Selenoproteins in Health

Subjects: Food Science & Technology

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Selenoproteins (SePs) from Se-enriched agricultural foods have attracted increasing attention due to their bioactivities, indicating that Se-containing foods have great potential to be used as natural functional materials for dietary Se supplements. Selenoproteins account for a significant portion of the total Se content in various Se-enriched foods. It can be obtained from plant-based, animal-based sources, and also fungi and yeast sources, which not only provide essential amino acids but also possess physicochemical properties of both Se and proteins. Additionally, Se-containing peptides (SePPs) have also been prepared from Se-enriched plants, such as rice, green tea, soybean, and tuna to explore their potential health benefits. In addition, a variety of factors, including components, amino acid species and sequences, molecular weight, Se status, and structure can significantly affect the bioactivities and functional applications. As several of the SePs identified in mammals are critical selenoenzymes in cells, animal foods that are rich in these SePs are of particular importance. Although Se is not deemed as a crucial element for higher plants, some plants can still integrate it into SePs. Several SePs have been identified in higher plants, including those found in mammalian cells such as GPxs, TrxRs, and selenocysteine methyltransferases. These proteins are also involved in various plant physiology processes, such as antioxidant defense, redox regulation, and Se metabolism.

selenium selenoprotein bioaccessibility bioactivity food resources

1. The Route from Selenoamino Acids to Selenoproteins

Selenoamino acids are present in various Se-containing foods, including soybean [1], rice [2][3], nuts and seeds [4], corns [5], violifolia [6], potato [7], mushroom [8], yeast (e.g., *Saccharomyces cerevisiae*) and some animal products such as seafood and organic meats [9]. However, the level of selenoamino acids in these foods vary widely depending on factors such as the content of Se in the soil where the food is grown and plant species differences, leading to inconsistencies in the SeP composition and content. It has been reported that SeCys, SeMet and MeSeCys are the primary selenoamino acid species found in plants and animals, and they can replace cysteine (Cys) and methionine (Met), respectively, in protein synthesis [10]. These organic Se compounds possesses higher bioavailability than inorganic Se [11]. Additionally, in many previous studies, it was found that a higher portion of protein-bound SeMet is observed in various SePs [4][12][13][14][15]. SeMet is the most common form of Se found in foods, and it can be easily absorbed by the human body, resulting in its high bioavailability [15]. Selenocysteine, on the other hand, is less common in foods and may have lower bioavailability than SeMet. It can be found in certain dietary sources, including soybean [1], corn [5], and rice [5], but its bioavailability can vary depending on the source. As mentioned above, the current understanding of SeP biosynthesis is that SeCys is incorporated into proteins through genetically encoded mechanisms via the normal protein synthesis pathway but utilizes specific

selenoamino acids codons. In contrast, SeMet can be incorporated randomly through non-specific methionine substitution, not as catalytic amino acids [16]. MeSeCys follows a different way, as it is first converted to methylselenol by β-lyase. It is primarily excreted in urine and exhalation or feces but may also pass in the selenide pool [17]. γ-glutamyl methyl-selenocysteine, present in allium and brassica vegetables, is firstly changed to MeSeCys and goes through the same metabolic pathways as MeSeCys [18]. Selenium and sulfur are chemical elements in group 16 of the periodic table. When incorporating oxygen, these elements are known as the oxygen family of molecules, sharing similar chemical properties. Therefore, the substitution of Cys or Met with SeCys or SeMet may have a limited effect on protein structure and function. For selenoenzymes, SeCys is insert specifically into the active site of the protein through a specific codon (UGA) in mRNA in human body [19][20]. In fact, some plant species have been found to contain multiple copies of the genes that encode selenocysteine tRNA and other components of the selenocysteine incorporation machinery, suggesting that the ability to synthesize selenoproteins may be particularly important for plants [21]. Up to now, several selenoenzymes have been identified that are reliant on Se for their catalytic activity, in which the active center contains Se in the form of SeCys moiety [22]. By contrast, to date, SeMet is not typically found in the catalytic site of selenoenzymes. SeMet can be incorporated into proteins during translation instead of methionine if it is present in the growth medium or added to the culture. However, it is not a natural amino acid for selenoenzymes and is not enzymatically converted to the active form of Se in selenoenzymes. Both Cys and SeCys can form reactive thiol (-SH) groups, which are essential for the catalytic function of selenoenzymes. However, SeCys is generally considered to be more reactive and better suited to certain redox reactions compared to Cys. This is due to its lower pKa value, which allows it to react more readily with the oxidizing target, making it well-suited for certain redox actions. However, this does not necessarily make it better suited for all redox reactions compared to Cys. It is important to note that the choice of which amino acid to use in a particular redox reaction depends on various factors, including the specific chemistry nature of the oxidizing reagent and the condition of the active site of the enzyme. It is also important to note that the specific role of selenocysteine and cysteine in selenoenzymes can vary depending on the individual enzyme and its catalytic mechanism. In some cases, Cys is more suitable than SeCys. This is because unwanted side reactions and oxidative damage may happen due to the higher activity of SeCys compared to Cys. Therefore, cysteine may be a better choice for redox reactions where stability and selectivity are important factors.

2. Functional Properties of Selenoproteins in the Human Body

Based on the SelenoDB database, 25 SeP encoded by genes have been identified in the human body, including glutathione peroxidase (GPx), thioredoxin reductase (TXNRD), and iodothyronine deiodinase (DIO). The glutathione peroxidase (GPx)/reductase system is a major antioxidant defense system in cells that is critical in maintaining cellular redox balance. The molecular mass of GPx ranges from 76ku to 95ku. It is a water-soluble tetrameric protein widely present in the body, containing four subunits that are the same or very similar, each subunit having one Se atom. Up to now, eight different isoforms of GPx (GPx 1–8) have been identified in humans, and five of them are seleno-isozymes that contain Se, including cytoplasmic GPx (CGPx or GPx1), gastrointestinal specific GPx (GI-GPx or GPx2), plasma GPx (PGPx or GPx3), phospholipid hydroperoxide GPx (PHGPx4 or

GPx4), and GPx6. Each of these isoforms has been shown to contain Se, with SeCys as the catalytic amino acid in the enzyme's active site [23]. Their activity can reflect the level of Se in the body. They are present in different tissues as biological catalysts in the removal of harmful metabolic peroxide products such as hydrogen peroxide, lipid peroxides, and organic peroxides from the cytoplasm, cell membrane, and extracellular space. This process uses GSH as the electron donor to the peroxide (**Table 1**) [24]. Oxidized GSH is regenerated back to reduced GSH by glutathione reductase, which is not a selenoenzyme, using NADPH as the electron donor. The first type, cytoplasmic GPx (CGPx or GPx1) consists of 4 subunits of the same molecular weight of 22kDa to form a tetramer [25]. Each subunit contains one molecule of SeCys [26], widely present in various tissues in the body, with the liver and red blood cells being the most predominant. Its physiological function is mainly to catalyze the GSH participation in peroxidation reactions, removing peroxide and hydroxyl free radicals produced in the process of cellular respiratory metabolism. This action alleviates the peroxidation of polyunsaturated fatty acids in cell membranes. The second type, gastrointestinal specific GPx2, is a tetramer composed of 4 subunits with a molecular weight of 22 kDa. It is only present in the gastrointestinal tract of rodents, and its function is to protect animals from the damage of ingesting lipid peroxides [27]. The third type, plasma GPx3, shares the same composition as CGPx and is mainly distributed in plasma. Its function is not well understood, but it has been confirmed to be related to the removal of extracellular hydrogen peroxide [28] and participation in GSH transport [29]. The last, phospholipid hydrogen peroxide GPx4, is a monomer with a molecular weight of 20 kDa, containing one molecule of SeCys. It shares the amino acid motif of SeCys, tryptophan, and glutamine with other GPxs [30]. Originally isolated from pig hearts and livers, it is mainly found in the testicles, but is also distributed to a small extent in other tissues. Its biological function is to inhibit membrane phospholipid peroxidation [31].

The thioredoxin peroxidase/reductase system (TrxP/TrxR) is another key antioxidant system in cells, essential for maintaining cellular redox balance. TrxP and TrxR have distinct active sites where their catalytic reactions take place. In TrxP, the active site includes a redox-active disulfide bond formed between two cysteine residues, which is crucial for its function as a thioredoxin peroxidase. In contrast, the active site of TrxR contains a SeCys residue and a flavin adenine dinucleotide (FAD) cofactor, which are important for its role as a thioredoxin reductase. Thioredoxin (Trx) is a ubiquitous small 12kDa peptide that contains a redox-active disulfide bond and acts as a reducing agent for TrxP, catalyzing the transfer of electrons peroxides and other oxidative molecules, thereby inactivating their reactivity. TrxP is not a selenoenzyme, whereas thioredoxin reductase (TrxR) is. It catalyzes the reduction of oxidized Trx back to its reduced form using NADPH as the electron donor. TrxR reduces oxidized Trx by transferring electrons from NADPH to the active site SeCys residue and then to FAD, leading to the formation of a reduced Trx molecule. On the other hand, TrxP reduces hydrogen peroxide and organic hydroperoxides using electrons from Trx, which itself receives electrons from TrxR. Therefore, TrxR and TrxP work together to maintain redox homeostasis within cells. Additionally, the Trx/TrxR system plays important roles in various other cellular processes, including DNA synthesis, protein folding, and cell signaling [32][33].

Iodothyronine deiodinases (DIOs) are selenoenzymes with three isoforms present in different tissues. All three isoforms are selenoenzymes with SeCys and two histidine residues in the catalytic domain of the enzyme [34][35], and a substrate-binding pocket that accommodates the thyroid hormone molecule. The core physiological functions of DIOs are to act as biocatalysts for the regulation of the activity of thyroid hormones. According to **Figure 1**, the

activation of thyroid hormone is achieved by catalyzing the conversion of inactive thyroid hormone thyroxine (T4) to the primary biologically active thyroid hormone triiodothyronine (T3) via outer-ring deiodination of T4 by DIO1 or DIO2. The inactivation of thyroid hormone occurs through the conversion of T4 to an inactive reduced form T3 (rT3) via inner-ring deiodination of T4 by DIO1 or DIO3, as well as the conversion of T3 and rT3 to diiodothyronine (3,3′-T2) by DIO1, DIO3, DIO1, and DIO2, respectively. This process regulates the levels of active thyroid hormone in the body, and the deiodination is facilitated by the SeCys residue in the active site of the DIOs. Due to the fact that thyroid hormone is linked to the activity level of body metabolism, the control of thyroid hormone activity would regulate the metabolism of the Se. Since DIOs are selenoenzymes, Se deficiency manifests as thyroid hormone dysfunction, which has been associated with various thyroid-related disorders [36][37][38][39]. Selenophosphate synthetase 2 (SEPHS2) is an enzyme that plays a critical role in the biosynthesis of SePs. SEPHS2 catalyzes the synthesis of selenophosphate, which is the activated form of Se used in the incorporation of SeCys into SePs. Dysregulation of SEPHS2 expression or activity has been associated with cancer and neurological disorders, linked to the down-regulation of SeP levels [40][41]. The active site of SEPHS2 is a complex of amino acid residues that cooperate to facilitate the catalytic activity of the enzyme. The crystal structure of SEPHS2 has been determined to have a conserved ATP binding site and a selenophosphate binding site that located at the interface of two domains of the enzyme. This site is formed by several amino acid residues that are critical for catalysis, including a Cys residue, which is involved in the SeCys formation. Other residues are vital for the catalytic capacity of SEPHS2, such as lysine and aspartate, which are involved in ATP binding and stabilization of the intermediate state [42][43][44].

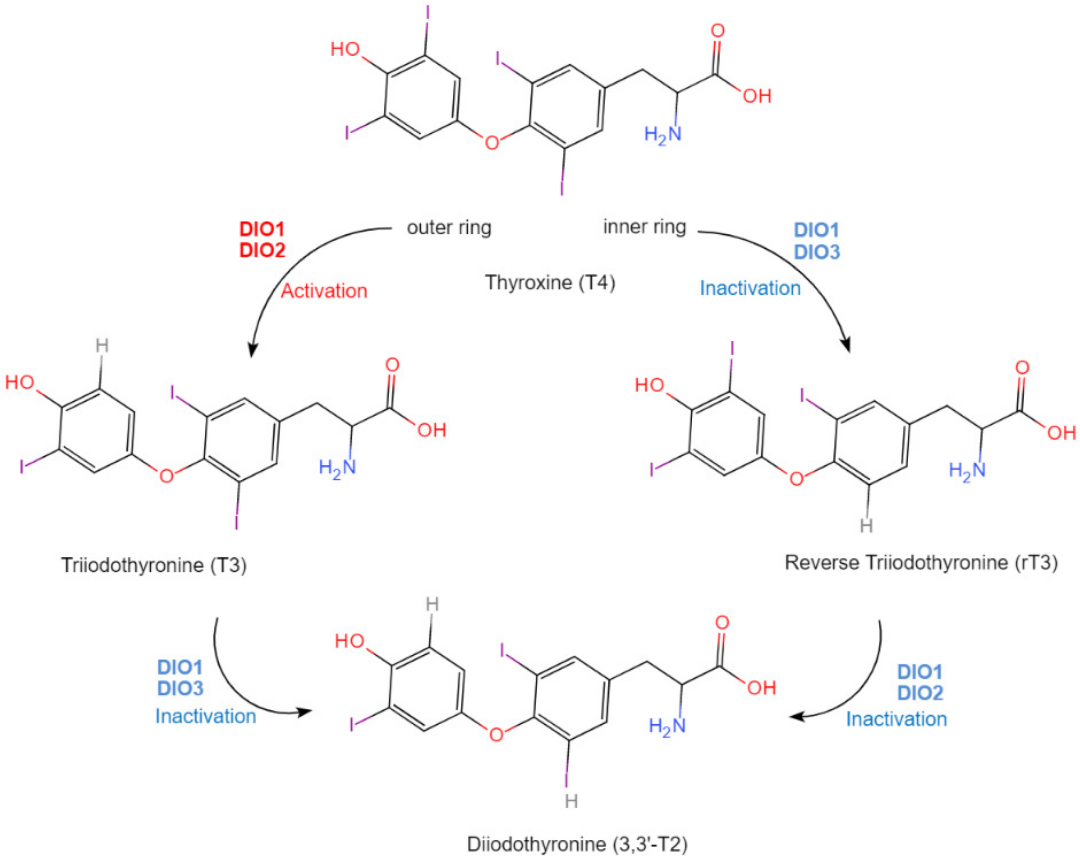

Figure 1. Schematic overview of deiodinase isoforms reactions. DIO1: deiodinase 1; DIO2: deiodinase 2; DIO3: deiodinase 3.

Selenoprotein methionine sulfoxide reductase B1 ($MsrB_1$), also known as selenoprotein R (SelR), is another selenoprotein that plays a role in maintaining cellular redox balance. The active site of MsrB1 is a complex and dynamic region of the enzyme that plays a crucial role in its catalytic activity. The active site of MsrB1 consists of several key amino acid residues that play a critical role in the reduction of oxidized methionine, including catalytic residue SeCys/Cys 95 and the resolving residue Cys 4, as well as Trp 43, His 80, Phe 82, Asp 83, Arg 93, and Phe 97, all of which assist in the catalytic process. $MsrB_1$ functions as a methionine sulfoxide reductase, catalyzing the reduction of methionine sulfoxide to methionine. This reaction is important for repairing oxidative damage to proteins, as oxidation of methionine residues in proteins can lead to loss of protein function and accumulation of damaged proteins. $MsrB_1$/SelR is also involved in regulating cellular signaling pathways, particularly those involved in cell survival and inflammation. $MsrB_1$/SelR has been shown to modulate the activity of various transcription factors, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and activator protein 1 (AP-1), which are involved in the regulation of immune and inflammatory responses [45]. In addition, $MsrB_1$/SelR has been implicated in the regulation of cell proliferation and apoptosis, as well as in the development of various diseases, such as cancer, neurodegenerative disorders, and cardiovascular disease [46].

Selenoprotein P (SelP), which contains ten Se atoms per molecule as SeCys, totaling about 60% of plasma Se [47], acts as a carrier of SeCys to tissues. Human clinical studies have shown that its low level is linked to Alzheimer's disease, type 2 diabetes, and cardiovascular disease [48][49]. **Table 1** lists other selenoproteins and their known functions to date.

Table 1. Functional selenoproteins.

Selenoprotein	Name	Specific/Rich in	Main Function(s)	Reference
Glutathione Peroxidase (GPx)	GPx1 (or CGPx)	Nearly all Mammalian Tissues	A family of peroxidases that reduces H_2O_2, lipid peroxides and organic peroxides from the cytoplasm, cell membrane, and extracellular space of human cells using glutathione as the e^- donor in reducing peroxide-induced oxidative stress.	[24][50]
	GPx2 (or GI-GPx)	Gastrointestinal Epithelial Cells (Cytoplasm, Extracellular)		
	GPx3 (or PGPx)	Plasma/Intestine (Extracellular, Plasma)		
	GPx4 (or PHGPx)	Sperm (Biological Membrane/Cytomembrane (Phospholipid))		
	GPx6	Embryonic Tissue/Epithelial Tissue of Olfactory Organs		
Thioredoxin Reductase (TrxR)	TrxR1	Extracellular Matrix	Reduces thioredoxin, the e^- donor for	[32][33][51]

Selenoprotein	Name	Specific/Rich in	Main Function(s)	Reference
			peroxiredoxin reduction of H_2O_2 and other peroxides. Using flavin adenine dinucleotide (FAD) as a coenzyme, it catalyzes the reduction of thioredoxin (Trx) by NADPH. It participates in various cellular processes, including DNA synthesis, protein folding, and cell signaling, and is implicated in several diseases, including cancer and neurodegenerative disorders.	
	TrxR2	Mitochondria		
	TrxR3	Testis		
Iodothyronine Deiodinase (DIO)	DIO1	Liver/Kidney	Regulation of thyroid gland secretion, thyroid hormone metabolism, and neuron health.	[36][52]
	DIO2	Pituitary Gland/Skeletal Muscle/Thyroid/Heart/Fat/CNS		
	DIO3	Brain/Fetal Tissue/Placenta		
Selenophosphate synthetase 2	SEPHS2	Testes/Liver/Kidney/Brain	Catalyzing the synthesis of selenophosphate from selenide and adenosine triphosphate (ATP), it serves as the selenium donor for selenoprotein and helps maintain proper functioning of selenoproteins.	[40][53][54]
Selenoprotein methionine sulfoxide reductase B1	SelR/$MsrB_1$	Cell Nucleus/Cytoplasm	Maintains cellular redox balance, repairs oxidative damage to proteins, regulates cellular signaling pathways, and regulates cell proliferation and apoptosis.	[45][46]
15-kDa Selenoprotein	Sep15	Various Tissues and Organs	Is involved in oxidative stress regulation, protein folding, thyroid hormone metabolism, and immune function.	[55]

Selenoprotein	Name	Specific/Rich in	Main Function(s)	Reference
Selenoprotein H	SelH	Brain/Nervous System	Cell cycle regulation. Regulates the activity of the nuclear kernel oxidative enzyme and exhibits potential in cancer prevention.	[56][57]
Selenoprotein I	SelI	Testes	Phospholipid biosynthesis.	[36]
Selenoprotein K	SelK	Endoplasmic Reticulum Membrane	Regulates oxidative stress and endoplasmic reticulum stress. Immunity, inflammation and calcium ion adjustment. Regulates endoplasmic reticulum homeostasis and protein folding. Protects skeletal muscles from damage and is required for satellite cells-mediated myogenic differentiation.	[58][59][60][61]
Selenoprotein M	SelM	Brain/Heart/Liver/Kidney/Skeletal Muscle	Maintenance of Ca^{2+} ions, protein folding, promotion of hypothalamic leptin signaling, and thioredoxin antioxidant activity; overexpression of Sel M; activates Parkin-mediated mitophagy to reduce mitochondrial apoptosis and remove HFD-damaged mitochondria.	[62][63]
Selenoprotein N	SelN	Skeletal Muscle	Growth and development of muscles and protein folding.	[64]
Selenoprotein O	SelO	Brain/Liver/Kidney/Testes	Regulation of redox reactions.	[65]
Selenoprotein P	SelP	Liver/Plasma	Se carrier. Transportation of Se to brain and other tissues of the body. Protein folding. Prevention of ferroptosis-like cell death and stress-	[66][67][68]

Selenoprotein	Name	Specific/Rich in	Main Function(s)	Reference
			induced nascent granule degradation.	
Selenoprotein S	SelS	Plasma/Endoplasmic Reticulum/Immune cells	Regulation of inflammation and redox reactions.	[69][70]
Selenoprotein T	SelT	Brain	Regulation of neuronal function and protection against oxidative stress; regulation of a variety of cellular processes, including calcium signaling, endoplasmic reticulum (ER) stress response, and regulation of protein synthesis.	[71]
Selenoprotein V	SelV	Testes	Expression of taste, regulation of redox homeostasis, and protection against oxidative stress.	[36]
[74] Selenoprotein W	SelW	Mitochondria/Skeletal Muscle/Heart/Brain/Liver/Testes	Oxidative stress regulation, bone remolding and muscle growth. Ensures physiological bone remodeling by preventing hyperactivity of osteoclasts.	[57][72][73]

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in the liver, which might be mediated by the gut microbiota. All these findings point to the possible use of sodium selenite as a functional supplement to support body health.

However, the safe and effective use of inorganic Se, such as sodium selenite as a supplement, is still a challenge, considering its low bioavailability and high cytotoxicity. Numerous evidence indicates that organic Se from foods is more effective than inorganic Se in providing antioxidant protection to cells and tissues, thereby contributing to the many documented health benefits of inorganic Se [2][76][77][78][79]. Selenium also occurs naturally as SeP in many plants and fungi, including *Cardamine violifolia* [6][80], soybean [1][15][81][82][83][84], corn [5], brown rice [2][3][85][86], rice [12][14][87][88], algae [89][90][91][92][93], mushroom [8][94][95], peanut [13], maize, cowpea, groundnut [96], etc. As different food categories contain a variety of inorganic and organic Se compounds, their Se profiles vary markedly. Therefore, it is necessary to delineate Se speciation in foods in order to understand their bioavailability and impact on health.

CNS: central nervous system; CGPx: cytoplasm glutathione peroxidase; GI-GPx: gastrointestinal glutathione peroxidase; PGPx: plasma glutathione peroxidase; PHGPx: phospholipid hydroperoxide glutathione peroxidase; MsrB1: methionine sulfoxide reductase B1; SEPHS2: Selenophosphate synthetase 2.

Table 2. Food source of selenoproteins and correlated biological effects.

Source	Se Content (μg/g)	Major Se Species	Identification Method	Study Model	Biological Effects	Reference
Se-enriched *Cardamine violifolia*	2450 ± 80	SeCys, SeMet, MeSeCys	HPLC-AFS LC-MS/MS	In vitro: antioxidant activity assessment assays (DPPH/OH/O_2^-·scavenging capacity test) In vivo: ICR mice (male, four-week-old, SPF grade).	Antioxidant activity and anti-fatigue activity (increase in SOD level, GSH level, and HG level, promotes GPxs activity, suppress MDA and protein carbonyl levels, decrease in BLA and BUN levels).	[6]
Se-enriched *Cardamine violifolia*	215–735	SeMet, MeSeCys, SeCys	HPLC-AFS Nano LC-MS/MS Preparative HPLC	In vitro: antioxidant activity assessment assays (DPPH/OH/O_2^-/ABTS+·scavenging capacity test).	Antioxidant activity.	[80]
Se-enriched soybean	0.33925	SeMet, SeCys	AFS	In vitro: Caco-2 cell In vivo: BALB/c mice (female, six to eight-week-old,18.0 ± 2.0 g body weight).	Antioxidant activity: the presence of SeP from soybean inhibited oxidative stress through upregulating the expression of antioxidant enzymes (GPx, SOD) via modulating the NRF-2/HO-1 signaling pathway. Additionally, the administration of soybean SeP to mice improved the activity of GPx and SOD.	[81]
Se-enriched soybean	6.35–11.47	SeMe, SeCys, SeMeCys	AFS, HPLC ICP-MS, FT-IR SEM	/	/	[15]
Se-enriched soybean	~40	SeMet, SeCys	AFS Q Exactive Orbitrap MS HPLC-MS/MS	In vitro: Caco-2, HepG2 and Endothelial EA. Hy926 cells. In vivo: ICR mice (female, six-week-old) ($_D$-galactose-induced aging mice).	Antioxidant activity: protected cells by suppressing the form of TNF-α inflammatory factors and down-	[84]

Source	Se Content (μg/g)	Major Se Species	Identification Method	Study Model	Biological Effects	Reference
					regulating the expression levels of cellular adhesion factors. Anti-inflammation and anti-aging: the administration of SeP enhanced SOD and GPx-1, reduced aspartate aminotransferase, amine aminotransferase, and NF-κB, and alleviated brain oxidative damage via modulating MAPK/NF-κB pathway in $_D$-galactose-induced aging in mice.	
Se-enriched soybean	Soybean protein isolate: 13.79 ± 0.11 Soybean peptides: 21.78 ± 0.17	SeCys	HPLC-ESI-MS/MS	In vivo: Sprague Dawley rats (male).	Hepatoprotective effects (alleviated liver fibrosis caused by CCL_4 by promoting GPxs synthesis and increasing MMP9 mRNA expression).	[1]
Se-enriched soybean	1.118	Se-MeSeCys, SeMet	AAS MRM HPLC-ESI-MS/MS	/	/	[83]
Se-enriched soybean	75 ± 5	SeMet, SeCys	ICP-MS 2D HPLC-ICP-MS; HPLC-Chip-ESI-ITMS	/	/	[82]
Se-biofortified corn (*Zea mays Lin*)	32.37	SeCys, SeMet, MeSeCys	AFS HPLC-ESI-MS/MS	In vitro: antioxidant activity assessment assays (DPPH/OH/O_2^-·scavenging capacity test, inhibition of linoleic acid peroxidation)	Antioxidant, hepatoprotective (suppressed MDA, improved SOD and GPxs activities, decreased	[5]

Source	Se Content (μg/g)	Major Se Species	Identification Method	Study Model	Biological Effects	Reference
				In vivo: BALB/c mice (male, SPF grade)	oxidative stress, inhibited hepatic injury).	
Se-enriched rice	Water-soluble SeP: 22.01 ± 0.34; alkali-soluble SeP: 8.26 ± 0.40; salt-soluble SeP: 1.67 ± 0.07; alcohol-soluble SeP: 0.073 ± 0.13	/	AFS	In vitro: antioxidant activity assessment assays (DPPH/OH) In vivo: Kunming mice (male, four-week-old, 20–25 g body weight)	Antioxidant activity: high free radical (DPPH, OH) scavenging effect. The administration of rice SeP (25 μg/kg/day) enhanced the activities of T-AOC, GPx, SOD, reduced MDA levels, reduces adipocytes, alleviates body weight, liver damage, and the abnormal decrease of the liver coefficient in aging mice. However, the high dose of SeP administration was found to cause hypertoxicity.	[87]
Se-enriched rice	12.84 ± 0.05	SeMet	ICP-MS, RP-UPLC-Triple-TOF MS/MS	In vitro: RAW264.7 cell study	Immunomodulatory activity: the SeP hydrolysate enhanced phagocytosis and proliferation of RAW 264.7 cell and suppressed NO production. However, phagocytosis rate declined when the SeP hydrolysate concentration exceeded 100 μg/mL.	[14]
Se-enriched	SeP hydro	SeMet	AFS, Scide Triple TOF-	In vitro: RAW264.7 cell study	Anti-inflammatory: suppressed the	[2]

Source	Se Content (μg/g)	Major Se Species	Identification Method	Study Model	Biological Effects	Reference
brown rice	lysates: 0.156–1.79		LC-MS/MS		production of NO, PGE_2, IL-6, IL-1β and TNF-α; inhibited the expression of iNOS and COX-2.	
Se-enriched rice	/	SeMet	SEC-HPLC HPLC-ICP-MS	In vitro: PC12 cell and RAW264.7 cell study	Protected against Pb_2^+ induced apoptosis.	[12]
Se-enriched brown rice	6.26	SeCys, MeSeCys, SeMet	2D-LC, HPLC-ICP-MS, ESI FT-ICR MS	In vitro: antioxidant activity determination (DPPH/ABTS + scavenging capacity test, ORAC value, chromium VI-reducing activity, and inhibition activity of linoleic acid emulsion peroxidation)	Antioxidant activity: SeP isolated from brown rice possessed higher ORAC values and free radical scavenging activity than native protein.	[3][86]
Se-fertilized maize, cowpea and groundnut	/	SeMet, SeMeSeCys, SeCys	ICP-MS, HPLC-ICP-MS	/	/	[96]
Se-enriched peanut	9.71	SeMet, SeCys, MeSeCys	ICP-MS, HPLC-ICP-MS	In vitro: AML-12 cell. In vivo: ICR mice (four-week-old)	Exhibited antioxidant activity: peanut SeP suppressed oxidative stress, reversed cell viability and cell death, inhibited ethanol-induced cytochrome P4502E1 activation, and restored GPx enzyme levels. Ameliorated alcohol-induced liver damage: the administration of peanut SeP reduced oxidative stress through modulating	[13]

Source	Se Content (μg/g)	Major Se Species	Identification Method	Study Model	Biological Effects	Reference
					MAPK/NF-κB pathway, regulated lipid metabolism, and minimized liver damage.	
Se-containing *Spirulina platensis*	0.67–1.99		ICP-MS	In vitro: antioxidant assessment assay (ABTS+); RAW264.7 cell study	Exhibited antioxidant and anti-inflammatory activities (suppressed inflammatory cytokines, including IL-6, TNF-α, MDA, and IL-1β; decreased the production of NO but promoted the activities of SOD and GPxs).	[89]
Se-containing *Spirulina platensis*	/	/	ICP-AES	In vitro: MC3T3-E1 mouse preosteoblast cells	Prevented mitochondrial dysfunction: balanced the expression of the Bcl-2 family while controlling the opening of the mitochondrial permeability transition pore (MPTP). Additionally, recovered oxidative damage induced by cisplatin. This effect was achieved by inhibiting the excessive generation of reactive oxygen species (ROS) and superoxide anions. Consequently, the process reversed both early and late	[90]

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than 90% as organic forms and as SeMet in maize (92.0%), groundnut (85.2%), and cowpea (63.7%) from biofortified crops. The mean bioaccessibility of the Se from the biofortified grains was 73.9%, with no significant difference across all crops, but there was a higher bioaccessibility of Se in the grains of legumes than in maize. Moreover, Se-enriched yeast is another way to obtain organic Se species, including SePs and selenoamino acids. Se-enriched yeast can be obtained through growing yeast in Se-containing cultures. Commonly, a culture with 30 μg/mL Na_2SeO_3 can result in Se accumulation in the range of 1200–1400 μg/g dried yeast (*Saccharomyces cerevisiae*), and the inorganic Se can be bio-transformed in yeast to form SePs [97][98].

Source	Se Content (μg/g)	Major Se Species	Identification Method	Study Model	Biological Effects	Reference
					apoptosis triggered by cisplatin, as it inhibited the cleavage of PARP and the activation of caspases.	
Se-enriched *Chlorella vulgaris*	/	SeMet, SeCys, MeSeCys	ICP-MS, GC-APCI-HRMS, HPLC-ICP-MS GC, MS	/	The SeP from *Chlorella vulgaris* has higher bioaccessibility (~49%) as compared to Se-supplements (~32%), Se-yeast (~21%), and Se-foods.	[13] [96] [59] [93] [15]
Se-containing monkeypot nut seeds (*Lecythis minor*)	4480 ± 22	SeMet	ICP-MS, ESI-Q-TOF LC–MS/MS	/	/	[8] [98] [1][84] [4] [83]
Se-enriched mushroom (*Agaricus blazei*)	8.2–26.1	SeCys, MeSeCys, SeMet	HG-AFS HPLC-MS/MS	/	/	[95]
Se-enriched mushroom (*Agaricus bisporus*)		$SeCys_2^{2+}$ [2]	LC-ESI-MS	In vivo: Sprague Dawley rats (male, 9-week-old).	Antioxidant activities and protection against colorectal cancer (promoted the gene expression of GPx-1 and GPx-2 and enzyme activity of GPx-1 in rat colon).	[6][80] [8][94] [12]

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protein's secondary structure, including the α-helix, β-sheet, β-turn, and random coil structures [99]. The resulting change in secondary structure arising from the change in the primary structure might further influence some physicochemical and biological properties of the protein. Within a polypeptide chain, Se can be incorporated as a SeCys residue which can form covalent Se-Se bonds with neighboring amino acids within the protein [70].

SeCys in SePs can influence both the disulfide bond and the secondary structure of proteins, and possibly protein folding, thus altering the protein functional properties. In addition, the tertiary structure of proteins depends on the disulfide bridge formation, which happens during the oxidation of two neighboring Cys. Proteins with diselenide bonds are more likely to undergo reduction than those with disulfide bonds due to the longer length of the diselenide bridge compared to the disulfide bridge, giving it a lower redox potential. But the effects of Se incorporation on protein structure and on the protein functional properties in foods are poorly documented [100].

HPLC: high performance liquid chromatography; RP-UPLC: reversed phase ultra-performance liquid chromatography; AAS: atomic absorption spectrometer; AES: atomic emission spectroscopy; AFS: atomic fluorescence spectrometry HG-AFS; ICP: inductively coupled plasma; MS: mass spectrophotometer; SEC: size exclusion chromatograph; ESI: electrospray ionization; FT-ICR MS: Fourier transform ion cyclotron resonance mass spectrometry; TOF-MS: time-of-flight mass spectrometry; Q-TOF-MS: Quadrupole time-of-flight mass

3.2. Biological Activity of Selenoproteins from Food

Food sources of SeAA and SeNPs and their corresponding biological effects are tabulated in Table 2.

It has been observed that SeP possesses higher antioxidant activity than Se-free protein/peptides [3][81][84]. The Se-enriched soybean protein isolate displayed stronger free radical scavenging ability compared to the native soybean protein isolate [81]. Selenoprotein from soybean inhibited induced oxidative stress in Caco-2 cell through upregulating the expression of selenium (GPx) and non-selenium (SOD) antioxidant enzymes and regulating the NRF-2/HO-1 signaling pathway. This pathway is responsible for modulating calcium levels, preventing pyroptosis, ferroptosis, autophagy, alkaliptosis, clockophagy, and programmed cell necrosis [101]. Administration of soybean SeP (5, 20, 40 µg/kg body weight/day) to mice improved the activity of GPx and SOD in tissues [81]. A SePP fraction isolated from Se-enriched brown rice has higher oxygen radical antioxidant capacity (ORAC), free radical scavenging activity, and chromium VI-reducing activity compared to original brown rice peptides without Se content [3]. It was also found that the administration of SeP extracted from *Cardamine violifolia* in mice (5, 10, 20 µg/kg body weight/day) increased the levels of GPxs, SOD, and glutathione (GSH) in tissues, while decreasing the levels of malondialdehyde (MDA) (indicative of lipid oxidation) and protein carbonyl (indicative of protein oxidation) in blood [6]. Moreover, dietary supplementation of SeP-containing Se-enriched yeast enhanced both the antioxidant capacity and immune response in juvenile *Eriocheir Sinensis* under nitrite stress [102]. It is recommended to incorporate dietary Se at a concentration of 3.98 mg Se//kg of diet, with 3 mg of Se provided in the form of Se-enriched yeast. This supplementation enhances the growth performance, feed utilization, and positively influence liver and kidney histology in juvenile meagre fish, thereby resulting in potential economic benefits [103].

Selenoprotein isolated from some foods has been shown to possess anti-inflammatory effects. The anti-inflammatory activity of SeP isolated from algae (*Spirulina platensis*) was evaluated on RAW264.7 macrophages. The results showed that treatment with SeP (0.31–125 µg/mL) suppressed production of inflammatory cytokines, including interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α), MDA, and interleukin-1β (IL-1β). Moreover, it led to a decrease in the production of nitric oxide (NO) while increasing the activities of SOD and GPxs [89]. Similarly, the SeP obtained from Se-enriched brown rice was found to suppress the production of NO, prostaglandin E2 (PGE_2), IL-6, IL-1β and TNF-α, as well as inhibit the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in cultured macrophages [2]. Selenoproteins from Se-enriched soybean protected endothelial cells through suppressing the production of TNF-α inflammatory factors and down-regulating the expression of cellular adhesion factors [56]. Administration of SeP (30 µg Se/kg body weight/day) enhanced SOD and GPx-1, reduced aspartate aminotransferase, amine aminotransferase, and NF-κB, and alleviated brain oxidative damage via modulating mitogen-activated protein kinase (MAPK)/NF-κB pathway in $_D$-galactose-induced aging mice. Rice SeP hydrolysate applied at 20–100 µg/mL enhanced phagocytosis and proliferation of macrophages and suppressed NO production by the cells.

Selenoproteins also possess hepatoprotective properties [1][5][13][87]. The SeP extracted from soybean alleviated liver fibrosis caused by chemokine ligands 4 (CCL_4) by promoting GPxs synthesis and increasing the mRNA expression of matrix metallopeptidase 9 (MMP9) in rats [1]. The administration of peanut SeP reduced oxidative stress through modulating MAPK/NF-κB pathway, regulate lipid metabolism, and alleviated liver damage in mice [13]. Administration of rice SeP (10, 25 µg/kg/day) enhanced the antioxidant capacity (T-AOC) and the activities of

Spectrometry; GSH-Px: glutathione peroxidase; H&E: hematoxylin and eosin; HPLC: high performance liquid chromatography; HRMS: high resolution mass spectrometry; MRM: multiple reaction monitoring; FR-IR: Fourier-transform infrared spectroscopy; SEM: scanning electron microscope; ABTS: 2,2′-azino-bis-3-ethylbenzthiazoline-6-sulphonic acid scavenging assay; CCL_4: chemokine ligands 4; MMP9: matrix metallopeptidase 9; IL-6: interleukin 6; TNF-α: tumor necrosis factor-α; MAPK: mitogen-activated protein kinase; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; T-AOC: total antioxidant capacity; MDA: malondialdehyde; IL-1β: interleukin-1β; NO: nitric oxide; SOD: superoxide dismutase; GPxs: glutathione peroxidase; PGE_2: prostaglandin E_2; iNOS: inducible nitric oxide synthase; COX-2: cyclooxygenase-2; GSH: glutathione; HG: hepatic glycogen; BLA: blood lactic acid; BUN: blood urea nitrogen; Bcl-2: B-cell lymphoma 2; PARP: poly ADP ribose polymerase; DPPH: 1,1-diphenyl-2-picrylhydrazyl free radical scavenging assays; ORAC: oxygen radical absorbance capacity; MMP: matrix metalloproteinase 9; Caco-2 cell: human colorectal adenocarcinoma cell; RAW 264.7: macrophage cell line that was established from a tumor in a male mouse induced with the Abelson murine leukemia virus; PC12 cell: a cell line derived from a pheochromocytoma of the rat adrenal medulla; HepG2 cell: hepatocellular carcinoma cell line; Endothelial EA. Hy926 cells: human umbilical vein endothelial cell line; AML-12 cell: alpha mouse liver 12 cell; MC3T3-E1 cell: osteoblast precursor cell line derived from Mus musculus calvaria.

total GPx and SOD, reduced MDA and adipocytes levels, and alleviated body weight, liver damage and the abnormal decrease of the liver coefficient in aging mice. Importantly, the high dose of SeP administration (50 μg/kg/day) was found to cause hypertoxicity [87].

Other bioeffects of SeP have also been reported. Selenoprotein isolated from *Spirulina platensis* was found to prevent mitochondrial dysfunction [62]. The presence of SeP balanced the expression of the Bcl-2 family while controlling the opening of the mitochondrial permeability transition pore (MPTP) and recovered oxidative damage induced by cisplatin. This effect is achieved by inhibiting the excessive generation of reactive oxygen species (ROS) such as superoxide anions. Consequently, the process reversed both early and late apoptosis triggered by cisplatin, as it inhibited the cleavage of poly ADP ribose polymerase (PARP) and the activation of caspases. Additionally, it was found that the administration of Se-enriched yeast exhibits protective effects against Cd-induced necroptosis injury by mitigating oxidative stress and suppressing the MAPK pathway in the chicken liver [104]. More studies are still required to uncover the bioactivity or alleviative effects of SeP associated with many other diseases.

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