microalgae

Microalgae type	Forms / Products	Key Compounds	Applications	Special Notes
Chlorella ( <i>Chlorella vulgaris</i> , <i>Chlorella sp.</i> , <i>Chlorella pyrenoidosa</i> )	Green tea powder, soups, noodles, bread, biscuits, ice cream, soy sauce, tablets, capsules, powder, granules, drinks	Vitamins C, K, A, E; proteins; carotenoids; minerals	Dietary supplement, antioxidant, pharmaceuticals, animal feed, food additive, aquaculture, cosmetics	Easy to grow with sunlight and CO <sub>2</sub> ; improves food appearance and flavor
Microalgae with selenoproteins	<i>Chlamydomonas</i> , <i>Volvox</i> , <i>Ostreococcus</i> , <i>Micromonas</i> , <i>Emiliana</i>	Selenoproteins	Biological effects of selenium	–
Spirulina	Dietary supplement	Proteins, vitamins, $\beta$ -carotene, phycocyanin, selenomethionine, selenocysteine	Anti-inflammatory, anti-cancer, antioxidant, reduces oxidative stress, enhances antioxidant enzyme activity	Selenium enrichment with sodium selenite or organic forms; recognized by World Health Organization as a future food

## 3. Biotechnological methods for selenium enrichment (cultivation methods and genetic modifications)

The ideal harvesting process for microalgae should maintain the integrity of the composition of the biomass and facilitate effective recovery of the target product. Traditional harvesting processes involve filtration,

centrifugation, flotation, flocculation, electroflocculation, sedimentation, electrolytic treatment, electrophoresis, and magnetic separation. Incorporating an additional step of chemical or biological coagulation or flocculation into these processes can enhance the efficiency of the process as well as reduce operating expenses. Centrifugation is widely utilized for microalgae harvesting due to its effectiveness and speed in cell recovery. Centrifugation involves



centrifugal force to separate microalgal biomass from the culture medium, from which excess water may easily be drained. Centrifugation can achieve up to 98% yield, but its greatest flaws are high energy demand and the potential for cellular structure breakdown during the process [23].

Microalgae are highly efficient at fixing carbon dioxide during their growth, so they do not require arable land for cultivation. Microalgae biomass production involves three main steps: cultivation, harvesting, and processing. Among these, harvesting is particularly challenging due to its high costs, and it has a direct impact on the processing stage [26]. The harvesting stage of microalgae is crucial for its overall production. Research has shown that harvesting accounts for 20–30% of the total production cost. Key challenges in the harvesting and dewatering process include the small size of the cells (<30  $\mu\text{m}$ ), their low concentration and dilute presence in the culture medium (<1  $\text{g}\cdot\text{l}^{-1}$ ), the highly electronegative nature of the cell membrane surface, and the relatively fast growth rate of the algae. As a result, the energy required for the harvesting process exceeds the energy content of the microalgal biomass itself [26].

Coagulation using polyaluminum chloride ( $\text{Al}_2\text{O}_3$ ) and hydrophilic polytetrafluoroethylene membranes has been used as a sustainable technology for harvesting microalgae. Transparent exopolymer particles that are also produced by microalgae have been used to reduce the fouling of membranes in microfiltration. The particles prevent membrane fouling when solutions are collected through the use of the filtration-based method, hence improving filtration efficiency [26].

Microalgae possess the ability to absorb inorganic Se and combine it with amino acids to create Se amino acids, including selenomethionine, selenocystine, which are advantageous for the health of both humans and animals. Furthermore, Se can be added from a primary source to cultivate Se-enriched microalgae in domestic wastewater, which can act as a nutrient base for microalgae growth. Low levels of Se may stimulate microalgae growth. Turbidity significantly increased over the incubation period, indicating that microalgae growing in domestic wastewater treatment systems can tolerate such high Se concentrations. The removal process facilitated by microalgae in HRAP involves biomass assimilation, as microalgae can use these substances to produce cellular components, including proteins, nucleic acids, and carbohydrates [27].

A post talks about various methods of cultivation, starting with open systems using open ponds for growing microalgae. They rely on natural water and sunlight but are

prone to environmental stresses and the risk of contamination. It also talks about closed systems, which use photobioreactors or bioreactors that yield closed environments for the growth of microalgae. These closed systems are efficient and less likely to cause contamination compared to open operations. In addition to this, advanced techniques like mutagenesis and genetic alteration are also discussed, which are used in order to enhance some characteristics of microalgae to maximize biomass production and quality. The article also emphasizes the necessity of specific environmental conditions, such as pH, temperature, and light intensity, in order for maximum growth and production. Altering these can lead to increased production of Se and other secondary products. Lastly, nutrient-rich conditions are suggested as an alternate approach to enhance microalgae production. Nevertheless, it is essential to maintain adequate levels of nutrients so as not to compete with Se absorption. These culture processes enhance microalgae productivity across various industries [16]. One advantage of cultivating microalgae in a mixotrophic manner is the increased biomass production [28].

Today, with advancements in microalgae harvesting, methods such as bioflocculation, electroflocculation, bio-electroflocculation, ultrasound/hydrodynamic techniques, magnetic nanoparticle flocculation, and phototaxis-based harvesting are employed [29]. Table 2 shows biotechnological methods for Se enrichment.

#### 4. Analysis of bioavailability of selenium in microalgae

The way Se is absorbed differs among animal species and is affected by various factors, including physiological traits, functional status, the number of intestinal contents, the chemical forms of Se, the duration of Se's stay in the intestine, and the methods of Se administration. Se is mainly found in the liver, kidneys, heart, and pancreas, with muscles, bones, and blood having the following highest levels, while fat tissues contain the least amount.

Typically, in normal circumstances, the Se that animals metabolize is mainly eliminated through urine and feces. However, when Se is consumed in excessive amounts, breathing also becomes a significant pathway for its excretion. Moreover, Se can be removed from the body through hair and sweat [30].



**Table 2.** Biotechnological methods for selenium enrichment

Method / Process	Brief Description	Advantages	Disadvantages / Challenges
Centrifugation	Separation of biomass using centrifugal force; excess water is drained	High efficiency (up to 98%), fast	High energy consumption, potential cell damage
Filtration	Passing the solution through a membrane to separate cells	Simple process	Membrane fouling
Chemical Flocculation (Polyaluminum Chloride)	Adding flocculants to aggregate cells	Increased efficiency, reduced cost	Requires chemicals
Electroflocculation / Bio-electroflocculation	Using electric current or combining with biological agents for flocculation	High efficiency	Equipment cost
Magnetic Harvesting	Using magnetic nanoparticles to separate cells	Fast and efficient	Cost of nanoparticles
Phototaxis-based Harvesting	Using algae's response to light for separation	Non-invasive, low-cost	Limited to certain species
Open System Cultivation	Outdoor ponds using natural sunlight	Low cost, simple	Risk of contamination, environment-dependent
Closed System Cultivation (Photobioreactor)	Controlled growth conditions	High yield, reduced contamination	High construction and maintenance cost
Mixotrophic Cultivation	Combining light and organic nutrient sources	Increased biomass production	Requires careful nutrient control
Selenium Enrichment in Domestic Wastewater	Using wastewater as nutrient source for microalgae	Low cost, utilizes waste resources	Potential chemical or microbial contamination

The bioavailability of Se in microalgae, indicating how much Se can be absorbed in the gastrointestinal tract, was assessed in a study. Grinding the microalgae, their cell walls are broken down, facilitating the release of Se from the biomass during digestion. Under gastrointestinal conditions, 49% of Se from raw microalgae and 63% from ground Se-enriched microalgae were solubilized, indicating their potential bioavailability. A similar level of Se bioavailability (approximately 49%) has been observed in Se-enriched *Chlorella vulgaris*. Additionally, it's important to highlight that the bioavailability of Se in Se-rich yeast widely recognized as a leading organic Se supplement is generally greater than that found in microalgae cultivated in HRAP-Se. Furthermore, the type of Se also influences absorption rates [27].

The Se in food sources is mainly in organic forms, including selenocysteine and selenomethionine, which are more easily absorbed than inorganic forms like selenite or selenate. There is a significant risk of losing dietary Se during processing and cooking; for instance, the refining of grains can diminish Se levels by 50 to 75%, while boiling can lead to an additional reduction of 45%. Microalgae that utilize Sec, such as *Nannochloropsis oceanica*, can enhance the organic Se content and can thus be used as Se-enriched food or feed additives [24].

Organic Se compounds have higher bioavailability and usability than their inorganic counterparts. Studies also indicate that Se-enriched plant products usually provide greater bioavailability than animal-based products.

Moreover, adding Se to proteins can not only increase their Se content but also improve their functional qualities, including emulsion stability and gelling properties, along with enhancing their bioavailability [31].

In numerous microalgal species, selenite may exhibit greater toxicity compared to selenate, while the opposite can be true for other species. Due to its high solubility, selenate is more readily bioavailable to aquatic organisms than selenite, indicating that selenate might be the predominant dissolved form. Prior research has shown that selenate does not pose toxicity risks for some microalgal species [8].

## 5. Applications in food biotechnology development and utilization of functional foods, fortified foods, beverages, and dietary supplements

Microalgae cultivation is one factor that can enhance world food security and reduce the environmental impact of rising agricultural food production. The quality and safety of microalgae product, in turn, are both a function of proper cultivation, harvesting, and processing protocols since foreign organic and inorganic material occur as a result of environmental contamination or process operations when dealing with microalgae biomass [28].

Functional food production with microalgal biomass will see growth in the coming years as a result of growing demand for healthy foods globally. Microalgae incorporation in food products is the next wave of evolution of



the functional food industry, given that there is continuous need to search for new raw materials for use in creating new foodstuffs. Nevertheless, some of the major questions need to be answered to facilitate the successful development of microalgal-derived food products. Some of the other questions that belong to this category are how microalgal biomass interacts with the other components of the food matrix, the effect of microalgal addition on the sensory attributes of food, particularly color and flavor, textural and rheological modification of food products with microalgal addition, and changes and stability of microalgal constituents under various processing conditions [32].

Understanding the mechanisms and potential for Se accumulation in plants and animals is one of the most critical directions in developing nutritional science and supplementation [33]. To create algae-based food products and by-products, the first essential step is enhancing our knowledge of the biochemical makeup and digestibility of microalgae. In line with this, it's important to assess more microalgal species for novel food approval, ultimately supporting the broader inclusion of these microorganisms in human diets over time [34].

Numerous studies have demonstrated that microalgae species, particularly from the *Chlorella* and *Spirulina* genera, are well-suited for direct use in their natural forms. This adaptability has led to their widespread application in the food industry, where they enhance the nutritional content of products like noodles, cookies, energy bars, and juices [23]. In the food and beverage industry, as well as within the cosmetics industry, the demand for spirulina has risen due to its fat-reducing, antioxidant, and anti-inflammatory properties [35]. An article discusses the production of beverages such as "selenized kawas," made from fennel grains soaked and germinated in solutions containing  $\text{Na}_2\text{SeO}_3$ . These beverages are considered a source of Se. Regarding Se in beer, yeasts (*S. cerevisiae*) can convert inorganic Se ( $\text{Na}_2\text{SeO}_3$ ) into bioactive organic forms that are utilized in selenized beers. This process enhances the Se content in the beverages [36].

In a study, *Chlorella vulgaris* was blended into spreadable processed cheese, leading to increased magnesium, potassium, Se, Zn, iron, and antioxidant capacity, with greater enhancements observed at higher formulation levels. Microalgae were also incorporated into various snacks, breads, isotonic drinks, and yogurts; however, these products did not attract consumer interest due to their unappealing green color and distinct flavor. On the other hand, a dehydrated soup prepared with *S. platensis* concentration demonstrated improved nutritional value, including enhanced protein, fiber, chlorophyll, lipids, and antioxidant capacity, without compromising sensory acceptability in taste tests. These results underscore the need for more in-depth research on formulation strategies that

enable effective use of microalgae to enhance functionality while preserving sensory quality [32].

## 6. Enhancing food products with immune-boosting properties

Since the early 1950s, microalgae have been included in human diets. Strains like *Chlorella*, *Dunaliella*, *Haematococcus*, *Schizochytrium*, and *Spirulina* are considered safe for consumption. Consequently, various nutrients (such as lipids, proteins, carbohydrates, pigments, and vitamins from these algae) can be consumed in dried powder form. Moreover, they can be added to various food products, including biscuits, candies, snacks, pasta, and soft drinks. Incorporating nutrient-dense microalgae into staple foods like bread can improve food security and help combat malnutrition in some developing regions. Including microalgal biomass (like *Spirulina*) in snacks and beverages also offers consumers a healthier option [21].

Research indicates that Se supplementation helps maintain bone homeostasis by balancing bone resorption by osteoclasts and bone formation by osteoblasts, a process linked to the activation of the Wnt/ $\beta$ -catenin pathway. These findings highlight a promising potential for the use of Se-based treatments in addressing osteoporosis [37]. Se supplementation has demonstrated effectiveness in preventing Hashimoto's thyroiditis and hyperthyroidism. Various studies suggest that Se not only offers nutritional benefits but also provides numerous additional health advantages. It exhibits strong antiviral properties, supports reproductive health in both males and females, and lowers the risk of autoimmune thyroid disorders [38].

*Spirulina* is a form of microalgae rich in proteins, vitamins, diverse pigments, and essential minerals like Se and Zn. It is a valuable resource for therapeutic diets, known for its anti-cancer and anti-inflammatory properties, antioxidant benefits, ability to fight malnutrition, prevent anemia, and its antiviral, antibacterial, and radiation-protective effects [35]. Recent studies have also demonstrated the antibacterial activity of Se nanoparticles. The mechanisms behind Se's antimicrobial properties are not yet fully understood. It is believed that the effects are likely due to oxidative stress, damage to the bacterial cell wall, and DNA degradation [39].

Microalgae synthesize important bioactive substances, including carotenoids, polyunsaturated fatty acids, phenolic compounds, terpenes, and sulfated polysaccharides. These compounds provide various health benefits, such as antimicrobial, anti-inflammatory, anti-aging, anti-tumor, antioxidant, and immunosuppressive effects [20]. A study investigated Se-enriched feed (SeE-SP) as a dietary supplement for juvenile fish, specifically focusing on its beneficial effects on antioxidant responses, immune



function, and disease resistance in *Lates calcarifer* (Asian sea bass). The findings revealed that Se boosts antioxidant activity, producing higher levels of selenoproteins [40].

## 7. Regulatory and safety aspects for Se-enriched products

The risk of Se poisoning in animals or plants intended for human consumption is a significant concern, as Se can bioaccumulate through food chains, particularly in aquatic environments contaminated with Se. This bioaccumulation can worsen toxicity problems in natural ecosystems. Extremely high levels of Se absorption or accumulation in animals can result in reproductive issues and congenital disabilities [41].

To ensure that microalgal products are of food quality and safety, the harvesting process must maintain the nutritional integrity of lipids, proteins, pigments, and other bioactive compounds. Microalgae grown for nutrition must be harvested under minimal physical or chemical damage. Minimal processing preserves nutrients within intact cells up to product formulation and consumption levels [29].

In an experiment, *Chlorella vulgaris* and *Scenedesmus* sp. showed resilience to the tested selenite concentrations ranging from 0 to 1000  $\mu\text{g}\cdot\text{l}^{-1}$  Se. No signs of toxicity were observed in either species, even at the highest concentration of 1000  $\mu\text{g}\cdot\text{l}^{-1}$  Se, and there were no significant differences in growth compared to the control cultures. Other research has similarly highlighted the high tolerance of microalgae to Se. For instance, in one study, *Chlamydomonas reinhardtii* only exhibited stress or toxicity at concentrations exceeding 734  $\mu\text{g}\cdot\text{l}^{-1}$  Se [42]. The Se-enriched supplement in *N. Oceania* was found to be non-toxic in rats and is identified as a safe source of Se in the diet [24].

Algae's use in supplement production is influenced by geographical location, seasonal changes, and specific aquaculture practices, which can all impact its nutritional profile [36]. Additionally, concerns about the safety of algae and the presence of microcystins in *Spirulina* highlight the need for safety evaluations and quality assessments of selenized supplements and algae-containing beverages [36]. Recognizing that Se supplementation involves more than just dosage is essential; the form of Se and an individual's health status also play a critical role. Enhancing Se's bioavailability can raise its levels within the body. Currently, clinical research on optimal intake thresholds for different Se types remains limited. Organic Se typically offers greater bioavailability and lower toxicity. Cultivating foods rich in Se presents a cost-effective way to enhance dietary Se. As understanding of Se absorption and the role of selenoproteins expands, bioavailability may further improve [38].

The safety of foods derived from microalgae depends primarily on the microalgae species utilized, and regulatory

bodies around the world have established general principles for their use. Although microalgae's safety profile is becoming more and more widely accepted, the limited number of approved species is still a significant limitation in their food applications. In addition, the culture and processing conditions of microalgae—the less discussed factors also take on a critical role in their safety. Microalgae can absorb toxic substances from various sources, such as water supplies and market fertilizers. They can absorb toxic elements, such as heavy metals, dyes, and antibiotics, in certain instances from bodies of water. Furthermore, open-air farming is capable of facilitating the growth of pathogens, and faulty processing procedures such as heat processing and drying are capable of enhancing the susceptibility to polycyclic aromatic hydrocarbons [25].

Se is found in various environmental forms, with selenate and selenite being the most toxic and responsible for 95% of its overall toxicity. While it is vital to fortify Se in areas where it is deficient for human health, its levels should be minimized or eliminated in environments where Se is abundant. Se is recognized as a minor contaminant in geological water pollution, with concentrations typically ranging from 0.1 to 100 micrograms per liter. Global daily intake recommendations for Se vary: in the UK, the advised amounts are 60 micrograms for adult women and 75 micrograms for adult men. In comparison, the World Health Organization recommends a maximum of 10 micrograms per liter in drinking water. In contrast, a study from Burundi, Africa, indicated a risk of deficiency with an average dietary intake of just 17 micrograms per day. Se intake can also vary based on age and gender. However, excessive Se consumption, even at low levels beyond the safe threshold, can lead to toxicity, resulting in issues such as hair and nail loss, cancer, and potentially death [41].

Se toxicity is broadly classified into two categories—acute and chronic—based on the duration and amount of ingestion. Acute toxicity occurs when an excessive amount of Se is consumed within a short time and causes immediate adverse effects such as respiratory distress, ataxia, diarrhea, vomiting, and abdominal pain, and even death in severe cases. Unlike this, chronic toxicity of Se occurs due to gradual build-up of Se due to long-term exposure to low concentrations, which presents as fatigue, depression, breath smelling like garlic, anemia, loss of appetite, hair loss, onychomadesis, hoof rot, stunted growth, and cirrhosis of the liver. Recent research indicates that the toxicity of Se is a function of its chemical state, and the extent of its toxicity can differ in diverse animal species, their nutritional statuses, and exposure routes. In general, inorganic compounds of Se are more toxic than organic forms [30].

The influence of Se on microalgae growth can vary widely, having either positive or adverse effects. Research on Se exposure in microalgae has identified several key



factors contributing to Se toxicity. These include the type of inorganic Se present, such as selenite or selenate; the concentration of Se in the growth environment; the specific response of the microalgae species involved; and the level of sulfur in the medium. Because Se and sulfur share similar chemical properties, they enter the cells using the exact transport mechanisms, leading to competitive uptake between the elements [43].

At high concentrations, Se can act as a pro-oxidant, leading to the generation of substantial amounts of ROS that attack biomolecules such as proteins and nucleic acids. This process causes oxidative damage and can ultimately result in cell death. [44]. Acute Se toxicity in grazing animals occurs when they consume excessive amounts of accumulator plants containing high Se levels over a short period. The symptoms of Se poisoning in mammals can differ widely, including issues such as nail abnormalities, hair and wool loss, weakness, vomiting, diarrhea, fatigue, reduced cognitive function, lethargy, immobility, weight loss, itchy skin, and irritation of mucous membranes. Affected individuals may also suffer from lateral sclerosis and experience irritation in the throat and bronchial tubes [45]. Younger animals show greater sensitivity to Se toxicity, and different chemical forms of Se can result in varying toxicity levels. Beyond mammals, Se poses several harmful effects in birds, with symptoms of toxicity appearing within a few hours to several days. In avian species, these toxic effects can manifest as increased mortality, reduced growth rates, histopathological changes, and disruptions in hepatic glutathione metabolism [45].

Selenium Nanoparticles have a greater impact on organisms compared to inorganic forms of Se. Additionally, the influence of Se on health is contingent upon the individual's requirement to develop antioxidant defenses. If this need is not met, excessive Se can result in toxicity. Overall, the toxicity of Selenium Nanoparticles is often linked to Se toxicity. Most research comparing Se and Selenium Nanoparticles indicates a consensus that Selenium Nanoparticles are less toxic [45].

Alkali disease, a livestock disorder of the Great Plains of the United States, has raised concern about acute and chronic Se toxicity. Laboratory animal studies with rabbits, rats, and cats have shown that the lethal dose of Se, administered either as sodium selenite or selenate, ranges from 1.5 to 3.0 milligrams per kilogram body weight, regardless of the route of exposure. Chronic consumption of Se as little as 4-5 parts per million in feed will stunt the growth of livestock. Acute Se poisoning in livestock typically results from consumption of Se-accumulating plants or over-supplementation and is marked by severe

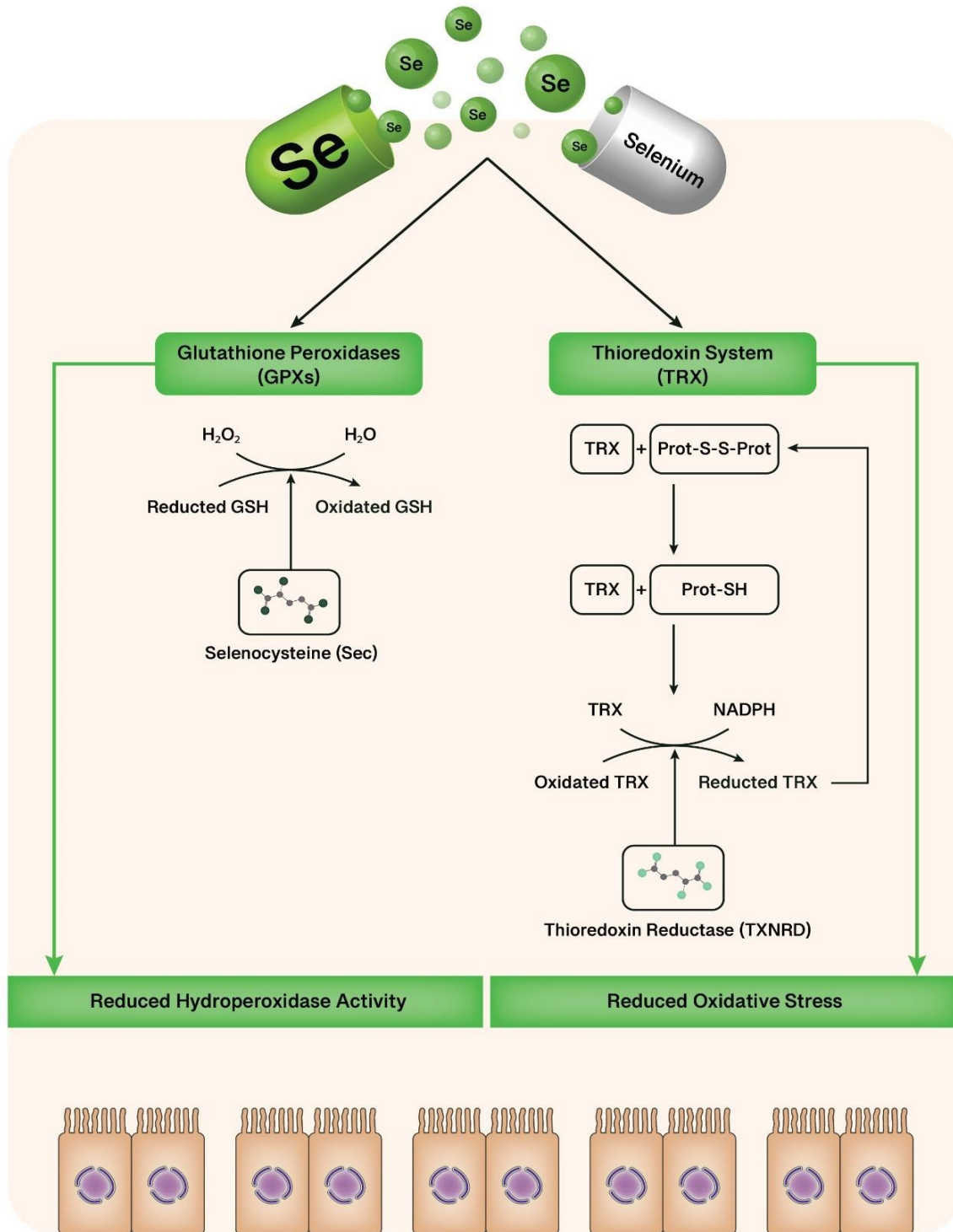
symptoms that include respiratory stress, abnormal movements, diarrhea, and, in some cases, acute death [41].

## 8. Mechanisms of immune system enhancement

Redox homeostasis is essential for the maintenance of vital cell and organism functions. Redox stress is a disturbance of the oxidative vs. antioxidative balance within a cell. This is typically marked by the production of significant quantities of ROS, more than the antioxidative defense system can clear, resulting in structural and functional damage to DNA, lipids, and proteins. Mitochondria are recognized as among the most important sources of ROS, and an excess of these molecules tends to damage mitochondrial structures. Hydroperoxides, particularly hydrogen peroxide ( $H_2O_2$ ), also serve as important ROS for redox regulation and participate in cell signaling, enzymatic reactions, energy metabolism, and the cell cycle. Excess hydroperoxides, nevertheless, can lead to non-specific oxidation of proteins and biomolecule destruction. To eliminate these hydroperoxides, effective reductive systems play a vital role. In this regard, Se is considered an essential antioxidant that helps in the removal of ROS, especially hydroperoxides, and contributes to the improvement of tissue and cellular conditions [12, 46]. This effect has been reported in the heart [46], liver [47], and kidneys [48].

One of the well-known and beneficial characteristics of Se is its antioxidant activity, which is particularly effective in countering oxidative damage at the cellular level (Figure 1). Antioxidant processes help maintain appropriate levels of ROS and reactive nitrogen species, thereby preventing oxidative damage and enhancing immune responses [49]. Oxidative stress occurs when the balance between the production of ROS and the ability of the system to neutralize them is disrupted. ROS are typically produced due to electron leakage from the mitochondrial electron transport chain and enzymes during the process of oxidative phosphorylation [50, 51]. Particular ROS is essential for the activation and differentiation of T cells, apoptosis, pathogen elimination, and other cellular signaling activities. However, excessive production of these free radicals can lead to severe cell damage, including lipid peroxidation, DNA damage, and protein degradation. Therefore, antioxidants, including Se, are crucial for counteracting oxidative damage and improving immune system function [12].





**Figure 1.** Schematic representation of the antioxidant roles of selenium via selenoproteins

Se defends cells against ROS through the mechanism of selenoproteins, which have redox activities. These proteins are able to reduce hydroperoxides in the presence of thiols and also have a pivotal role in redox homeostasis. The best-known among these proteins are GPXs (glutathione peroxidases) and the thioredoxin (Trx) system. Five of the eight human GPX types are selenoproteins, and Se is found

in the active site of these proteins. These proteins are particularly involved in the detoxification of hydroperoxides and, consequently, oxidative stress. The GPXs' active site contains a conserved structure made up of Se, glutamine, tryptophan, and asparagine. These Se residues could be oxidized with hydroperoxides to produce selenic acid or selenoamide products that are then reduced

quickly to selenate by thiols. Since Se residues are extremely reactive, GPXs react immediately, especially in the case of reaction with  $H_2O_2$ , reducing its cellular level. GPX1 was the first mammalian selenoprotein discovered and is referred to as an essential protein in mitochondria and the cytoplasm. The enzyme uses glutathione to reduce hydroperoxides and is extremely sensitive to Se levels. GPX2, with substrate-like properties of GPX1, is found mainly in the mucosal membrane of the gastrointestinal tract and endothelial cells and plays a role in regulating mucosal homeostasis and intestinal cell turnover. Interestingly, GPX2 expression is reduced only in patients with Se deficiency of a high grade. GPX3 is a glycoprotein located outside cells that is able to decrease hepatic glutathione oxidation, Trx, and glutaredoxin and is found importantly in white and brown adipose tissue. GPX4 is the only isoform with a capacity to decrease phosphatidylcholine hydroperoxides and has a distinctive function of protecting cells against oxidative damage in mitochondria. Antioxidant defense also plays a significant role in the Trx system, comprising nicotinamide adenine dinucleotide phosphate, Trx, and thioredoxin reductase. Trx acts by transferring electrons to thioredoxin peroxidases and converting oxidized Cys disulfides or Cys-SOH residues in proteins to thiols. In addition, Trx is able to engage in the formation of intracellular gradients of  $H_2O_2$ . Thioredoxin reductase, being an oxidoreductase enzyme, employs nicotinamide adenine dinucleotide phosphate as a co-substrate to reduce oxidized Trx, and its activity plays an important role in controlling redox reactions. The system also participates in the reduction of methionine sulfoxide reductases and ribonucleotide reductases and controls activities of redox-sensitive transcription factors like AP-1 and NF- $\kappa$ B. Overall, the GPX and Trx systems with their antioxidant functions are crucial in cellular protection and maintain redox homeostasis, finally safeguarding cells from oxidative damage and functioning normally. Se in the body primarily exerts its action through selenoproteins, which carry out many antioxidant functions. Selenoproteins contain GPXs and thioredoxin reductases, neutralizing harmful free radicals by reduction reactions. For example, GPXs catalyze the reduction of water and oxygen from  $H_2O_2$ , while GPX4 reduces membrane lipid hydroperoxides. Additionally, thioredoxin reductases reduce disulfides of proteins [52-55].

Se exerts its cellular antioxidant defense primarily through two key selenoprotein systems: GPXs and the Trx system. GPXs catalyze the reduction of  $H_2O_2$  and lipid hydroperoxides by utilizing glutathione as a reducing agent, thereby preventing oxidative damage to cellular macromolecules. This enzymatic activity depends on the presence of selenocysteine at the active site. Concurrently, the Trx system maintains redox homeostasis by reducing oxidized Trx through thioredoxin reductase in a

nicotinamide adenine dinucleotide phosphate-dependent manner. Reduced Trx subsequently facilitates the conversion of protein disulfides (Prot-S-S-Prot) back to their thiol forms (Prot-SH), preserving the functional integrity of cellular proteins. Collectively, these mechanisms contribute to the detoxification of hydroperoxides and the mitigation of oxidative stress, thereby safeguarding cellular integrity and function. However, when these antioxidant processes are under stress, the risk of various diseases such as cancers, neurodegenerative diseases, fertility problems, and kidney disorders increases [55].

Studies have shown that Se can effectively enhance antioxidant activities and improve immune function. For example, in a study on pigs, supplementation with organic Se (4-methylselenobutanoic acid, HMSeBA) led to an increased expression of GPXs and thioredoxin reductases in various tissues, and a reduction in malondialdehyde levels, which is an indicator of lipid peroxidation. Additionally, the study showed that Se supplementation reduced the levels of inflammatory cytokines IL-6 and TNF- $\alpha$  while increasing IL-2 levels in the pigs [56].

These results suggest that Se may effectively help counteract oxidative and inflammatory damage and improve immune function. Similar studies have also been conducted on chickens and fish. In one study on chickens, Se deficiency led to a significant reduction in the expression of selenoproteins in the thymus, spleen, and bursa of Fabricius [54]. Additionally, feeding chickens yeast-derived Se increased the expression of genes related to antioxidant selenoproteins in the intestines [57]. In another fish experiment, feeding with organic, inorganic, or nano Se resulted in a decrease in serum malondialdehyde levels and an increase in the levels of antioxidant enzymes such as GPX, Catalase, and Superoxide dismutase [58].

While similar results in other studies indicate the need for a thorough evaluation of different Se dosage regimens in various species, the overall findings suggest that Se, especially in its nano form, can have positive effects on reducing oxidative stress [59]. It has also been reported in a study that stabilized Se nanoparticles can effectively reduce the excessive production of intracellular ROS induced by patulin. Additionally, these nanoparticles can improve the reduction in glutathione peroxidase activity and suppress cell viability [60]. However, it is also accepted that high doses of Se (sodium selenite) can induce oxidative stress in living organisms and increase the process of lipid peroxidation. This suggests that excessive accumulation of Se within cells is toxic to living organisms [61].

Although Se, as a potent antioxidant, can be effective in regulating the immune system and reducing inflammation, further research in humans is needed to confirm optimal dosages and its impact on clinical conditions [62, 63].



Se affects the immune system through three main pathways: cellular immunity, humoral immunity, and non-specific immunity. Se enhances the production of interferon and increases the activity of gamma interferon in the laboratory setting, which boosts the cytotoxic effect of human NK cells without damaging the target cell membrane. Additionally, Se significantly increases the secretion of IL-1 and IL-2 from lymphocytes, stimulates the formation of immunoglobulins, and improves the body's ability to synthesize antibodies such as IgG and IgM [64]. Furthermore, Se has various effects on chemotaxis, phagocytosis, and phagocytes viral killing. Previous studies have shown that Se can regulate the differentiation of mouse helper T cells (Th), antibody production, leukocyte adhesion and migration, and macrophage phagocytosis. Recent studies have confirmed that Se can modulate the immune response of dendritic cells in chickens, mice, and humans [65-67].

Se increases the production of immunoglobulins, which enhances the proliferation and differentiation of lymphocytes and improves the production of antibodies such as IgM and IgG. In the case of Se deficiency, the process of immunoglobulin and antibody synthesis is disrupted [68]. In Se deficiency, the production of leukotriene B<sub>4</sub>, essential for attracting neutrophils to the site of infection, is impaired; however, with the addition of Se supplementation, this process returns to normal. Additionally, Se has both direct and indirect effects on the activity of NK cells [69]. The ability of NK cells to eliminate cancerous or virus-infected cells is influenced by the amount of Se consumed in the diet. In a study involving over 300 men in North America, it was found that Se supplementation increased plasma Se levels and improved the number of NK cells in the bloodstream. Additionally, in older adults, higher Se levels in the blood were positively correlated with a greater number of CD16<sup>+</sup> NK cells (a type of NK cell) in the plasma. This indicates the role of Se in enhancing NK cell function and strengthening the body's immune response [68].

These findings reveal that Se not only occupies a core role in immunostimulating effects but also has the potential to be a good means of enhancing immune well-being. Se has multiple immunomodulatory roles, which are primarily identified as functions of selenoproteins, especially in redox control and antioxidant defense. These actions are mediated by selenoprotein enzymes such as GPx and Thioredoxin reductase, and by the non-enzymatic protein K, which possess roles in immune functions. Adequate Se ingestion is required to trigger immune reactions and selenoprotein formation. Optimal Se status enhances immune reactions, such as the production of interferons and interleukins, while excessive Se consumption has negative impacts [70-72].

Se has diverse and widespread effects on the immune system. These effects are observed in the two main parts of the immune system (Figure2): innate immunity (which includes macrophages and neutrophils) and adaptive immunity (which provides for T and B lymphocytes).

1. Effect on Macrophages: When macrophages are confronted with Se deficiency, Se supplementation alters the activation of these cells. Specifically, Se reduces the activation change of macrophages from the inflammatory M1 phenotype to the anti-inflammatory M2 phenotype. M2 macrophages secrete anti-inflammatory cytokines like IL-10, which can help inhibit tumor growth. Additionally, Se protects macrophages from oxidative stress and enhances their functionality.

2. Effect on Neutrophils: Se indirectly affects neutrophils. One of its effects is reducing the synthesis of leukotriene B<sub>4</sub> in macrophages, a molecule essential for attracting and migrating neutrophils to inflammation sites.

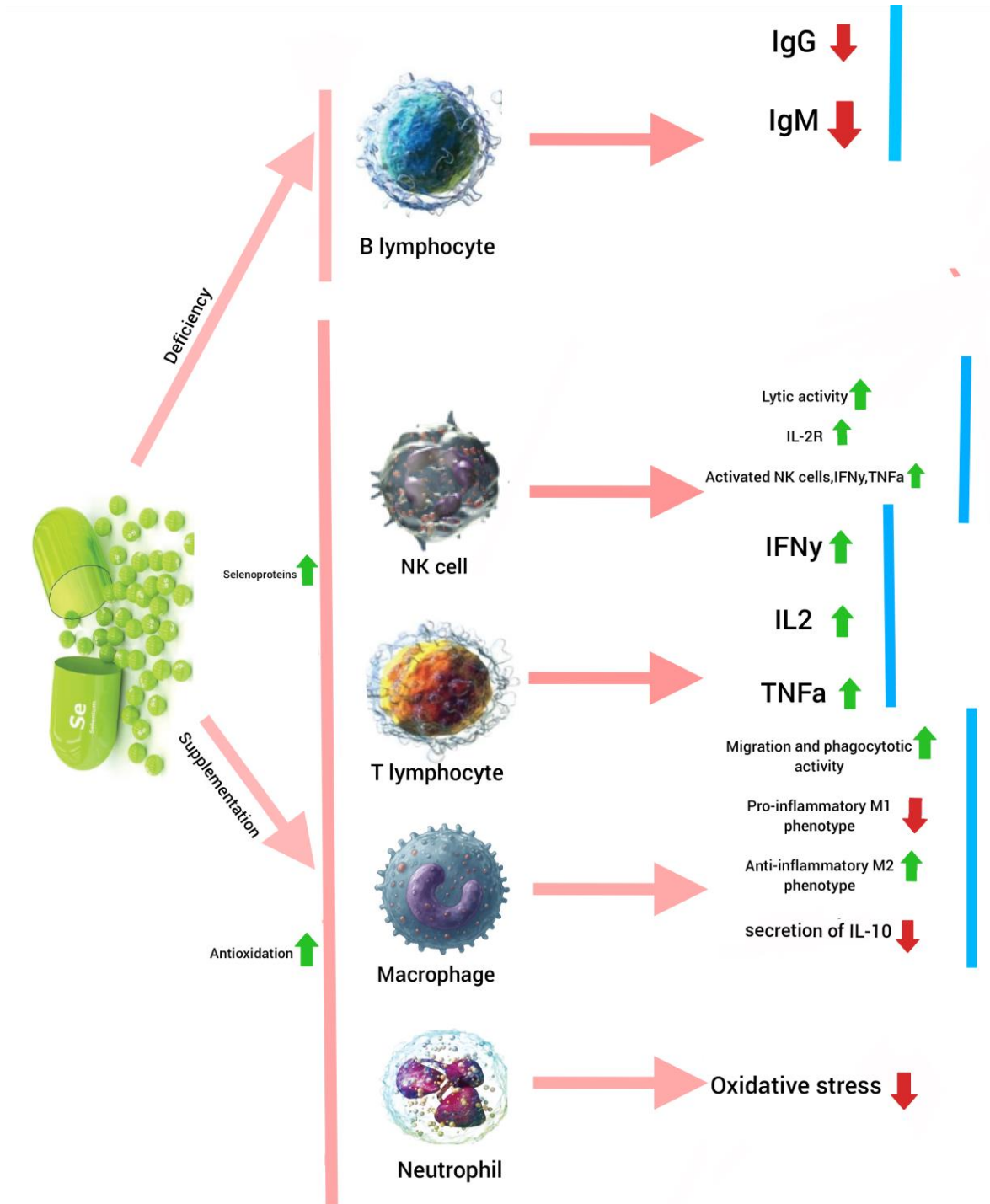
3. Effect on NK Cells: Se enhances the activity of NK cells in the body. Se supplementation increases the expression of IL-2 receptors (IL-2R) on the surface of these cells. These changes strengthen the cytotoxic function of NK cells, increase their proliferation, and expand cytotoxic precursors. As a result, NK cells can effectively target cancer cells and produce cytokines such as IFN- $\gamma$  and TNF- $\alpha$ , which play a crucial role in the anti-tumor immune response.

4. Effect on Dendritic Cells: Se can activate specific kinases involved in the immune response by increasing levels of ROS or glutathione. These kinases help stimulate antigen phagocytosis by immature dendritic cells. This process can enhance the immune response against infections and tumors. Additionally, Se reduces the expression of matrix metalloproteinases, which can inhibit the migration of cells to inflammatory areas.

5. Dual Effect on ROS: Se can increase the production of ROS, which can have beneficial and harmful effects. On one hand, ROS production can stimulate the immune response, including the activation of dendritic cells. On the other hand, excessive ROS production can impair the function of cytotoxic T lymphocytes and other anti-tumor immune components.

6. Effect on T and B Lymphocytes: Se deficiency can reduce the ability of lymphocytes to proliferate in response to immune stimuli. In animal models, a Se-enriched diet shifts the balance of Th1 and Th2 phenotypes in favor of Th1, increasing interferon-gamma (IFN- $\gamma$ ) levels. Furthermore, Se supplementation improves humoral immunity (related to B lymphocytes), such that in Se deficiency, immunoglobulin production (IgG and IgM) is reduced [65, 67, 73, 74].





**Figure2.** Immunomodulatory effects of selenium (Se) [75].

Optimal Se status enhances innate immune function by improving neutrophil oxidative stress resistance through selenoprotein upregulation, boosting macrophage chemotaxis and phagocytic activity while promoting M2 polarization, and increasing NK cell cytotoxicity and proinflammatory cytokine secretion. In adaptive immunity, Se supports Th1 lymphocyte responses and their cytokine production. However, Se deficiency compromises humoral immunity by reducing B cell differentiation and antibody (IgG/IgM) synthesis. Immunological enhancements and

suppressions are indicated by green (↑) and red (↓) arrows, respectively.

Innate immunity is characterized by the rapid response of the immune system to infection. The innate immune system employs various mechanisms such as activation of the complement system, activation of phagocytic cells, and antimicrobial peptide production to control and eliminate pathogens. Mast cells, NK cells, monocytes, macrophages, dendritic cells, neutrophils, basophils, and eosinophils are some of the cells that are involved in innate immunity. One



of the primary means through which such cells eliminate pathogens is by producing ROS during the "oxidative burst" process. This process is partly regulated by selenoproteins such as SelK and GPx, which participate in calcium ( $\text{Ca}^{2+}$ ) signal transduction pathways and redox reactions, respectively [2].

Se controls the excessive production of ROS through antioxidant mechanisms and prevents damage to host tissues. At the same time, adequate intake of this element enhances the effectiveness of the oxidative burst process, which is initiated in phagocytes when stimulated by pathogens. Se deficiency can disrupt these mechanisms, but by increasing Se levels, both the oxidative burst process and antioxidant activities in other parts of the body are strengthened. These two processes operate independently of each other, and neither inhibits the function of the other. This characteristic enables the immune system to effectively eliminate microbes while preventing damage to host tissues caused by ROS [2].

Se plays a crucial role in the survival and differentiation of leukocytes. Specifically, Se facilitates the differentiation process of pro-inflammatory M1 macrophages to anti-inflammatory M2 macrophages. Additionally, Se activates calcium ( $\text{Ca}^{2+}$ ) signaling in macrophages, essential for initiating Fc $\gamma$ R-dependent phagocytosis. Moreover, Se supplementation can reduce the adhesion of leukocytes to endothelial cells, potentially affecting how they are transported to various tissues [76]. Se plays its role by becoming a component of a protein called SelK, which is present in the endoplasmic reticulum of leukocytes (white blood cells), i.e., neutrophils and macrophages. This protein helps to allow calcium ( $\text{Ca}^{2+}$ ) into the cell, which is required for immune response signaling. It has been observed that mice in which the SELENOK gene is knocked out (where Se is unable to play any role) have impaired immune responses compared to normal mice. For example, they have defective neutrophil migration, reduced production of required chemicals (chemokines), defective oxidative burst in macrophages to eliminate pathogens, and defective release of important cytokines like IL-6 and TNF- $\alpha$  [2].

Another prominent feature of Se is its ability to regulate the adaptive immune system. The adaptive immune system is divided into two parts: the cellular component, which is T cell-dependent, and the humoral component, which relies on B cells. In addition to Se's role in regulating ROS signaling for the production of free radicals and enhancing protein biosynthesis, this element also increases the production of cytokines IL-2 and IFN- $\gamma$  by T cells. This process promotes T cell proliferation and differentiation, influences epigenetic regulation, prevents endoplasmic reticulum stress, and reduces leukocyte infiltration into tissues. One of the crucial selenoproteins in the adaptive immune system is SelK. This protein is found in the endoplasmic reticulum of B and T

cells and, as mentioned, supports calcium ion flow for signaling and cellular activation [2].

T cells are one of the most important types of white blood lymphocytes, playing vital roles in adaptive immune responses and effectively in protecting the body against infections, cancer, inflammatory diseases, and other chronic conditions. In recent decades, various types of T cells, including helper, regulatory, cytotoxic, and memory T cells, have been extensively studied, significantly enhancing our understanding of T cell immune function. Due to their critical roles in combating cancer and infections, T cells have become primary targets in immunotherapy strategies such as PD1/PD-L1 and CAR-T therapy. Currently, T cells are the most commonly used immune cells authorized for clinical immunotherapy, especially in cancer treatment. However, challenges such as low efficacy, off-target side effects, and high treatment costs still exist and require further investigation.

Se, as an essential micronutrient for human health, has garnered significant attention. In recent decades, various studies have clarified the relationship between Se and T-cell function. Se deficiency in mice leads to thymus, spleen, and lymph node atrophy, and the populations of CD3<sup>+</sup> and CD8<sup>+</sup> T cells in these mice are significantly reduced, indicating a disruption in T cell function [77].

Research has also shown that Se deficiency can inhibit the activation and proliferation of T cells, highlighting the importance of Se in the proper functioning of T cells. On the other hand, excessive Se intake can also affect adaptive immunity, directing the proliferation and differentiation of activated CD4<sup>+</sup> helper T cells toward Th1 cells. These cells play vital roles in T-cell immune responses against viral or bacterial infections [77].

The biological effects of Se on T cells are likely mediated through the function of selenoproteins, which have various roles in these cells. These roles include regulating calcium flux resulting from T cell receptor interactions, controlling the redox status of T cells before, during, and after activation, as well as reprogramming the metabolism necessary for T cell proliferation and differentiation in response to T cell receptor activation [72].

In recent years, Se nanoparticles (Se NPs) have been shown to enhance T cell proliferation and regulate their functions as an immune modulator. For example, Shams et al. found that the combination of aerobic exercise training and Se NP administration could reduce tumor volume and increase Th1 cytokines in the splenocytes of tumor-bearing mice. These findings indicate that Se NPs enhance the anti-tumor T cell immune responses [72].

$\gamma\delta$  T cells are a type of immune cell that have a unique combination of surface proteins and play an important role in immune responses. These cells are positioned at the interface between innate and adaptive immunity and are



particularly effective in combating tumors and infectious diseases. For this reason,  $\gamma\delta$  T cells have great potential for immunotherapy in cancer treatment [78].

One of the new approaches is using Se nanoparticles to enhance the function of  $\gamma\delta$  T cells in combating tumors. Se nanoparticles increase the anti-tumor activity of  $\gamma\delta$  T cells while causing less damage to the treated cells. Compared to a similar form of Se compound ( $\text{Na}_2\text{SeO}_3$ ), cells treated with Se NPs showed lower cytotoxicity, indicating better compatibility of these nanoparticles with the body [78, 79]. Se NPs, which are produced in the form of Se nanoparticles, have similar properties to Se itself. However, due to their microscopic size, they can more effectively enter cells and perform their therapeutic functions. These nanoparticles are especially effective in reducing inflammation and oxidative stress (cellular damage caused by free radicals) [79].

## 9. Studies conducted on the effectiveness of Se, Se-nanoparticles, and Se-enriched

In rats, the brain appears to be well-protected from Se deficiency, and Se-enriched spirulina proved to be more effective in replenishing Se levels in tissues than sodium selenite. Both types of supplementation, whether spirulina-enriched or regular Se, led to partial or complete restoration of Se concentrations in various tissues. For example, spirulina supplementation fully restored Se levels in plasma, urine, liver, kidneys, and the soleus muscle. Regular Se supplementation also completely restored Se in plasma, urine, and kidneys, while partially doing so in the liver, heart, and soleus. Interestingly, no change in Se levels was observed in the brain, indicating it may be an exception. These results imply that Se distribution in the body prioritizes specific tissues depending on the type of supplementation used [5].

In a study investigating selenoprotein expression in Se-deficient rats, Se-enriched *Spirulina platensis* produced by TAM company (Plougastel, France) was used. Se-enriched spirulina and Se-free spirulina were dried, powdered, and used simultaneously. The Se concentration in the enriched sample was 55  $\mu\text{g}$  of Se per 1 gram of Se-enriched spirulina based on dry weight [5].

In a study, the effects of Se and probiotics on Alzheimer's disease were examined. Although the primary goal of this research was not to investigate the innate immune system, the results showed that daily consumption of 200 micrograms of Se for 12 weeks significantly reduced the concentration of C-reactive protein in the blood [80].

Hypercholesterolemia can lead to the accumulation of cholesterol in macrophages, increased signaling of TLR receptors, increased numbers of monocytes and neutrophils in the blood, and, consequently, higher production of

inflammatory cytokines. Se's ability to reduce blood LDL levels may help mitigate these inflammatory responses. This regulatory effect is particularly beneficial for individuals suffering from autoimmune diseases, inflammatory disorders, or chronic infections from an immunological perspective [2].

In a study on Nile tilapia fish with Se deficiency, the results showed that Se nanoparticle supplementation significantly increased serum lysozyme activity, improved oxidative burst capacity, and enhanced the expression of pro-inflammatory cytokines (such as  $\text{TNF}\alpha$ ,  $\text{TGF}\beta 1$ , and  $\text{IL}1\beta$ ). Additionally, fish receiving Se nanoparticles performed better in phagocytosis and bactericidal tests. However, no significant changes were observed in leukocyte concentrations. Overall, Se nanoparticle supplementation had the most positive effect on the innate immune system of the fish [58].

In a study on European sea bass, the effects of different doses of Se nanoparticles (0, 1, 5, and 10 mg per kg) on the innate immune system were investigated. The results showed that in the 1 mg Se group, IL-6 expression decreased, while in the 5 and 10 mg groups, it increased. Chronic elevation of IL-6 could lead to issues such as autoimmune disorders. In all Se-treated groups,  $\text{TNF}\alpha$  expression was increased. In the 1 mg Se group, IL-12 expression increased, while in the 5 and 10 mg groups, it remained stable. These results suggest that different doses of Se have varying effects on the innate immune responses of the fish [59, 81, 82].

In recent years, there has been growing interest in the anticancer and antimicrobial properties of NK cells. One study has shown that inorganic selenite (a form of Se) can increase the sensitivity of mesothelial cells to NK cells. This is achieved by reducing the expression of a specific protein called HLA-E. This finding suggests that NK cells may have high potential in cancer treatment. NK cells play a crucial role in the body's innate immune responses, particularly in combating cancer and infections. These cells can identify tumor cells or pathogen-infected cells using specific receptors on their surface and then eliminate them. Additionally, during this process, NK cells produce cytokines that help enhance the immune response [79]. The ability of NK cells to eliminate cancer cells is typically limited by inhibitory signals. One such signal is generated through a receptor called NKG2A, which prevents NK cell function [83].

Se-containing nanoemulsions can effectively enhance the ability of NK cells to recognize and attack tumor cells. This is achieved by increasing the expression of the NKG2D receptor and its related ligands, which are associated with DNA damage response pathways. This finding suggests that using simple nanoemulsions could be an effective strategy for accompanying adjuvant drugs in cancer treatment using



NK cells [84]. In addition, Se -containing compounds can help enhance the effects of immunotherapy against prostate cancer. This is achieved by activating TRAIL/FasL signaling, which strengthens NK cell activity and thereby contributes to more effective cancer-fighting. These results suggest that Se -containing nanosystems can assist in regulating and enhancing NK cell function in cancer treatment [85].

Pan et al., in a study, introduced the drug pemetrexed into a Se -nanosystem, which enhanced human non-small cell lung cancer cell sensitivity towards NK cells. This was achieved by regulating pro-inflammatory cytokines such as IFN- $\gamma$  and TNF- $\alpha$ , which are responsible for promoting NK cell immune responses. Further studies need to be carried out in order to understand the comprehensive mechanisms in which Se regulates NK cell immune responses. Since Se nanoparticles possess significant benefits, following researches showed that Se nanoparticles are used to establish new therapeutic approaches for enhancing NK cell activity and more effective cancer treatment [85].

Wei et al., in a study, designed Se -based cell-penetrating nanoparticles that combine various motifs for tumor targeting and NK cell activation. These nanoparticles include motifs for binding to tumor cells, enzymatic cleavage (PLGVR), and response to ROS to enhance anticancer activity. This system can improve chemo-immunotherapy by activating NK cells and reducing tumor size by producing oxidative metabolites and desalinization [86].

Gao et al. reported a nano drug called PSeR/DOX, a combination of radiation-sensitive nanoparticles that not only carry the chemotherapy drug (DOX) but also have tumor-targeting properties. These nanoparticles contain Se (diselenide), which, in addition to its anticancer effects, acts as an immune checkpoint inhibitor. Therefore, these nanoparticles can be combined with radiotherapy and immunotherapy to create more effective cancer treatments with fewer side effects [87].

In another study conducted using a mouse model, cytokine concentrations in the placenta were examined following immune system activation in the mother. In this study, mice were given Se from day 9 of pregnancy until birth, and on day 17 of pregnancy, they were challenged with polyinosinic: polycytidylic acid. The results showed that compared to mice that did not receive Se, those receiving Se daily had significantly reduced protein concentrations of IL-17 and IL-1 $\beta$  in their placental tissues, while IL-6 levels remained unchanged. This study indicated that Se may reduce the activities of adaptive immune system T cell branches and some components of the innate immune system during pregnancy, potentially showing anti-inflammatory and immune-modulatory effects for the fetus during critical growth periods [88].

Another study conducted using a pig model demonstrated the positive effects of Se on the humoral branch of the adaptive immune system. The researchers observed that the concentrations of intestinal immunoglobulin A (sIgA) and serum immunoglobulin G (IgG) were significantly higher in pigs treated with HMSeBA (a Se compound) compared to the control group. These results suggest that Se is essential for regulating adaptive humoral immune responses and helps enhance the production of antibodies (such as sIgA and IgG), which play an essential role in the body's defense against infections [56].

Another study conducted on chickens investigated the effects of Se on the adaptive immune system. In this study, the chickens were fed different forms of Se at a dose of 0.3 mg of Se per kg of their basal diet, and various results were observed. By day 42, serum concentrations of IgG, IgA, and IgM were significantly higher in all groups that received Se supplementation. These findings indicate the positive impact of Se in enhancing humoral immune responses in chickens [89].

In another study, broiler chickens were tested with different doses of Se (0, 0.25, 0.50, or 1.00 mg of Se per kg) to evaluate the immune response against *Clostridium perfringens*. The results showed that Se had a significant immunostimulatory effect on these birds, leading to a substantial increase in the expression of cytokines IL-1 $\beta$ , IL-6, and IL-8 in their jejunum and spleen. These findings highlight the role of Se in enhancing the body's immune responses to pathological challenges [90].

Finally, studies on fish have shown that Se supplementation has a significant positive impact on improving the adaptive immune system. In a feeding experiment, Nile tilapia were fed different doses of mineral Se (1 mg.kg<sup>-1</sup>), organic Se (1 mg.kg<sup>-1</sup>), and nano Se (1 mg.kg<sup>-1</sup>). The results showed that treatment with nano-Se led to a significant increase in total IgM levels, while treatment with organic Se significantly increased serum protein levels. Additionally, treatment with nano-Se increased IL-2 levels, a cytokine responsible for limiting inflammation. These findings suggest that nano Se can effectively enhance adaptive immune responses and regulate inflammation [12, 58, 59].

Several randomized clinical trials have been conducted to examine the effects of Se supplementation on immune function. Overall, supplementation with Se may positive effect on immune system performance, particularly in individuals with low Se levels. However, its effects can vary depending on the dose, type of supplement, and immune response. Additionally, some studies have not shown significant improvements in immune function, highlighting the complexities of the impact of Se supplements on the immune system [91].



A study on children with systemic inflammation (a type of widespread inflammation in the body) showed that increased Se levels in their blood plasma were associated with better treatment outcomes [79]. These results indicate that adequate Se intake can help control inflammation and improve patient conditions.

A study by Mahana et al. showed that Se nanoparticles could prevent kidney damage caused by the antibiotic vancomycin. This antibiotic is used to treat antibiotic-resistant bacteria, but one of its significant side effects is nephrotoxicity (kidney toxicity). In this study, Se nanoparticles were able to reduce inflammatory factors and oxidative molecules (such as malondialdehyde and nitric oxide) that cause kidney damage, thus preventing further kidney injury [40].

Additionally, research by Xiao et al. demonstrated that Se nanoparticles could reduce vascular inflammation, which is commonly seen in cardiovascular diseases. The results showed that Se nanoparticles could increase nitric oxide (an anti-inflammatory molecule) levels in the blood and remove macrophages (a type of immune cell involved in inflammation) from the vessel walls. Furthermore, Se nanoparticles inhibit the NF- $\kappa$ B signaling pathway, which is usually activated in inflammatory responses [92].

Amini et al. also used Se nanoparticles for targeted stroke treatment. In this study, Se nanoparticles helped reduce stroke-induced damage by regulating inflammatory and metabolic signaling pathways, presenting a new therapeutic strategy for stroke [42].

For a summary and better understanding, refer to Table 3, which shows a qualitative comparison of selenium-enriched microalgae and sodium selenite.

## 10. Addressing global nutrition challenges

Low Se status is a widespread public health issue, affecting people across the world. Most of these people live in sub-Saharan Africa, South Asia, and China, where the soil is low in Se. The deficiency can weaken the immune system, making people more vulnerable to infection and other diseases [10, 93].

Our examination shows that microalgae like Spirulina and Chlorella, which contain high concentrations of Se, may indeed be the key. Not only do they provide enhanced bioavailability, but they also have the advantage of being produced through a more environmentally friendly process. We know all the disadvantages of traditional sources of Se. For instance, inorganic Se supplements, including sodium selenite, are not effective because they are not well absorbed. In addition, Se-enriched crops demand large expanses of agricultural land. Microalgae offer a better alternative with multiple methods to supply Se efficiently [6, 7].

Microalgae culture offers some great benefits when it comes to sustainability. They can thrive in different settings, including wastewater systems [16, 27]. This improved bioavailability is especially important for people who have trouble absorbing nutrients.

With regard to the microalgae culture in providing a sustainable technology, the primary environmental benefit is that it provides a tried one. They are able to grow in an exceedingly wide variety of locations, beyond filthy wastewater systems, and they are not even freshwater or on farm land [24, 42].

Field tests with undernourished populations were successful. This activity can be demonstrated when Se-enriched Chlorella is added to the Indian and Bangladeshi diet, with clear amelioration in Se deficiency markers [40].

**Table 3.** Qualitative comparative contrasting selenium-enriched microalgae with sodium selenite

Attribute	Sodium Selenite (Inorganic Se)	Selenium-Enriched Microalgae
Selenium form	Inorganic form ( $\text{Na}_2\text{SeO}_3$ ) [13–15]	Primarily organic forms (selenomethionine, selenocysteine, methyl selenocysteine) [16, 24]
Bioavailability	Moderate bioavailability; less efficient absorption [31]	Higher bioavailability; easily absorbed and utilized in the body [16, 24, 31]
Toxicity risk	Higher toxicity potential, especially with prolonged high intake [41]	Lower toxicity at equivalent Se doses; organic forms generally safer [24, 38]
Health effects	Supports immune function but with higher risk of oxidative damage at high doses [61]	Enhances antioxidant capacity, supports immune function, reduces oxidative stress [12, 20, 35]
Sustainability	Synthetic chemical production; non-renewable raw materials [13–15]	Derived from renewable biomass; microalgae cultivation can sequester $\text{CO}_2$ and reduce land/water use [21]
Applications	Primarily used in supplements and animal feed [13–15]	Functional foods, dietary supplements, fortified beverages, cosmetics [22, 32, 35]



These findings suggest the possibility of using microalgae-based solutions to treat Se deficiency at the population level. Immunological effects of Se derived from microalgae are especially important in the wake of prevailing global health trends. Se deficiency for extended periods has been linked to various unfavorable health outcomes. For instance, during viral infections like COVID-19, Se levels have been proven to be a determining factor in the severity and mortality of the disease [11, 49]. Moreover, low Se intake has also been associated with increased risk of certain cancers, especially gastric and prostate cancers [73, 74]. The metabolic impacts are just as serious, since Se deficiency can exacerbate oxidative stress and chronic inflammation to induce conditions like cardiovascular disease and non-alcoholic fatty liver disease [47, 79].

Microalgae-derived Se affects the immune system at the cell level. Experiments have demonstrated that Se-enriched *Spirulina* supplementation is able to enhance NK cell activity [3]. Its immunostimulating effect is accompanied by strong antioxidant activity, increasing synthesis of key selenoproteins like GPx and selenoprotein P that guard vital tissues against oxidative damage [3, 94]. Furthermore, research has established that microalgae-based Se is able to decrease pro-inflammatory cytokines, including IL-6 and TNF- $\alpha$ , in clinical groups that are consuming such supplements [80].

To successfully move these scientific developments into successful interventions, we require an interdisciplinary strategy for policy action. We propose the following three-pronged strategy for implementation: First, incorporating Se-enriched microalgae into existing nutrition programs via cooperation with global health organizations may complement current supplementation, like that for vitamin A and iron [8]. Second, embracing controls and providing economic incentives drawn from the successful aquaculture policy in Norway could convince the industry to adopt and expand this initiative [6, 7]. Finally, forming strategic public-private partnerships could improve production and distribution capabilities, especially in areas where Se is lacking [42].

The immunological and nutritional synergy gives Se-enriched microalgae a distinct reaction to worldwide health concerns. The strategy is well-addressed to the World Health Organization's Immunonutrition Aims for 2030 by treating micronutrient malnutrition as well as immune system dysfunction simultaneously. We need to consider decentralized production networks, education programs among consumers, and facilitating policy frameworks that ensure equitable access to all in the future. As the evidence mounts, Se-enriched microalgae must not only be considered as a food supplement, but as an essential element of sustainable, responsive food systems that have the

potential to contribute to the solutions for some of the world's most recalcitrant public health problems.

## 11. Conclusion

Studies highlight the vital role of Se in enhancing and regulating adaptive immune responses across different species. Se, by affecting various branches of the immune system (cellular and humoral), helps improve immune activities against pathogens and reduce inflammation. The results show that this element can increase the production of antibodies, such as IgM, IgG, and IgA, and cytokines like IL-1 $\beta$ , IL-6, and IL-8 in various species (mice, pigs, chickens, and fish). Additionally, Se can modulate innate and adaptive immune activities during sensitive periods, such as pregnancy, and exert anti-inflammatory effects. Overall, Se is effective in enhancing immune responses and regulating inflammation and can be used as an immunostimulatory agent to improve immune system efficiency.

Se-enriched microalgae, such as *Chlorella vulgaris*, provide organic Se with high and suitable bioavailability, such as selenomethionine, making them ideal for use as functional foods and nutrients to address Se deficiency. This is supported by their potential to alleviate Se deficiency and their complementary role in enhancing immune system health. Therefore, these positive attributes position microalgae as potential candidates for microbiome engineering and enable support for nutrition-focused health interventions due to their bioactive compounds. Furthermore, optimized cultivation techniques can enhance Se composition, enabling the scalable production of safe, Se-enriched biomass for dietary supplements and bridging biotechnology with nutrition.

As per the discovery through research, Se nanoparticles and also Se possess highly conspicuous anti-inflammatory activity. These can be used in the treatment of chronic inflammation and oxidative stress-related disease. These are kidney diseases, cardiovascular diseases, and even stroke, in which inflammation is a leading factor for the progression of the disease. All these could be cured with this new and possible therapeutic method. Se-enriched microalgae are a new and promising bioactive solution to the boosting of the immune system and general well-being. Since such algae can sequester Se and metabolize it into more bioactive forms, they represent an inexpensive and renewable source of this essential micronutrient. In this review, the importance of Se to human health is discussed, such as its role in antioxidant function, immune system regulation, and capability to reverse oxidative stress and inflammation.

Microalgae can be enriched with Se through biotechnological methods such as selective cultivation and genetic modifications, leading to the creation of functional foods, dietary supplements, and fortified products with



immune-boosting properties. A growing body of research, including animal studies and human clinical trials, has confirmed the immune-modulating effects of Se-enriched microalgae and demonstrated their potential to improve health outcomes and prevent various diseases.

Despite the promising outlook, many challenges remain, especially in understanding the underlying mechanisms of Se action and optimizing biotechnological processes for large-scale production. Further research is needed to bridge knowledge gaps, improve yield and efficacy, and ensure the safety and regulatory compliance of Se-enriched products. Market opportunities for these bioactive products are expanding, particularly with the increasing consumer demand for functional foods and natural supplements.

Looking ahead, the future of Se-enriched microalgae in food biotechnology and health promotion appears promising, with advancements in genetic engineering, production techniques, and product development likely to drive the next growth phase. Interdisciplinary collaboration and innovation will remain essential to overcoming existing challenges and unlocking the full potential of Se-enriched microalgae for global health benefits.

## 12. Declaration of competing interest

The authors report no conflict of interest.

## 13. Authors' Contributions

Conceptualization, A.D., M.A.; methodology A.D., M.A.; investigation, F.F., Y.B.; data curation, A.D.; writing (original draft preparation, A.D., A.Gh., F.F., Y.B.); writing review and editing, A.D., M.A.; visualization, A.Gh., Y.B.; supervision, M.A.; project administration, A.D, M.A. .

## 14. Using Artificial Intelligent Chatbots

The authors did not use artificial intelligence

## 15. Ethical Consideration

This study does not require approval from an ethics committee.

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## ریزجلبک‌های غنی‌شده با سلنیوم: یک رویکرد نوین زیست‌فعال برای ارتقای سیستم ایمنی

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### تاریخچه مقاله

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### چکیده

**سابقه و هدف:** ریزجلبک‌های غنی‌شده با سلنیوم به‌عنوان یک منبع نوظهور در حوزه غذاهای فراسودمند و مکمل‌های تغذیه‌ای شناخته می‌شوند و ترکیبی هم‌افزا از ترکیبات زیست‌فعال و ریزمغذی‌های ضروری را فراهم می‌کنند. سلنیوم، به‌عنوان یک عنصر کمیاب، نقش کلیدی در تنظیم ایمنی، سیستم‌های دفاع آنتی‌اکسیدانی و هموستاز سلولی دارد. ریزجلبک‌ها به دلیل ارزش غذایی بالا و رشد سریع، قادرند سلنیوم را در قالب ترکیبات آلی همچون سلنومتیونین و سلنوسیستین تجمع دهند. این اشکال آلی نسبت به مکمل‌های سلنیوم معدنی، زیست‌فراهمی بیشتری داشته و سمیت کمتری دارند. این مرور به بررسی تازه‌ترین پیشرفت‌ها در زمینه کشت، راهبردهای غنی‌سازی با سلنیوم و آثار زیستی ریزجلبک‌های غنی‌شده با سلنیوم می‌پردازد، با تمرکز ویژه بر ویژگی‌های ایمنی‌تنظیمی آن‌ها.

**یافته‌ها و نتیجه‌گیری:** شواهد موجود نشان می‌دهد ریزجلبک‌های غنی‌شده با سلنیوم ظرفیت بالایی در پیشگیری از بیماری‌ها، ایمنی‌درمانی و توسعه غذاهای فراسودمند دارند. اثرات تعدیل‌کننده سیستم ایمنی این ریزجلبک‌ها، شامل تقویت عملکرد ایمنی، کاهش التهاب و تأمین سلنیوم با زیست‌فراهمی بالا، بر پتانسیل آن‌ها در زیست‌فناوری غذایی و مکمل‌های تغذیه‌ای تأکید دارد. علیرغم چالش‌های موجود در بهینه‌سازی فرآیندهای تولید و شفاف‌سازی مکانیسم‌های عمل، چشم‌انداز آینده با توجه به تقاضای رو به رشد برای غذاهای فراسودمند و راهکارهای طبیعی ارتقای سلامت بسیار امیدوارکننده به نظر می‌رسد.

**واژگان کلیدی:** آنتی‌اکسیدان، زیست‌فراهمی، کلرلا و لگاریس، غذاهای فراسودمند، تعدیل سیستم ایمنی، ریزجلبک غنی‌شده با سلنیوم، سلنوپروتئین‌ها، اسپیرولینا، زیست‌فناوری پایدار