Chapter

An Overview of the Antioxidant and Anti-Inflammatory Activity of Selenium

Mehmet Başeğmez

Abstract

Selenium, whose name comes from the Greek word for "Selene," has been a topic of interest as a micronutrient ever since it was described in 1817 as a by-product of sulfuric acid manufacturing. Selenium, the most important micronutrient for both humans and animals, must be consumed daily to support the body's natural metabolism and homeostasis. The small intestine is responsible for the absorption of selenium in both its organic and inorganic forms. Selenium is then able to be widely distributed throughout the body's diverse tissues, where it plays an important role in the regulation of the synthesis of selenoproteins. The synthesis of human selenoproteins involves the incorporation of a selenium-containing homolog of cysteine in each of the 25 selenium-containing proteins that make up this series. Many selenoproteins, including glutathione peroxidase (GPX), thioredoxin reductase (TrxR), and iodothyronine deiodinases (IDD), function as crucial cellular defenses against oxidative stress. Therefore, selenium is extremely important in boosting antioxidant defense. Recent studies have also shown that there is a close relationship between selenium and inflammation, and that selenium has regulatory effects on inflammation by affecting the expression of various cytokines. This chapter's goal was to thoroughly review the research on how selenium is related to antioxidant and anti-inflammatory activity.

Keywords: antioxidant, anti-inflammatory, human nutrition, selenium, selenoproteins

1. Introduction

Selenium, which takes its name from the Greek word "Selene," has been attracting attention as a trace element since 1817 as a by-product of sulfuric acid [1]. Both environmental and endogenous factors affect body selenium homeostasis [2]. Selenium can be absorbed by the small intestine in both organic and inorganic forms, after which it can be distributed throughout the body and perform important biological functions, most particularly by controlling the synthesis of selenoproteins [3]. Selenoproteins play an important role in many biochemical and physiological processes in both humans and animals because of their antioxidant properties [4]. They have antioxidant and anti-inflammatory properties that help to regulate

immune cell functions [5]. Twenty-five genes in the human genome are responsible for the coding of selenocysteine-containing proteins. The selenoprotein family, whose functions are known, is named according to these functions: glutathione peroxidases (GPX1, GPX2, GPX3, GPX4, and GPX6), thioredoxin reductases (TrxR1–3), iodothyronine deiodinases (DIO1–3), selenophosphate synthetase 2 (SEPHS2), methionine sulfoxide reductase B1(MSRB1), SEP15 (SELENOF), SELH (SELENOH), SELI (SELENOI), SELK (SELENOK), SELM (SELENOM), SELN (SELENON), SELO (SELENOO), SELP (SELENOP), SELS (SELENOS), SELT (SELENOT), SELV (SELENOV), and SELW (SELENOW) [6]. The primary function of multiple selenoproteins is to protect cells from oxidative damage by taking action as major antioxidants.

In this review, I want to show how selenium affects many biological effects, mostly through selenoproteins, as well as how it affects the physiological and biochemical processes it interacts with. Furthermore, the effect of deficiency and excess selenium in the body on the antioxidant and anti-inflammatory systems and the most recent findings on human health are highlighted.

1.1 Selenium requirement in the human body

Selenium is a crucial trace element required for the proper working of all organisms. It is emphasized that very high and very low selenium levels in humans are harmful to health [7]. For instance, not getting sufficient selenium can cause oxidative stress, which decreases the concentrations of selenoproteins, such as GPx and TXNRD, in the body. On the other hand, too much selenium can cause oxidative stress by oxidizing and cross-linking protein thiol groups, which causes reactive oxygen species to form [8]. The amount of this element, which varies according to bioavailability, geographical region, and nutrition, plays an important role in selenium homeostasis in the organism. It has been determined that 40–70 micrograms [9] of this element is optimal for normal biochemical and physiological processes [10, 11]. The World Health Organization suggests that adults consume 55 μg of selenium per day [12]. The US Food and Nutrition Board determined it to be 40–70 μg for men and 45–55 μg for women [13–15]. The determination of reference values for selenium in adults is based on saturation of the plasma selenoprotein P (SePP) level with adequate selenium intake. SePP saturation was reached in people with an average body weight of 58 kg who lived in areas with low selenium levels by giving them 49 microgram of selenium every day [16]. This is equivalent to getting about 1 micrograms of selenium per kilogram of body weight every day [17]. Reference values for children and teens are based on values made for adults, with their body weight and growth factors taken into account. Estimated values for selenium intake by age groups and body weights are as follows: 15 μg/day for 1 to 4 years old, 20 μg/day for 4–7 years old, 30 μg/day for 7 to 10 years old, 45 μg/day for 10 to 13 years old, and 60 μg/day for 13 to 15 years old. The estimated daily value of selenium intake for boys aged 15 to 19 is 70 micrograms, while for girls of the same age, it is 60 micrograms Daily [17]. The determination of selenium requirements in newborns and 4-month-old infants is based on the selenium content of breast milk [17]. A daily average of 750 ml of breast milk [18] results in a selenium intake of nearly 11 μg/day. An estimate of optimal selenium intake for breastfed infants between new-born and 4 months of age is 10 micrograms. However, considering the average body weight differences and solid food intake processes in infants aged 4–12 months, an estimated daily 15 micrograms was determined for infants (**Table 1**) [17].

	Selenium µg/day		References
Age	**Male (µg)**	**Female (µg)**	
Birth–4 months	10		
4–12 months	15		
1–4 years	15		
4–7 years	20		
7–10 years	30		
10–13 years	45		[17, 19]
13–15 years	60		
15–19 years	70	60	
19–25 years	70	60	
25–51 years	70	60	
51–65 years	70	60	
Pregnant women		60	
Lactating women		75	

Table 1.
Values predicted to ensure sufficient selenium consumption.

1.2 Source of selenium in the human body

Selenium is mostly orally taken into the human organism. Plant and animal products are the main sources of this element. Selenium can be found in foods and biological materials as inorganic compounds, as well as organic compounds [20, 21]. Plants store selenium in the form of inorganic compounds called selenate (IV) or (VI) and then convert them into organic forms such as selenomethionine and selenocysteine [7]. Selenocysteine levels are high in animal-derived products [22]. Selenium is found in low concentrations in vegetables and fruits, but in high concentrations in seafood, grains, and meat products [23, 24]. On the other hand, protein-rich foods contain higher levels of selenium than foods low in protein [7]. Cereal products provide approximately 50% of the daily selenium intake, while meat, fish, and poultry products provide approximately 35%. Water and beverage products provide about 5–25% of selenium. Fruit, on the other hand, meets about 10% of the selenium demand (**Table 2**).

2. The role of selenium in oxidative stress, inflammation, and immunity

Oxidative stress is a disruption of the balance between the prooxidant and antioxidant systems in the body [27, 28]. In normal circumstances, the prooxidant system and the antioxidant system work together to maintain the body's homeostasis. However, increased prooxidant system activity and deterioration of the antioxidant system (**Table 3**) result in oxidative stress. The development of many chronic diseases, including diabetes [30], cancer [31], antiviral agents [32], and various aging-related and central nervous system (CNS) disorders [33], can result in high levels of reactive oxygen and nitrogen species production. In addition, reactive oxygen

Selenium Source	Food	Selenium concentration(mg/kg)	Selenium forms	References
Meat and meat products	Beef	0.042–0.142	Selenomethionine	[19, 25]
	Lamp	0.033–0.260		
	Chicken	0.081–0.142	Selenomethionine/ Selenocysteine	
	Pork	0.032–0.198	Selenomethionine/Selenate	
	Fish	0.1–5.0	Selenomethionine/Selenite/ Selenate	[19]
Milk and dairy products	Milk	0.01–0.03	Selenocysteine/Selenite	
Vegetable products	Broccoli	0.5–1.0	Selenomethionine/Selenate	
	Garlic	0.05–1.0	Selenomethionine/ Selenocysteine	
	Potatoes	0.12	Selenomethionine	[19, 25]
	Mushrooms	0.01–1.40	Selenomethionine/ Selenocysteine/ Selenomethylselenocysteine	[26]
	Onions	0.02–0.05	Selenomethionine/ Selenocysteine	[19]
Grain products	Bread	0.01–30	Selenomethionine/Selenate	
	Cereal	0.02–35		
	Lentils	0.24–0.36		[19, 25]
	Rice	0.05–0.08	Selenomethionine	
Other food products	Yeast	0.6–15		[19]
	Eggs	3–25	Selenomethionine/ Selenocysteine	

Table 2.
Selenium concentrations in various foods.

production causes intense lipid peroxidation in cells, causing the breakdown of cell membranes [5]. As a result, cellular homeostasis is disrupted, and human health is affected. Antioxidant activity as a free radical scavenger is linked to protecting cells from autooxidation and keeping their structure so that the immune system can work at its best [34].

In the process of regulating antioxidant activities, various selenoproteins are essential players [35]. Glutathione peroxidase GSH-Px, which contains one selenium atom in each subunit, was one of the first highly effective selenoproteins [36]. The glutathione peroxidase enzyme reduces reactive oxygen and nitrogen species by converting hydrogen peroxide (H_2O_2) to water (H_2O) and organic hydroperoxides (ROOH) to alcohol (ROH) [14, 37]. The selenium dependent (GPXs 1–4) significantly detoxifies cellular peroxides that protect against reactive oxygen species [38]. Glutathione peroxidase 1 (GPX1) is the most common selenoprotein that protects the body from oxidative stress caused by reactive oxygen and nitrogen [39]. On the other

	Radicals	Non- Radicals
Reactive oxygen species	O_2.-, Superoxide	H_2O_2, Hydrogen peroxide HOCI, Hypochlorous acid $^1O_2$, Singlet oxygen O_3, Ozone
	OH., Hydroxyl	
	RO_2., Peroxyl	
	RO., Alkoxyl	
	HO_2., Hydroperoxyl	
	NO., Nitric oxide	
	NO_2., Nitrogen dioxide	
Reactive nitrogen species	NO., Nitric oxide NO_2., Nitrogen dioxide	HNO_2, Nitrous acid
		N_2O_4, Dinitrogen tetroxide
		N_2O_3, Dinitrogen trioxide
		ONOO-, Peroxynitrite
		ONOOH, Peroxynitrous acid
		NO_2+, Nitronium cation
		ROONO, Alkyl peroxynitrites

Table 3.
Reactive oxygen and nitrogen species [29].

hand, GPX1 may also decrease the concentration of lipid hydroperoxides and other hydroperoxides once they have been released from membrane lipids [40]. In the same way, as GPX1 does, GPX2 neutralizes H_2O_2 and fatty acid hydroperoxides [41]. This selenoprotein, which was expressed in the intestinal tract in the early 1990s, has also attracted attention with its antioxidant activities by affecting apoptosis and regulating the self-renewal of the intestinal epithelium [42]. GPX3, found in plasma and milk [38], is an important selenoprotein that serves as a source of extracellular antioxidant capacity, especially in the kidney proximal tubule epithelial cell [43], by reducing oxidative stress in the heart, liver, lungs, skeletal muscle, and thyroid gland [44, 45]. GPX4 is unique among GPXs in that it has the ability to catalyze the reduction of hydrogen peroxide and other lipid hydroperoxides in addition to reducing phospholipid hydroperoxides [46]. GPX6 enzyme expression was detected only in the embryo and olfactory epithelium [47]. In an *in vivo* study, supplementation of selenium-rich, rice-extracted selenoproteins to male mice modeled aging by abdominal D-galactose injection and increased GSH-Px and superoxide dismutase (SOD) enzyme activation in the liver and serum of mice compared to the control group [48]. TrxR enzymes, which function in concert with NADPH to clear the redox system in mammals, have been identified in three different forms [49]. Trx1 is responsible for the reduction of thioredoxins in the cytosol, TrxR2 for the reduction of thioredoxins in the mitochondria, and TrxR3 for the reduction of glutathione and glutaredoxin [50]. DNA synthesis, which occurs at the beginning of cellular processes, relies on the existence of selenium in the catalytic region of TrxR [51]. Furthermore, mammalian TrxRs are selenoproteins that play an essential function in many cellular processes by modulating the action of the core redox molecule thioredoxin, as well as directly reducing a variety of substrates [50]. DIOs are members of the selenoprotein family that include the three enzymes (DIO1, DIO2, and DIO3) that catalyze the activation (DIO1) and inactivation (DIO2) of the thyroid hormone

thyroxine (T4), respectively [52]. DIO1 is involved in T3 production in the thyroid gland and controlling circulating T3 levels, while DIO2 and DIO3 are involved in local deiodination processing processes at the tissue and organ level [53]. Increased oxidative damage in thyroid tissue has been associated with decreased DIO and GPx activity in the organism and insufficient GPx concentration [54]. In mammals, selenophosphate synthetase 2 (SEPHS2) is a selenoprotein involved in the biosynthesis of the amino acid selenocysteine, which catalyzes the formation of selenophosphate from selenide and ATP [55, 56]. SelR, commonly referred to as methionine-R-sulfoxide reductase B1 (MsrB1), is a protein that helps reduce oxidized methionine (Met) residues (methionine sulfoxides) [57]. SelR comprises a redox effective selenoprotein containing a particular enzymatic activity that is necessary for oxidative protein repair [50]. SEP15 is the first selenoprotein [58] to be widely distributed across multiple organs including the brain, lung, testis, liver, thyroid, and kidney [59]. Sep15, belonging to the class of thiol-disulfide oxidoreductase-like selenoproteins [60], is a selenoprotein exhibiting redox activity [61]. Selenoprotein K is mainly expressed in the heart and skeletal muscle, but it is also found in other tissues such as the placenta, liver, and pancreas. Increasing levels of SELK in the organism exhibit antioxidant properties in the heart by reducing intracellular ROS levels and protecting cardiomyocytes against oxidative damage [62]. Selenoprotein M, a selenoprotein distantly related to Sep15, acts as a redox regulator with the amino acid selenocysteine [63]. SELM, induced by sodium selenite, which has prooxidant properties, has a functional role in catalyzing free radicals [64]. SELN, which is an endoplasmic reticulum glycoprotein and has important functions in muscle tissue, has been associated with myopathies [65]. SELN, which draws attention with its cell proliferation and regeneration, is significantly effective in the early embryonic development process [66]. It plays an important role in the redox system by contributing to calcium homeostasis in the organism [67] and protecting the cells from oxidative stress [68]. SelO, which is located in the mitochondria of the organism and draws attention with its feature of being the biggest selenoprotein [69], plays a role in oxidative stress by controlling S-glutathionylation levels [70]. Selenoprotein P is estimated to contain 50% of plasma selenium [71]. The plasma concentration of SELP varies depending on selenium supplementation. These changes in selenium intake, together with its concentration at the plasma SELP level, may reflect an indication of the amino acid protein residues of selenite in its molecule [72]. SELP, which exhibits antioxidant properties, has been shown to protect astrocytes [73] and endothelial cells from oxidative stress [74, 75]. In addition, it has been demonstrated that SELP prevents the oxidation of low-density lipoproteins [76]. Selenoprotein S, one of the resident proteins of the endoplasmic reticulum, is a selenoprotein involved in the reduction of reactive oxygen species and redox signaling [77]. This selenoprotein plays critical functions in protein quality control processes, cytokine modulation, and signaling [78]. Selenoprotein T is the only protein among the selenoproteins located in the membrane of the endoplasmic reticulum. The decrease in the expression of selenoprotein T, known for its suppressive effect on reactive oxygen and nitrogen species, has been shown as a possible factor in the deterioration of the antioxidant balance [79]. Selenoprotein V, which is predominantly localized in the intracellular cytoplasm, plays an important role, such as other selenoproteins, in the elimination of oxidative stress by protecting against endoplasmic reticulum stress and apoptosis caused by prooxidants [80]. Selenoprotein W, which is expressed in every tissue, is one of the well-known selenoproteins with antioxidant properties that are very important for the proper growth of the brain and embryo [81, 82].

Selenium, which plays an important role in antioxidant defense for body homeostasis, also plays an important role in the regulation of different inflammatory processes in the organism [83]. Adequate selenium supplements are essential for the immune system. For example, selenoprotein expression is affected in male mice supplemented with selenium, and immune response pathways, such as Interferon-γ and IL-6, are supported [84]. Interleukin IL-2, IL-4, IL-5, IL-13, and IL-22 cytokine levels were significantly higher in plasma and peripheral blood mononuclear cells in people who ate 200 mg of selenium-rich broccoli per serving for three days [85]. A previous study showed that increasing selenium supplements increased antigen-specific $CD4^+$ T cell responses. In addition, high selenium diets increased interferon-gamma (IFN-γ) and IL-2 expression levels compared to low and moderate selenium diets [86]. The higher contents of selenium in the blood of older individuals have been shown to have a positive correlation with a higher percentage and activity of natural killer (NK) cells [87]. In patients with acute respiratory distress syndrome, intravenous selenium supplementation attenuated inflammatory responses and significantly improved respiration by restoring the antioxidant capacity of the lungs *via* IL-1β and IL-6 proinflammatory cytokine levels [88]. Selenium supplementation significantly affects both innate immunity (neutrophils, macrophages, and NK) and acquired immunity (T and B lymphocytes) [89]. The phagocytosis functions of macrophages and the T cell activities of the body were significantly boosted by selenium-containing proteins [90]. Selenoprotein K plays an important role in the regulation of immunity by affecting the proliferation of T cells and the transport of neutrophils as a cofactor for the enzyme involved in the maturation of proteins in the endoplasmic reticulum to support calcium influx [5, 91].

3. Conclusions

These findings suggest that adequate selenium supplements may contribute to the body's immune homeostasis. It also shows that the selenoprotein family can prevent damage to cellular proteins by directly scavenging reactive oxygen and nitrogen species. In this respect, selenium appears to have both a protective and a therapeutic role in immune dysfunction, and further research is needed to understand the effect of selenium at different pharmacological doses, different administration methods, and in different age and gender groups. However, with new studies to be done, it is necessary to reveal the mechanisms that play a role in selenium homeostasis depending on oral or parenteral supplements in humans and animals. In addition, due to the fact that the drugs used in the treatment of chronic diseases all over the world, including in our country, have both side effects and are expensive, it leads to an increase in health costs and causes countries to determine new principles in health services. In recent years, scientists have accelerated their studies to find more accessible, inexpensive, and low side effect products such as selenium instead of expensive, prescription-only pharmacological agents with high side effects. As a result of the promising findings on the effects it creates in the organism, selenium supplements may be used as a potential pharmacological agent in the prevention of oxidative stress and regulation of inflammation in the near future.

Author details

Mehmet Başeğmez
Department of Veterinary, Acıpayam Vocational High School, Laborant and Veterinary Health Program, Pamukkale University, Denizli, Turkey

*Address all correspondence to: mehmetbsgmz@gmail.com

IntechOpen

References

[1] Shahzad SA, Shahzad SA. General introduction on selenium. In: Novel Selenium-Mediated Rearrangements and Cyclisations. 2013. pp. 1-12

[2] Park K, Rimm E, Siscovick D, Spiegelman D, Steven Morris J, Mozaffarian D. Demographic and lifestyle factors and selenium levels in men and women in the U.S. Nutrition Research and Practice. 2011;**5**(4):357-364. DOI: 10.4162/NRP.2011.5.4.357

[3] Burk RF. Biological activity of selenium. Annual Review of Nutrition. 1983;**3**(1):53-70. DOI: 10.1146/annurev.nu.03.070183.000413

[4] EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). Scientific opinion on dietary reference values for niacin. EFSA Journal. 2014;**12**(7):3759. DOI: 10.2903/j.efsa.2014.3759

[5] Zoidis E, Seremelis I, Kontopoulos N, Danezis GP. Selenium-dependent antioxidant enzymes: Actions and properties of selenoproteins. Antioxidants. 2018;**7**(5):66. DOI: 10.3390/antiox7050066

[6] Regina BF, Gladyshev VN, Arnér ES, et al. Selenoprotein gene nomenclature. Journal of Biological Chemistry. 2016;**291**(46):24036-24040. DOI: 10.1074/jbc.M116.756155

[7] Kieliszek M. Selenium–fascinating microelement, properties and sources in food. Molecules. 2019;**24**(7). DOI: 10.3390/molecules24071298

[8] Lee KH, Jeong D. Bimodal actions of selenium essential for antioxidant and toxic pro-oxidant activities: The selenium paradox (review). Molecular Medicine Reports. 2012;**5**(2). DOI: 10.3892/mmr.2011.651

[9] Combs GF. Selenium in global food systems. British Journal of Nutrition. 2001;**85**(5). DOI: 10.1079/bjn2000280

[10] Pophaly SD, Poonam SP, Kumar H, Tomar SK, Singh R. Selenium enrichment of lactic acid bacteria and bifidobacteria: A functional food perspective. Trends in Food Science and Technology. 2014;**39**(2). DOI: 10.1016/j.tifs.2014.07.006

[11] Krohn RM, Lemaire M, Negro Silva LF, et al. High-selenium lentil diet protects against arsenic-induced atherosclerosis in a mouse model. Journal of Nutritional Biochemistry. 2016;**27**:9-15. DOI: 10.1016/j.jnutbio.2015.07.003

[12] Organization WH. Trace Elements in Human Nutrition and Health World Health Organization. Geneva: World Health Organization; 1996. Published online. ISBN 92 4 156173 4

[13] Tamari Y, Kim ES. Longitudinal study of the dietary selenium intake of exclusively breast- fed infants during early lactation in Korea and Japan. Journal of Trace Elements in Medicine and Biology. 1999;**13**(3):129-133. DOI: 10.1016/S0946-672X(99)80002-9

[14] Kieliszek M, Błazejak S. Current knowledge on the importance of selenium in food for living organisms: A review. Molecules. 2016;**21**(5). DOI: 10.3390/molecules21050609

[15] Kieliszek M, Błazejak S. Selenium: Significance, and outlook for supplementation. Nutrition. 2013;**29**(5). DOI: 10.1016/j.nut.2012.11.012

[16] Xia Y, Hill KE, Li P, et al. Optimization of selenoprotein P and other plasma selenium biomarkers for the assessment of the selenium nutritional

requirement: A placebo-controlled, double-blind study of selenomethionine supplementation in selenium-deficient Chinese subjects. American Journal of Clinical Nutrition. 2010;**92**(3). DOI: 10.3945/ajcn.2010.29642

[17] Kipp AP, Strohm D, Brigelius-Flohé R, et al. Revised reference values for selenium intake. Journal of Trace Elements in Medicine and Biology. 2015;**32**:195-199. DOI: 10.1016/j.jtemb.2015.07.005

[18] Neville MC, Keller R, Seacat J, et al. Studies in human lactation: Milk volumes in lactating women during the onset of lactation and full lactation. American Journal of Clinical Nutrition. 1988;**48**(6):1375-1386. DOI: 10.1093/ajcn/48.6.1375

[19] Hariharan S, Dharmaraj S. Selenium and selenoproteins: It's role in regulation of inflammation. Inflammopharmacology. 2020;**28**(3). DOI: 10.1007/s10787-020-00690-x

[20] Dumont E, Vanhaecke F, Cornelis R. Selenium speciation from food source to metabolites: A critical review. Analytical and Bioanalytical Chemistry. 2006;**385**(7). DOI: 10.1007/s00216-006-0529-8

[21] Lobinski R, Edmonds JS, Suzuki KT, Uden PC. Species-selective determination of selenium compounds in biological materials (technical report). Pure and Applied Chemistry. 2000;**72**. DOI: 10.1351/pac200072030447

[22] Pezzarossa B, Petruzzelli G, Petacco F, Malorgio F, Ferri T. Absorption of selenium by Lactuca sativa as affected by carboxymethylcellulose. Chemosphere. 2007;**67**(2). DOI: 10.1016/j.chemosphere.2006.09.073

[23] Tinggi U. Determination of selenium in meat products by hydride generation atomic absorption spectrophotometry. Journal of AOAC International. 1999;**82**(2). DOI: 10.1093/jaoac/82.2.364

[24] Tinggi U, Reilly C, Patterson CM. Determination of selenium in foodstuffs using spectrofluorometry and hydride generation atomic absorption spectrometry. Journal of Food Composition and Analysis. 1992;**5**(4). DOI: 10.1016/0889-1575(92)90061-N

[25] Kieliszek M, Bano I, Zare H. A comprehensive review on selenium and its effects on human health and distribution in middle eastern countries. Biological Trace Element Research. 2022;**200**(3). DOI: 10.1007/s12011-021-02716-z

[26] Reilly C. Selenium: A new entrant into the functional food arena. Trends in Food Science and Technology. 1998;**9**(3). DOI: 10.1016/S0924-2244(98)00027-2

[27] Persson T, Popescu BO, Cedazo-Minguez A. Oxidative stress in alzheimer's disease: Why did antioxidant therapy fail? Oxidative Medicine and Cellular Longevity. 2014:11. DOI: 10.1155/2014/427318

[28] Salim M, Durmuş İ, Başeğmez M, Küçükkurt İ, Eryavuz A. Effects of age on the concentrations of plasma cytokines and Lipidperoxidation in sheep. Kocatepe Veterinary Journal. Published online. 2021;**14**:37-44. DOI: 10.30607/kvj.798623

[29] Halliwell B. Antioxidants in human health and disease. Annual Review of Nutrition. 1996;**16**:33-50. DOI: 10.1146/annurev.nu.16.070196.000341

[30] Oguntibeju OO. Type 2 diabetes mellitus, oxidative stress and inflammation: Examining the links. International Journal of Physiology Pathophysiology Pharmacology. 2019;**11**(3):45-63 http://www.embase.

com/search/results?subaction=viewrecord&from=export&id=L2002518543

[31] Hayes JD, Dinkova-Kostova AT, Tew KD. Oxidative stress in cancer. Cancer Cell. 2020;**38**(2):167-197. DOI: 10.1016/j.ccell.2020.06.001

[32] Doğan MF, Kaya K, Demirel HH, Başeğmez M, Şahin Y, Çiftçi O. The effect of vitamin C supplementation on favipiravir-induced oxidative stress and proinflammatory damage in livers and kidneys of rats. Immunopharmacology and Immunotoxicology. Published online. 2023:1-6. DOI: 10.1080/08923973.2023.2181712

[33] Harman D. Free radical theory of aging. Mutation Research DNAging. 1992;**275**(3-6):257-266. DOI: 10.1016/0921-8734(92)90030-S

[34] Ang A, Pullar JM, Currie MJ, Vissers MCM. Vitamin C and immune cell function in inflammation and cancer. Biochemical Society Transactions. 2018;**46**(5):1147-1159. DOI: 10.1042/BST20180169

[35] Cai Z, Zhang J, Li H. Selenium, aging and aging-related diseases. Aging Clinical and Experimental Research. 2019;**31**(8):1035-1047. DOI: 10.1007/s40520-018-1086-7

[36] Katarzyna Z, Sobiech P, Radwińska J, Rekawek W. Effects of selenium on animal health. Journal of Elementology. 2013;**18**(2):329-340. DOI: 10.5601/jelem.2013.18.2.12

[37] Bjørklund G, Shanaida M, Lysiuk R, et al. Selenium: An antioxidant with a critical role in anti-aging. Molecules. 2022;**27**(19):6613. DOI: 10.3390/molecules27196613

[38] Antonyak H, Iskra R, Panas N, Lysiuk R. Selenium. In: Healthy Ageing and Longevity. 2018. pp. 63-98. DOI: 10.1007/978-3-030-03742-0_3

[39] Wu M, Porres JM, Cheng WH. Selenium, selenoproteins, and age-related disorders. In: Bioactive Food as Dietary Interventions for the Aging Population: Bioactive Foods in Chronic Disease States. 2012. p. 227. DOI: 10.1016/B978-0-12-397155-5.00019-2

[40] Lubos E, Loscalzo J, Handy DE. Glutathione peroxidase-1 in health and disease: From molecular mechanisms to therapeutic opportunities. Antioxidants & Redox Signaling. 2011;**15**(7):1957-1997. DOI: 10.1089/ars.2010.3586

[41] Arthur JR. The Glutathione Peroxidases. Cellular and Molecular Life Sciences CMLS. 2000;**57**:1825-1835. DOI: 10.1007/PL00000664

[42] Flohé L, Toppo S, Orian L. The glutathione peroxidase family: Discoveries and mechanism. Free Radical Biology & Medicine. 2022;**187**:113-122. DOI: 10.1016/j.freeradbiomed.2022.05.003

[43] Avissar N, Ornt DB, Yagil Y, et al. Human kidney proximal tubules are the main source of plasma glutathione peroxidase. American Journal of Physiology. Cell Physiology. 1994;**266**(2):35-32. DOI: 10.1152/ajpcell.1994.266.2.c367

[44] Schmutzler C, Mentrup B, Schomburg L, Hoang-Vu C, Herzog V, Köhrle J. Selenoproteins of the thyroid gland: Expression, localization and possible function of glutathione peroxidase 3. Biological Chemistry. 2007;**388**(10):1053-1059. DOI: 10.1515/BC.2007.122

[45] Chung SS, Kim M, Youn BS, et al. Glutathione peroxidase 3 mediates the antioxidant effect of peroxisome

proliferator-activated receptor γ in human skeletal muscle cells. Molecular and Cellular Biology. 2009;**29**(1):20-30. DOI: 10.1128/mcb.00544-08

[46] Imai H, Matsuoka M, Kumagai T, Sakamoto T, Koumura T. Lipid peroxidation-dependent cell death regulated by GPx4 and ferroptosis. Current Topics in Microbiology and Immunology. 2017;**403**. DOI: 10.1007/82_2016_508

[47] Kryukov GV, Castellano S, Novoselov SV, et al. Characterization of mammalian selenoproteomes. Science (1979). 2003;**300**(5624):1439-1443. DOI: 10.1126/science.1083516

[48] Zeng R, Farooq MU, Zhang G, et al. Dissecting the potential of Selenoproteins extracted from selenium-enriched Rice on physiological, biochemical and anti-ageing effects In vivo. Biological Trace Element Research. 2020;**196**(1):119-130. DOI: 10.1007/s12011-019-01896-z

[49] Lu J, Holmgren A. The thioredoxin antioxidant system. Free Radical Biology & Medicine. 2014;**66**:75-87. DOI: 10.1016/j.freeradbiomed.2013.07.036

[50] Papp LV, Lu J, Holmgren A, Khanna KK. From selenium to selenoproteins: Synthesis, identity, and their role in human health. Antioxidants & Redox Signaling. 2007;**9**(7):775-806. DOI: 10.1089/ars.2007.1528

[51] Holmgren A. Thioredoxin and glutaredoxin systems. Journal of Biological Chemistry. 1989;**264**(24):13963-13966

[52] Bianco AC. Minireview: Cracking the metabolic code for thyroid hormone signaling. Endocrinology. 2011;**152**(9):3306-3311. DOI: 10.1210/en.2011-1104

[53] St. Germain DL, Hernandez A, Schneider MJ, Galton VA. Insights into the role of deiodinases from studies of genetically modified animals. Thyroid. 2005;**15**(8). DOI: 10.1089/thy.2005.15.905

[54] Köhrle J, Jakob F, Contempré B, Dumont JE. Selenium, the thyroid, and the endocrine system. Endocrine Reviews. 2005;**26**(7). DOI: 10.1210/er.2001-0034

[55] Low SC, Harney JW, Berry MJ. Cloning and functional characterization of human selenophosphate synthetase, an essential component of selenoprotein synthesis. Journal of Biological Chemistry. 1995;**270**(37). DOI: 10.1074/jbc.270.37.21659

[56] Tamura T, Yamamoto S, Takahata M, et al. Selenophosphate synthetase genes from lung adenocarcinoma cells: Sps1 for recycling L-selenocysteine and Sps2 for selenite assimilation. Proceedings of the National Academy of Sciences of the United States of America. 2004;**101**(46). DOI: 10.1073/pnas.0406313101

[57] Stadtman ER. Protein oxidation and aging. Free Radical Research. 2006;**40**(12). DOI: 10.1080/10715760600918142

[58] Behne D, Kyriakopoulos A, Kalcklösch M, et al. Two new Selenoproteins found in the prostatic glandular epithelium and in the spermatid nuclei. Biomedical and Environmental Sciences. 1997;**10**(2-3)

[59] Kumaraswamy E, Malykh A, Korotkov KV, et al. Structure-expression relationships of the 15-kDa selenoprotein gene: Possible role of the protein in cancer etiology. Journal of Biological Chemistry. 2000;**275**(45). DOI: 10.1074/jbc.M004014200

[60] Labunskyy VM, Hatfield DL, Gladyshev VN. The Sep15 protein family:

Roles in disulfide bond formation and quality control in the endoplasmic reticulum. IUBMB Life. 2007;**59**(1). DOI: 10.1080/15216540601126694

[61] Ferguson AD, Labunskyy VM, Fomenko DE, et al. NMR structures of the selenoproteins Sep15 and SelM reveal redox activity of a new thioredoxin-like family. Journal of Biological Chemistry. 2006;**281**(6). DOI: 10.1074/jbc.M511386200

[62] Lu C, Qiu F, Zhou H, et al. Identification and characterization of selenoprotein K: An antioxidant in cardiomyocytes. FEBS Letters. 2006;**580**(22). DOI: 10.1016/j.febslet.2006.08.065

[63] Korotkov KV, Novoselov SV, Hatfield DL, Gladyshev VN. Mammalian Selenoprotein in which Selenocysteine (sec) incorporation is supported by a new form of sec insertion sequence element. Molecular and Cellular Biology. 2002;**22**(5). DOI: 10.1128/mcb.22.5.1402-1411.2002

[64] Hwang DY, Cho JS, Oh JH, et al. Differentially expressed genes in transgenic mice carrying human mutant presenilin-2 (N141I): Correlation of selenoprotein M with Alzheimer's disease. Neurochemical Research. 2005;**30**(8). DOI: 10.1007/s11064-005-6787-6

[65] Castets P, Lescure A, Guicheney P, Allamand V. Selenoprotein N in skeletal muscle: From diseases to function. Journal of Molecular Medicine. 2012;**90**(10). DOI: 10.1007/s00109-012-0896-x

[66] Castets P, Maugenre S, Gartioux C, et al. Selenoprotein N is dynamically expressed during mouse development and detected early in muscle precursors. BMC Developmental Biology. 2009;**9**(1). DOI: 10.1186/1471-213X-9-46

[67] Arbogast S, Ferreiro A. Selenoproteins and protection against oxidative stress: Selenoprotein N as a novel player at the crossroads of redox signaling and calcium homeostasis. Antioxidants & Redox Signaling. 2010;**12**(7). DOI: 10.1089/ars.2009.2890

[68] Moghadaszadeh B, Rider BE, Lawlor MW, et al. Selenoprotein N deficiency in mice is associated with abnormal lung development. FASEB Journal. 2013;**27**(4). DOI: 10.1096/fj.12-212688

[69] Han SJ, Lee BC, Yim SH, Gladyshev VN, Lee SR. Characterization of mammalian selenoprotein O: A redox-active mitochondrial protein. PLoS One. 2014;**9**(4). DOI: 10.1371/journal.pone.0095518

[70] Sreelatha A, Yee SS, Lopez VA, et al. Protein AMPylation by an evolutionarily conserved Pseudokinase. Cell. 2018;**175**(3). DOI: 10.1016/j.cell.2018.08.046

[71] Burk RF, Hill KE. Selenoprotein P-expression, functions, and roles in mammals. Biochimica et Biophysica Acta - General Subjects. 2009;**1790**(11). DOI: 10.1016/j.bbagen.2009.03.026

[72] Turanov AA, Everley RA, Hybsier S, et al. Regulation of selenocysteine content of human selenoprotein p by dietary selenium and insertion of cysteine in place of selenocysteine. PLoS One. 2015;**10**(10). DOI: 10.1371/journal.pone.0140353

[73] Steinbrenner H, Alili L, Bilgic E, Sies H, Brenneisen P. Involvement of selenoprotein P in protection of human astrocytes from oxidative damage. Free Radical Biology & Medicine. 2006;**40**(9). DOI: 10.1016/j.freeradbiomed.2005.12.022

[74] Steinbrenner H, Bilgic E, Alili L, Sies H, Brenneisen P. Selenoprotein P protects

endothelial cells from oxidative damage by stimulation of glutathione peroxidase expression and activity. Free Radical Research. 2006;**40**(9). DOI: 10.1080/10715760600806248

[75] Atkinson JB, Hill KE, Burk RF. Centrilobular endothelial cell injury by diquat in the selenium-deficient rat liver. Laboratory Investigation. 2001;**81**(2). DOI: 10.1038/labinvest.3780227

[76] Traulsen H, Steinbrenner H, Buchczyk DP, Klotz LO, Sies H. Selenoprotein P protects low-density lipoprotein against oxidation. Free Radical Research. 2004;**38**(2). DOI: 10.1080/10715760320001634852

[77] Steinbrenner H, Speckmann B, Klotz LO. Selenoproteins: Antioxidant selenoenzymes and beyond. Archives of Biochemistry and Biophysics. 2016;**595**. DOI: 10.1016/j.abb.2015.06.024

[78] Ghelichkhani F, Gonzalez FA, Kapitonova MA, Rozovsky S. Selenoprotein S interacts with the replication and transcription complex of SARS-CoV-2 by binding nsp7. Journal of Molecular Biology. 2023;**435**(8):168008. DOI: 10.1016/j.jmb.2023.168008

[79] Pothion H, Jehan C, Tostivint H, et al. Selenoprotein T: An essential oxidoreductase serving as a Guardian of endoplasmic reticulum homeostasis. Antioxidants & Redox Signaling. 2020;**33**(17):1257-1275. DOI: 10.1089/ars.2019.7931

[80] Zhang X, Xiong W, Chen LL, Huang JQ, Lei XG. Selenoprotein V protects against endoplasmic reticulum stress and oxidative injury induced by pro-oxidants. Free Radical Biology & Medicine. 2020;**160**:670-679. DOI: 10.1016/j.freeradbiomed.2020.08.011

[81] Whanger PD. Selenoprotein W: A review. Cellular and Molecular Life Sciences. 2000;**57**(13-14). DOI: 10.1007/PL00000666

[82] Loflin J, Lopez N, Whanger PD, Kioussi C. Selenoprotein W during development and oxidative stress. Journal of Inorganic Biochemistry. 2006;**100**(10). DOI: 10.1016/j.jinorgbio.2006.05.018

[83] Duntas LH. Selenium and inflammation: Underlying anti-inflammatory mechanisms. Hormone and Metabolic Research. 2009;**41**(6). DOI: 10.1055/s-0029-1220724

[84] Tsuji PA, Carlson BA, Anderson CB, Seifried HE, Hatfield DL, Howard MT. Dietary selenium levels affect selenoprotein expression and support the interferon-γ and IL-6 immune response pathways in mice. Nutrients. 2015;**7**(8). DOI: 10.3390/nu7085297

[85] Bentley-Hewitt KL, Chen RKY, Lill RE, et al. Consumption of selenium-enriched broccoli increases cytokine production in human peripheral blood mononuclear cells stimulated ex vivo, a preliminary human intervention study. Molecular Nutrition & Food Research. 2014;**58**(12). DOI: 10.1002/mnfr.201400438

[86] Hoffmann FKW, Hashimoto AC, Shafer LA, Dow S, Berry MJ, Hoffmann PR. Dietary selenium modulates activation and differentiation of CD4 + T cells in mice through a mechanism involving cellular free thiols. Journal of Nutrition. 2010;**140**(6). DOI: 10.3945/jn.109.120725

[87] Ravaglia G, Forti P, Maioli F, et al. Effect of micronutrient status on natural killer cell immune function in healthy free-living subjects aged ≥90 y. American Journal of Clinical Nutrition. 2000;**71**(2):590-598. DOI: 10.1093/ajcn/71.2.590

[88] Mahmoodpoor A, Hamishehkar H, Shadvar K, Ostadi Z, Sanaie S, Saghaleini SH, et al. The effect of intravenous selenium on oxidative stress in critically ill patients with acute respiratory distress syndrome. Immunological Investigations. 2009;**48**(2):147-159. DOI: 10.1080/08820139.2018.1496098

[89] Razaghi A, Poorebrahim M, Sarhan D, Björnstedt M. Selenium stimulates the antitumour immunity: Insights to future research. European Journal of Cancer. 2021;**155**:256-267. DOI: 10.1016/j.ejca.2021.07.013

[90] Carlson BA, Yoo MH, Shrimali RK, et al. Role of selenium-containing proteins in T-cell and macrophage function. Proceedings of the Nutrition Society. 2010;**69**:300-310. DOI: 10.1017/S002966511000176X

[91] Marciel MP, Hoffmann PR. Molecular mechanisms by which Selenoprotein K regulates immunity and cancer. Biological Trace Element Research. 2019;**192**(1):60-68. DOI: 10.1007/s12011-019-01774-8