

# Role of Selenoproteins in Human Health and Diseases

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Received: 13.01.2024; Accepted: 7.07.2024; Published: 6.09.2025

**Abstract:** Selenium is an essential element in biological systems, performing various roles in association with different selenoproteins and selenocompounds. After overcoming several debates and claims of selenium being “The Essential Poison”, it has been shown to be one of the important elements that have a role in different metabolic pathways, antioxidant defense systems, and some long-term conditions in humans. Selenium intake in the case of humans has its own Pros and Cons, with some adverse physiological effects such as toxicity, hair loss, nail loss, poor dental health, skin conditions, etc. Therefore, the ideal specifications for selenium intake in order to maintain good health are still an issue. The center of attention of this review is mainly to understand different categories of selenoproteins and their roles in human health and nutrition, along with their role in human diseases and disorders such as inflammation, cardiovascular diseases, infectious diseases, neuromuscular disorders, neurodegenerative disorders, endocrine disorders, and cancer. With some unknown functions and unidentified mechanisms of action in the case of human health, this is an emerging field of attention for the scientific community.

**Keywords:** selenoproteins; selenoproteome; diet and nutrition; diseases and disorders.

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## 1. Introduction

Biomolecules are the building blocks of life that make up the cells and other structures of organisms and carry out all the life processes [1,2]. These biomolecules are composed of various chemical elements. In living organisms, about 30 different types of chemical elements are found, and these are commonly called biogenic elements. These elements are required to perform important functions in many physiological and biochemical processes. These elements are broadly classified into macrobiogenic, microbiogenic, and trace elements. The macrobiogenic elements (C, O, H, N, S, P, Na, K, Ca, Mg, Cl, Fe) are the basic components of

biomacromolecules and nutritionally important elements called principal elements. Microbiogenic elements (Cu, I, Mo, Mn, Zn, Co) have catalytic functions, i.e., they are part of enzymes. At the same time, the trace elements (Al, As, B, Br, F, Li, Ni, Se, Si, Ti, V) are essential elements. A deficiency of macrobiogenic, microbiogenic, and trace elements can lead to various disorders and may be fatal [3]. In addition to macrobiogenic and microbiogenic elements, trace elements are also essential and required for life processes at chemical, biological, and molecular levels [4]. The trace elements act as cofactors for many enzymes and play a vital role in biochemical reactions, as they are centers for stabilizing protein structures and are involved in oxidation-reduction reactions in energy metabolism [5]. So, there is a requirement for trace elements in the regular diet of humans and animals. The human body daily requires <100 mg of trace elements in their diet. The level higher than needed can be toxic to human health [6]. Therefore, the imbalances in the optimum levels of these trace elements may adversely affect biological processes and are associated with many diseases, such as cardiovascular diseases and cancers.

In the present review, we have focused on the role of selenium and selenoproteins in human health and diseases. Out of the above essential trace elements, selenium (Se) is an important trace element required for vital biological processes in living organisms [7,8]. It is naturally found in organic and inorganic forms. The inorganic forms of selenium, such as selenate, selenide, selenite, and elemental selenium, get deposited in the plants through one of the important sulfur assimilation pathways [9,10], and later converted into organic forms of selenocompounds including selenocysteine (Sec), selenomethionine (SeMet), selenopeptides and selenoproteins (Table 1). Thus, the conversion of inorganic to organic selenium is essential and important for living organisms. There were so many misconceptions about the use of selenium in the diet due to its toxicity. Initially, the discovery by Jons Jacob Berzelius in 1818 was declared one of the essential nutritional components required for various metabolic pathways in biological systems. After a long time, in 1943, it was shown to be a carcinogenic element, resulting in the end of its further use, and it was referred to as "the essential poison" [11]. In 1957, Schwarz and Foltz proved that selenium is one of the important nutritional elements of diet. Daily intake is required for the body to maintain good health. At the optimum level, it is important for the stabilization of the cellular structures. At the same time, low level of selenium may stimulate alternate pathways that lead to deficiency disorders of the skin, lungs, thyroid, and heart as well as necrotic liver degeneration, cardiovascular diseases, cancers, Keshan disease, Kashin–Beck disease, hepatopathy, arthropathy, etc. [12–15]. The higher level of selenium may lead to some serious adverse symptoms, including diarrhea, fatigue, nausea, increased heart rate, neurological damage [16] as well as nail and hair loss, garlic breath, nervous system disorders, poor dental health, and paralysis in some cases [17]. There is still an issue about the specification of intake for good health. It varies from deficient to toxic concentrations. So, there is a need to maintain the selenium intake level in our diet to overcome these deficiencies and toxic diseases.

**Table 1.** List selenocompounds found in dietary supplements and the bodies of humans and animals [18–23].

Chemical Formula	Name of selenocompounds
H <sub>2</sub> Se	Hydrogen selenide
SeO	Selenoxide
SeO <sub>2</sub>	Selenium dioxide
H <sub>2</sub> SeO	Selenious acid
H <sub>2</sub> SeO <sub>4</sub>	Selenic acid
SeO <sub>3</sub> <sup>2-</sup>	Selenite

Chemical Formula	Name of selenocompounds
SeO <sub>4</sub> <sup>2-</sup>	Selenate
GS-Se-H	Glutathionylselenol
GS-Se-SG	Selenodiglutathione
CH <sub>3</sub> -Se-H	Methylselenol
(CH <sub>3</sub> ) <sub>2</sub> Se	Dimethyl selenide
(CH <sub>3</sub> ) <sub>3</sub> Se <sup>+</sup>	Trimethylselenide ion
CH <sub>3</sub> -Se-CH <sub>2</sub> CH <sub>2</sub> - CH(NH <sub>2</sub> )COOH	Selenomethionine
H-Se-CH <sub>2</sub> -CH(NH <sub>2</sub> )COOH	Selenocysteine
HCOO-(NH <sub>2</sub> )CHCH <sub>2</sub> -Se-Se- CH <sub>2</sub> -CH(NH <sub>2</sub> )COOH	Selenocystine
H-Se-CH <sub>2</sub> -CH <sub>2</sub> -CH(NH <sub>2</sub> )COOH	Selenohomocysteine
CH <sub>3</sub> -Se-CH <sub>2</sub> -CH(NH <sub>2</sub> )COOH	Se-methylselenocysteine
NH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -Se-Se-CH <sub>2</sub> -CH <sub>2</sub> - NH <sub>2</sub>	Selenocystamine
HCOO-CH(NH <sub>2</sub> )-CH <sub>2</sub> -Se-CH <sub>2</sub> - CH <sub>2</sub> -CH(NH <sub>2</sub> )COOH	Selenocystatnine
CH <sub>3</sub> -Se-CH <sub>2</sub> -C(O)-COOH	Methylselenopyruvate
GS-Se	GSH-conjugated selenide
FeSe <sub>2</sub>	Iron (II) selenide
(NH <sub>2</sub> ) <sub>2</sub> CSe	Selenourea
Na <sub>2</sub> Se	Sodium selenide
Na <sub>2</sub> SeO <sub>3</sub>	Sodium selenite
Na <sub>2</sub> SeO <sub>4</sub>	Sodium selenate
K(SeCN)	Potassium selenocyanide
SeOCl <sub>2</sub>	Dichloro selenium tetrachloride
SeOF <sub>2</sub>	Difluoro selenium tetrachloride
C <sub>12</sub> H <sub>10</sub> Se <sub>2</sub>	Diphenyl diselenide
CuSeO <sub>4</sub>	Copper (II) selenate
CdSe	Cadmium selenide

## 2. Role of Selenoproteins in Human Health and Nutrition

The fundamental micronutrient selenium influences human health outcomes, e.g., autoimmune diseases, cardiovascular diseases, and cancers. Therefore, the intake of selenium and selenocompounds is essential for proper biological function. In the case of humans, the nourishing elements of selenium are accomplished by 25 selenoproteins. Well-portrayed selenoproteins, such as GPXs, TXNRDs, and DIOs, are oxidoreductases that work as antioxidant enzymes and cell reinforcement proteins in order to regulate redox-sensitive pathways and thyroid hormone metabolism. Some selenoproteins are involved in the maintenance of endoplasmic reticulum homeostasis, such as selenoprotein S, K, and Sep15, encourage selenium transport (selenoprotein P) while some are involved in the biosynthesis of selenocysteine (selenophosphate synthetase2) [23,24]. Numerous selenoproteins are significant in the well-being of humans, which appear by the impact of single nucleotide polymorphisms (SNPs) in their genes that affect their ability to deal with selenium, resulting in disease risk or mortality [25].

### 2.1. Dietary selenium and selenoproteins.

For the synthesis of selenium or selenocysteine-containing biomolecules, selenium can be consumed from dietary sources (Table 2). There are different dietary sources, such as plants, algae, seafood, animals, fungi, and bacteria. The content and the amount of selenium can depend on the availability of selenium in the surroundings. In the case of plants or vegetables,

it can vary widely depending on the selenium content of the soil in which it is grown and will also depend on the type of plant species, salinity, accumulation capacity, organic matter, pH, etc. [26–28]. Globally, the Se content of soils varies widely by region. So, the level of Se in vegetables obtained from soil can affect the amount of selenium in animals. In addition to that, Se is found in a plethora of seafood, fungi, and animal sources, and it is fed to them with Se feed additives. The recommended levels of selenium intake for maintaining the metabolism and homeostasis in the human body are 55 µg/day for males and 70 µg/day for females, and may vary across various locations [27]. The higher or lower consumption of selenium causes Se-related diseases. Generally, Se deficiency is caused by poor dietary intake of Se and leads to infertility, heart disease (e.g., cardiomyopathy, arrhythmias), neuronal or neuromuscular diseases, and increased susceptibility to cancer, heavy metal toxicity, and infection [29]. The upper level of Se concentration is <400 µg for adults/per day [30]. Excess dietary Se causes adverse effects known as selenosis, including acute food poisoning symptoms, such as nausea, vomiting, and diarrhea, as well as chronic toxicity manifested by gastrointestinal disturbances, hair and nail brittleness and loss, infertility, and nervous system abnormalities [31,32]. Therefore, there is a need to take a selenium-containing diet to fulfill the needs of the day. The various dietary sources are depicted in Table 2, and the intake and tolerance levels of selenium are reported by Hariharan et al., 2020 [27].

**Table 2.** List some major dietary selenocompounds and their sources.

Selenocompounds	Sources	Ref.
Selenocysteine (Sec)	Animal foods	[21]
Selenomethionine(SeMet)	Plant sources	[21,33,34]
Se-methylselenocysteine(MeSeCys)	Selenium-enriched plants such as garlic, onions, broccoli florets, sprouts and wild leeks	[21,33,35]
γ-glutamyl-Se-methylselenocysteine	Plant sources such as selenium-enriched garlic, onions, broccoli and yeast	[21]
Selenoneine (2-selenyl-Nα,Nα,Nα-trimethyl-L-histidine)	Squid, tilapia, pig, chicken, tuna and mackerel	[21]
Selenate	Fish, animals, and plant sources	[21,33]
Sodium selenite	Plant sources	[21]

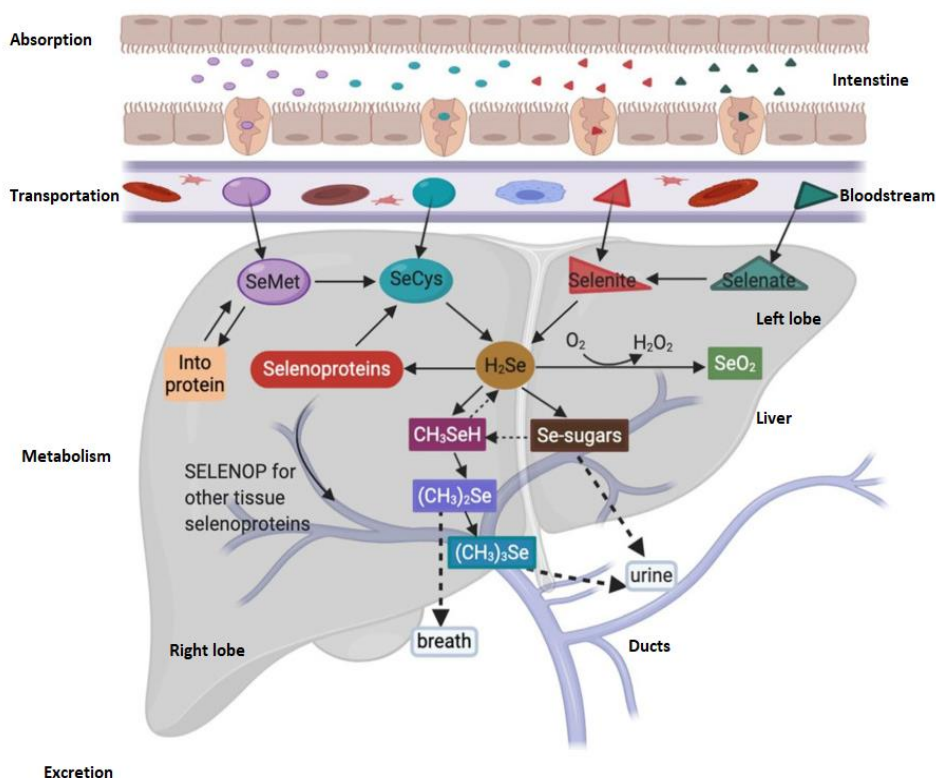
### 2.2. ADME of selenium and selenocompounds.

It is now clear that selenium plays vital roles in different metabolic pathways, including thyroid hormone metabolism, immune functions, antioxidant defense systems, etc. [37]. In humans and animals, selenium enters with food in the form of various selenomethionine (SeMet) and other selenocompounds (Table 1) through the digestive tract. The process of transportation is different depending on the chemical form of selenocompounds [38]. After intestinal absorption, different forms of Se enter the bloodstream and are transported to the liver via the portal vein, where they are metabolized, transported, and distributed to different body tissues (Figure 1) [39,40]. The steps involved in the transportation of Se in the form of various selenocompounds to different parts of the body are shown in Table 3 and Figure 1.

**Table 3.** List of reactions or steps involved in the transportation of dietary selenium or selenocompounds to various parts of the human body.

Steps	Reaction or activity
<b>Absorption and metabolism</b>	
1	$2H^+ + 4GSH + SeO_3^{2-} \rightarrow GSSG + Gs-Se-SG + 3H_2O$
GS-Se-SG decomposition	
2	<ul style="list-style-type: none"> <li>• <math>GS-Se-SG + NADPH \rightarrow GS-Se^- + GSH + NADP</math></li> <li>• <math>GS-Se^- + H_2O \rightarrow Se^0 + GSH + OH^-</math></li> </ul>

	<ul style="list-style-type: none"> <li>• <math>GS-Se^- + NADPH + H_2O \rightarrow HSe^- + GSH + NADP^+ + OH^-</math></li> <li>• <math>GS-Se^- + GSH \rightarrow HSe^- + GSSG</math></li> <li>• <math>HSe^- (O) \rightarrow Se^0 + OH^-</math></li> <li>• <math>HSe^- + (O) + 2GSH \rightarrow HSe^- + GSSG + H_2O</math></li> </ul>
3	Selenite reduction to selenide
4	Selenate absorption and reduction to selenite
5	Incorporation of SeMet
6	SeMet transformation (SeCys)
7	SeCys to selenide via trans-selenation pathway
8	Methylation of excess SeMet
9	Hydrolysis of GGSeMCys
10	GGSeMCys absorption and methylation to Mse
<b>Utilization</b>	
11	SePhp generation (Se donor)
12	Incorporation of SeCys into the amino acids (Selenoprotein synthesis)
13	Selenoprotein catabolism, SeCys release
<b>Excretion</b>	
14	Methyltransferases mediated methylation
15	Selenide conversion into an intermediate selenosugar-GS conjugated and then into SeMethyl-N-acetyl-galactosamine (followed by excretion) HSe <sup>-</sup> enters into methylation pathway.



**Figure 1.** Metabolism of various forms of dietary selenocompounds. SeMet, (selenomethionine); SeCys, (selenocysteine); H<sub>2</sub>Se, (dihydrogen selenide); SELENOP, (selenoprotein P); CH<sub>3</sub>SeH, (methyl selenol); (CH<sub>3</sub>)<sub>2</sub>Se, (dimethyl selenide); (CH<sub>3</sub>)<sub>3</sub>Se<sup>+</sup>, (trimethyl selenonium); SeO<sub>2</sub>, (selenium dioxide) [29].

### 2.3. Biosynthesis of selenocysteine and selenoproteins.

Selenoproteins enter with food and are processed through absorption, transportation, and excretion by human or animal metabolism. The process begins with the ingestion of inorganic selenium, which is further reduced to hydrogen selenide (H<sub>2</sub>Se) through glutathione and thioredoxin systems. Further, H<sub>2</sub>Se is reduced to selenophosphate by the selenophosphate synthetase 2 (SEPHS2) enzyme. This activated selenium is then non-specifically incorporated into human proteins by substituting methionine (Met). The SeMet derivatives are then converted into Sec by the action of β-lyase and selenophosphate synthetase.

In this way, human selenoproteins are formed and involved in various cellular functions. The subsequent reaction with phosphoryl-tRNA (PSertRNA[Ser]Sec) yields Sec-tRNA[Ser]Sec. Sec amino acids are inserted into the protein chain through the machinery utilizing the UGA codon. Selenocysteine insertion sequence binding protein 2 binds to SECIS element, which is located in the 3'-untranslated region (3'UTR) of selenoproteins mRNA and mediates the transfer of SectRNA[Ser]Sec to the A-site of the ribosome and recognizes the UGA codon as the Sec integration codon. In some studies, it has been reported that UGA can code for both cysteine and selenocysteine [41]. It can depend on the presence and absence of the SECIS element and the location of UGA on selenoproteins mRNA. This dual activity of the UGA codon makes it difficult to predict selenoproteins from given sequences, and as a result, they are usually misannotated. Selenoproteins' translational mechanism differs from regular protein translation and is composed of Sec-specific eukaryotic elongation factor (eEFSEC), SBP2, SECIS element, and aminoacylated Sec-tRNA [Ser]Sec. This special translation machinery incorporates selenium into various selenoproteins or selenoenzymes [42].

#### *2.4. Classification of selenoproteins.*

There are 25 selenoproteins found in humans, and they are involved in vital human processes such as immune functions, thyroid hormone metabolism, antioxidant defense systems, etc. [43]. Some selenoproteins are involved in the maintenance of endoplasmic reticulum homeostasis, such as selenoprotein S, K, and Sep15, encourage selenium transport (selenoprotein P) while some are involved in the biosynthesis of selenocysteine (selenophosphate synthetase2) [24,25]. Selenoproteins can be broadly classified on the basis of their activity into three classes such as glutathione peroxidases (GPXs), thioredoxin reductases (TXNRDs), and iodothyronine deiodinases (DIOs). The GPXs such as cytosolic (GPX1), gastrointestinal (GPX2), and phospholipid hydroperoxide (GPX4) play a vital role in the decomposition of various peroxides, thereby protecting cells against oxidative damage [14]. The TXNRDs are mostly involved in cellular redox pathways by employing NADPH as an electron donor to revert oxidized TXN to a reduced dithiol and help regulate various cell behaviors, including proliferation and apoptosis [44]. Whereas DOIs help in the regulation of thyroid hormone metabolism by catalyzing the conversion of thyroid hormones from precursor thyroxine (T4) to biologically active triiodothyronine (T3) or inactive reverse T3 (rT3) [45]. Furthermore, Selenoproteins are classified into subfamilies based on their cellular functions such as those implicated in antioxidation (GPX1, GPX2, GPX3, GPX4), redox regulation (TXNRD1, TXNRD2, TXNRD3, MSRB1, SELENOH, SELENOM, SELENOW), thyroid hormone metabolism (DIO1, DIO2, DIO3), selenium transport and storage (Selenoprotein P), selenophosphate synthesis (Selenophosphate synthetase 2), calcium metabolism (Selenoprotein K, Selenoprotein T), myogenesis (Selenoprotein N), protein folding (Selenoprotein F, Selenoprotein I, Selenoprotein S), and protein AMPylation (Selenoprotein O) [11]. The mammalian selenoproteins can also be classified into two groups based on the location of Sec residue in their sequence. The first group contains mammalian selenoproteins K, S, O, I, R, and TRs, which has Sec close to C-terminus of the proteins, whereas the second group contains mammalian selenoproteins H, M, T, V, W, Sep15, SPS2 (selenophosphate synthetase 2), GPXs and DIOs which has Sec in the N-terminal segment of the proteins [46]. Some earlier studies classified selenium-containing proteins into three groups based on the binding mode of selenium to protein such as noncovalent binding selenium-containing proteins, nonspecific covalent binding selenium-containing proteins, and specific covalent

binding selenium-containing proteins. There are so many selenocysteine (Sec)-containing proteins (selenoproteins) that have been identified in all domains of life (Table 4) [27]. A set of these selenoproteins in an organism is known as the selenoproteome, and the discipline is called selenoproteomics, which can be subdivided into subcellular or organelle selenoproteomes such as mitochondrial selenoproteome, nuclear selenoproteome, etc. The organelle selenoproteomes help us to understand the function of selenoproteins at the organelle level. These proteins are involved in various important functions of the cell metabolism. Knowing the structure, function, physicochemical properties, and metabolism of these proteins will help us to understand their role in health and diseases.

**Table 4.** List of human selenoproteins with Sec location, protein size, molecular weight, gene, cellular location, structure, functions, and related health effects.

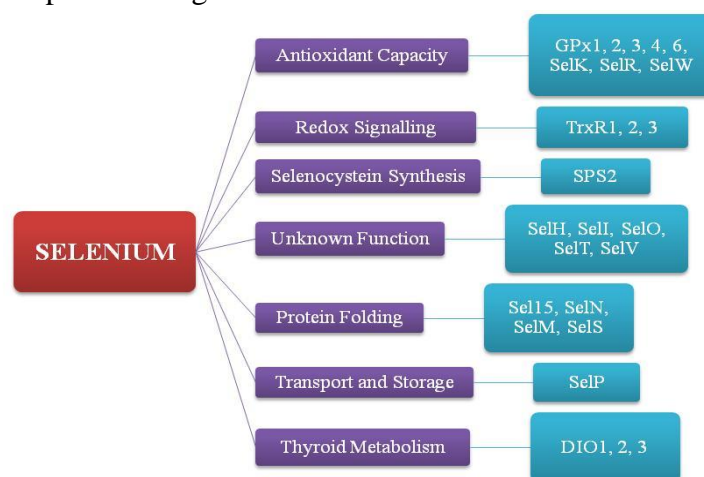
Selenoprotein name	Gene Ref. [33,47]	Sec location, Protein size, Mol. Wt. (kDa) Ref. [38,47]	Structure	Transcript expression	Protein cellular localization Ref. [5]	Function	Health effects and diseases Ref. [27,48,49]	References
Selenoprotein H	<i>SELEN OH</i>	38 116 13	NA	Brain and muscle cells	Cytosol, nucleus	Gene regulation of glutathione, transcription factor, role in oxidative stress	Not known	[27,49]
Selenoprotein I	<i>SELEN OI</i>	387 397 45	NA	Not known	Cytosol	Phospholipid biosynthesis	Not known	[49,50]
Selenoprotein K	<i>SELEN OK</i>	92 94 10	NA	Immune cells and spleen	ER and plasma membrane	Antioxidant activity, role in ER degradation	Not known	[27,38, 45]
Selenoprotein M	<i>SELEN OM</i>	48 145 14	NA	Neuronal cells	ER	Antioxidant activity	Not known	[27,49]
Selenoprotein N	<i>SELEN ON</i>	428 556 61-62	NA	Ubiquitous	ER membrane	Redox signaling, calcium hemostasis, muscle development,	Multimimicore diseases, muscular dystrophy	[41,49, 50]
Selenoprotein O	<i>SELEN OO</i>	667 669 73	NA	Not known	Cytosol	Redox function, ER localization	Not known	[49,50]
Selenoprotein P	<i>SELEN OP</i>	300, 318 381 45-53	NA	Brain, liver and testes	Plasma	Transportation of selenium to tissues, antioxidant activity, a regulator of homeostasis, and metal detoxification	Infertility in males, abnormal kidney movements, prostate cancer	[27,41, 49]
Selenoprotein S	<i>SELEN OS</i>	188 189 21	Yes [4 (X-ray)]	Ubiquitous	ER and plasma membrane	Regulate inflammation in endoplasmic reticulum misfolded proteins are removed, induce ER stress apoptosis, regulation of cellular redox balance	High risk of colorectal and gastric cancer, pre-eclampsia, and ischaemic stroke	[27,38, 41,49]
Selenoprotein T	<i>SELEN OT</i>	36 182 20	NA	Ubiquitous (predominant in prostate)	ER and Golgi body	Calcium mobilization, ER localization	Not known	[49,50]
Selenoprotein V	<i>SELEN OV</i>	273 346 17	NA	Not known	Cytosol	Tess-specific expression,	Not known	[41,50]
Selenoprotein W	<i>SELEN OW</i>	13 87 9	NA	Colon, prostate, heart and Skeletal muscle	Cytosol	calcium-binding	Not known	[27,49]
15 kDa Selenoprotein/ Selenoprotein F	<i>SELEN OF</i>	93 162 13,15	NA	Prostate, thyroid, parathyroid	ER	Affects glycoprotein folding, role in protein folding in ER, cancer prevention	Prostate and lung Cancers	[38,41, 50]
Thioredoxin reductase 1	<i>TXNRD I</i>	498 499 60-108	Yes [7 X-ray]	Ubiquitous	nucleus and cytosol	Antioxidant activity, reduction of Thioredoxin, control of apoptosis,	Mutations during DNA synthesis,	[19,41, 43,47,5 0]

Selenoprotein name	Gene Ref. [33,47]	Sec location, Protein size, Mol. Wt. (kDA) Ref. [38,47]	Structure	Transcript expression	Protein cellular localization Ref. [5]	Function	Health effects and diseases Ref. [27,48,49]	References
						transcription factors, cell proliferation, and Vit C recycling.	adenoma, colorectal, and lateral sclerosis	
Thioredoxin/glutathione reductase	<i>TXNRD2</i>	655 656 75	NA	Liver, kidney, heart	Mitochondria	Cell growth factor in DNA synthesis and apoptosis inhibition	Gastric cancer and ulcers	[27,38,41,49,50]
Thioredoxin reductase 3	<i>TXNRD3</i>	522 523 60-106	Yes [1 X-ray]	Testes	Cytosol	Glutaredoxin reduction, Oxidative stress, Vit C recycling	Not known	[27,38,41,49]
Selenoprotein R/ Methionine-R-sulfoxide reductase	<i>MSRB1</i>	95 116 5-14	Yes [1 X-ray]	Pancreas, liver, kidney, leukocytes	Cytosol	Methionine residue reduction, cytoplasmic	Not known	[41,49,50]
Selenophosphate synthetase 2	<i>SEPHS2</i>	60 448 47	NA	Kidney and liver	Cytosol	Synthesis of selenophosphate for selenocysteine biosynthesis	Thyroid dysfunction	[27,41]
Glutathione peroxidase 1	<i>GPX1</i>	47 201 87	Yes [1 X-ray]	Erythrocytes, liver, lungs and kidneys	Cytosol	Antioxidant activity prevents viral mutations	Deficiency can lead to cardiomyopathy, autism, high blood pressure, vascular disease, Keshan disease, cancers such as lung, prostate, bladder and primary liver damages	[24,27,41,49]
Glutathione peroxidase 2	<i>GPX2</i>	40 190 93	Yes [1 X-ray]	Gastrointestinal tissues and Human liver	Cytosol	Antioxidant activity, protection against oxidative damage, anti-apoptotic function in the colon	free radical sedimentation and Oxidative stress	[24,27,41,49]
Glutathione peroxidase 3	<i>GPX3</i>	73 226 93	Yes [1 X-ray]	Liver, GI tract, male reproductive system, heart, breasts, kidneys and placenta	Extracellular fluid and plasma.	Reduce lipid hydroperoxides, antioxidant in plasma region, protection of thyroid gland from hydrogen peroxide in thyrocytes	Thyroid cancer, oxidative stress, and ischaemic stroke,	[24,38,41,49]
Glutathione peroxidase 4	<i>GPX4</i>	73 197 22	Yes [19 X-ray]	Testes	Cytosol, nucleus, and mitochondria	Antioxidant protects brain membranes, sperm motility and viability, and the conversion of cholesterol and cholesterol esters to less toxic derivatives.	Colorectal cancer, prostate cancer	[27,49]
Glutathione peroxidase 6	<i>GPX6</i>	73 221 23	NA	Not known	Cytosol	Antioxidants protect brain membranes from peroxidative degradation and the conversion of cholesterol to less toxic derivatives. Essential for sperm motility and viability	Not known	[27,41]
Iodothyronine deiodinase 1	<i>DIO1</i>	126 249 4-29	NA	Liver, thyroid, kidney	Plasma membrane	Production of active T3 hormones in thyroid and peripheral tissues.	Loss of appetite, muscle strength, and free IGF-1 concentration	[27,41]
Iodothyronine deiodinase 2	<i>DIO2</i>	133,266 273 30	NA	The central nervous system, Brown adipose tissue, and skeletal	ER	T3 production in peripheral tissues. Activation of thyroid hormones	Diabetes type-2, reduction in bone mineral density, mental retardation, Osteoarthritis	[27,41]

Selenoprotein name	Gene Ref. [33,47]	Sec location, Protein size, Mol. Wt. (kDA) Ref. [38,47]	Structure	Transcript expression	Protein cellular localization Ref. [5]	Function	Health effects and diseases Ref. [27,48,49]	References
				muscle, pituitary and heart				
Iodothyronine deiodinase 3	<i>DIO3</i>	144 278 31	NA	Placenta, uterus, fetal, skin, cerebral cortex and CNS	Plasma membrane	Prevents high exposure of foetus towards T3 cells. Deactivation of thyroid hormones	Osteoarthritis	[27,41]

### 3. Role of Selenoproteins in Human Diseases and Disorders

All these selenoproteins have been identified as enzymes and are involved in various physiological processes associated with health and diseases. Among them, GPxs and TrxRs families have been known to be strongly associated with human health and disorders because of their reduction of oxidative stress, which is the main reason behind the development of many pathologies along with alteration or underexpression of genes associated with Se deficiency. Most of the selenoproteins are also involved in functions such as spermatogenesis, Ca<sup>2+</sup> signaling, and brain functions [47]. From a broader aspect, selenocompounds and selenoproteins have been shown to play a vital role in the prevention of cancer, immune function, and different neuromuscular, neurodegenerative, endocrine, and cardiovascular disorders. Various disease risks associated with the amount of selenium intake in Humans are listed in **Table 5**. Se plays a vital role in the human body, including anti-inflammatory, antioxidant, antimutagenic, anti-carcinogenic, antibacterial, and antifungal effects [46]. Therefore, various selenoproteins have their desired functions due to the presence of Se in its primary structure, as depicted in Figure 2.



**Figure 2.** Classes of selenoproteins with their desired functions.

**Table 5** A list of various disease risks associated with the amount of selenium intake in humans [21].

Sr.No.	Disease Risk	Dietary Intake	Selenium Status	Recommendation
1	Keshan disease	Deficient	Low	Supplement
2	Kashin-Beck disease	Deficient	Low	Supplement
3	Increased viral virulence	Deficient	Low	Supplement
4	Increased mortality	Deficient	Low	Supplement
5	Poorer immune function	Deficient	Low	Supplement
6	Problematic fertility/reproduction	Deficient	Low	Supplement
7	Thyroid autoimmune disease	Deficient	Low	Supplement
8	Cognitive decline/dementia	Deficient	Low	Supplement
9	Type 2 diabetes	Deficient	Low	Supplement

Sr.No.	Disease Risk	Dietary Intake	Selenium Status	Recommendation
10	Prostate cancer risk	Deficient	Low	Supplement
11	Colorectal cancer risk <i>in women</i>	Deficient	Low	Supplement
12	Reduced oxidative stress	Adequate	Optimal	Do not supplement
13	Decreased viral virulence	Adequate	Optimal	Do not supplement
14	Type 2 diabetes	Adequate	Optimal	Do not supplement
15	Reduced cancer risk	Adequate	Optimal	Do not supplement
16	Cognitive decline/dementia	Adequate	Optimal	Do not supplement
17	Fertility/reproduction	Adequate	Optimal	Do not supplement
18	Selenosis (Se toxicity)	Excessive	High	Do not supplement
19	Alopecia	Excessive	High	Do not supplement
20	Dermatitis	Excessive	High	Do not supplement
21	Non-melanoma skin cancer	Excessive	High	Do not supplement
22	Increased mortality	Excessive	High	Do not supplement
23	Type 2 diabetes (seen in the NPC trial)	Excessive	High	Do not supplement
24	Increased prostate cancer risk	Excessive	High	Do not supplement

### 3.1. Cardiovascular diseases.

GPxs selenoproteins family is involved in detoxifying intracellular hydrogen peroxide, thus protecting the cell from lipoprotein and DNA damage. GPxs consist of GPx1 (cytosolic), GPx2 (intestinal), GPx3 (plasma), GPx4 (membranal), and GPx6 (olfactory with undeveloped applications). Among these proteins, GPx1 helps regulate redox balance and prevent I/R (ischemia/reperfusion) related injuries, and its overexpression can protect the heart. GPx3, present in human plasma, acts as a marker for selenium status, helps in endothelial function, and initiates normal platelet inhibition. It prevents atherogenesis and vascular inflammation by preventing oxidation of low-density lipoprotein (LDL) present in plasma along with the removal of hydroperoxide. GPx4, being an intracellular enzyme, can reduce complex hydroperoxides and mainly protects I/R-specific injuries [51].

TrxRs is another family of selenoproteins that helps regulate cardiac function, myocardial remodeling, and cardiovascular diseases. TrxR1 present in cytosol plays a vital role by maintaining a continuously reduced environment by regeneration of thioredoxins in a NADPH/H<sup>+</sup> dependent manner and reducing cardiac hypertrophy. Mitochondrial TrxR2 and testis-specific TrxR3 proteins also help maintain cellular redox balance and the synthesis of selenoproteins [51]. Thyroid Hormone Deiodinases (DIO) is an oxidoreductase selenoproteins family consisting of three isoforms that are mainly involved in direct action on thyroid hormones by catalyzing iodine and activating or deactivating hormone precursors T4 (thyroxine) and T3 (triiodothyronine). In order to maintain good health and proper development of a mature heart to prevent cardiovascular perturbations like increased heart rate, hypertrophy, and contractility, thyroid hormone metabolism is important [51]. Along with GPxs, TrxRs, and DIOs, other selenoproteins are also equally important during cardiac stress, hypertrophy, and cardiomyocyte fate. Overexpression of SelK can help to protect cardiomyocytes from oxidative stress and decrease ROS levels. Another ER membrane selenoprotein, named SelS, has been suggested that a specific gene polymorphism plays a role in the development of subclinical cardiovascular disease during type-2 diabetes [51].

### 3.2. Infectious diseases.

In order to maintain good host immune resistance and defense against pathogens (bacteria, fungi, and viruses), sufficient amounts of micro and macro-nutrients are important.

An adequate amount of selenium is required in order to eliminate pathogens through innate and adaptive responses. Before studying the role of selenocompounds on the immune system, it was important to focus on the fact that even bacterial species can express selenoproteins and host microbiota composition is regulated by dietary selenium. Therefore, microbiome, bacterial pathogens, and host immune cells may be competing for a limited supply of selenium. Further, selenoproteins may be involved in the regulation of pathogen virulence, microbiome diversity, and host immune response during a bacterial infection [52].

In the case of viruses, selenium intake and antioxidant properties of selenoproteins have a major role in some viral infections and the development of antiviral immunity. Some recent studies reported that selenium and its compounds have the ability to oxidize sulfhydryl groups by attaching to the active site of viral protein disulfide isomerase (PDI), rendering it unable to penetrate the healthy cell membrane. Most selenoenzymes require selenium for their activity, or selenium is a cofactor. For example, glutathione peroxidase, a biologically powerful antioxidant enzyme, is involved in reducing the viral load or antiviral property. In this way, the viral spike proteins lose their ability to undergo the exchange reaction with disulfide groups of cell membrane proteins and prevent virus entry into the healthy cell [53]. Therefore, the improved quality of health and well-supported chemotherapy can be achieved by regular dietary selenium intake of about 200 µg/d, along with inexpensive and safe therapy in viral infections [54]. Multi-micronutrient supplementation with selenium can be useful in improving the immune system of patients affected by newly emerging viral infections.

### *3.3. Immune and inflammatory disorder.*

Selenoproteins affect inflammatory responses in the most promising way by regulating oxidative stress, as inflammatory gene expression is always influenced by the level of ROS in immune cells. So, most of the selenoproteins are associated with immune cells via redox regulation and oxidative stress management, while some work as ROS-independent response modulators [55]. The glutathione peroxidases (GPXs) family, known as an antioxidant protein family, plays a vital role in the wound healing process because of its unique characteristics, such as progressive mode of action, chemical structural forms, location, and functions. There are eight isoforms of GPXs, among which five have Sec residue in their side chain, which acts as a catalyzing agent for heavy metals, hydrogen peroxidases, and lipid peroxidases. Strong mRNA expression of GPX1 was important during inflammatory processes as the human system cannot synthesize ascorbic acid, an important antioxidant that helps cells maintain oxidative stress and protect inflammatory responses. Therefore, the TrxRs selenoprotein family plays a vital role during the wound-healing process [27,55]. Lack of selenium and different selenoproteins associated with it can lead to immune incompetence, which can result in increased responsiveness to infections and possibly to different types of cancer, along with increased levels of inflammatory cytokines in the uterus, mammary glands, gastrointestinal tract, and other tissues [24]. In the case of the use of other members of the selenoprotein families, further studies and analysis have to be done.

### *3.4. Neuromuscular disorders.*

Expression of selenoproteins and involvement of selenocompounds in case of neuromuscular disorders is usually secondary and depends on the amount of selenium present in the system. SelenoproteinN1 (SEPN1) was the first selenoprotein involved in human genetic

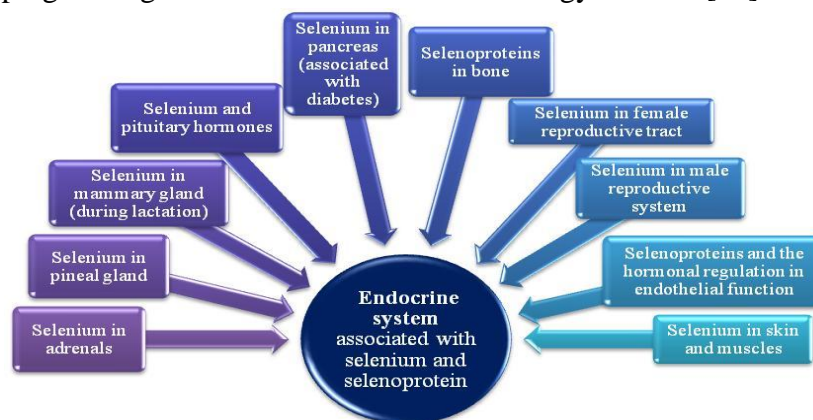
disease, i.e., congenital muscular dystrophy with spinal rigidity [50,56]. Further studies have successfully depicted the role of selenoproteins in the case of other myopathies, such as congenital fiber-type disproportion myopathy, multiminicore myopathy, and desmin-related myopathy associated with Mallory body-like inclusions. Keshan disease is another type of cardiomyopathy that occurs in children of age group between 2 to 10 years with symptoms such as cardiogenic shock, cardiac enlargement, congestive heart failure, and abnormal ECG patterns with multifocal necrosis of the myocardium. Many studies have shown an extensive relationship between low Se intake and GPxs activity in Keshan disease. Another disease, white muscle disease (WMD), has also been linked to low SelW levels, which have a role in  $Ca^{2+}$  regulation. In improper regulation, it results in the calcification of cardiac and skeletal muscles [47].

### 3.5. Neurodegenerative disorders.

Higher levels of selenium can be seen in gray matter regions of the brain with specific patterns. Ultimately resulting in neurological dysfunction in case of lower intake or knockout of its supply routes [46]. Many studies have shown a major impact of selenium and selenoproteins on brain tendencies, oxidative stress management, and brain functioning. There are many neurodegenerative disorders, such as Parkinson's disease (PD), Alzheimer's disease (AD), Ischemic damage, Batten's disease, Epilepsy, drug dependency, effects of environmental toxins, multiple sclerosis, and brain tumors [47,57,58]. In the case of Alzheimer's disease, damage due to oxidative stress is an early indication, along with a few of the major clinical symptoms such as behavioral changes, personality changes, memory loss, and impaired cognitive function. SelM has a protective role in AD, whereas both plasma and serum SelP proteins have direct neuroprotective roles as they are abundant in neurons [59,60]. The rest of the associations and roles of different selenocompounds in the case of mechanisms involved in neurodegenerative disorders are still unknown and under study. It may take proper analysis and future human trials to understand the exact role of different selenoproteins.

### 3.6. Endocrine disorders.

Selenium plays a vital role in the early organization of processes such as lactation and gestation by helping in long- and short-term endocrine energy balance [61].



**Figure 3.** Representation of different categories of endocrine system associated with selenium and selenoproteins.

Both high and low intakes lead to different mechanisms that make offspring insulin and leptin-resistant. Therefore, selenium level in such cases needs to be monitored regularly [61].

High selenium intake results in high insulin secretion, inflammation, obesity, and a decrease in leptin levels, whereas low intake leads to non-operative high serum leptin level, underdeveloped and non-functional exocrine and endocrine pancreas, high appetite, underdeveloped mucous layer of the duodenum and growth retardation in some cases [61,62]. All these effects are associated with high oxidative stress and low selenoprotein expression. Diagrammatic representations of different categories of the endocrine system associated with selenium and selenoproteins are shown in Figure 3.

### 3.7. Cancer.

These days, selenocompounds have been used in cancer diagnosis and treatment on a large scale. The use of selenium nanoparticles has been a major domain of study and attraction in the medical and pharmaceutical world [63]. Increased oxidative stress, i.e., the imbalance between reactive oxygen species (ROS) and antioxidants, is a sign of metabolic disorders in tumor cells. Selenium is an essential element that shows strong antioxidant action, acts as an antimutagenic agent, and prevents the malignant transformation of normal cells [64]. It is also suggested to act as an anticarcinogen by performing ROS detoxification. Enzymes belonging to the selenoprotein family that protect cellular DNA and other components from oxidative damage, such as glutathione peroxidase and thioredoxin reductase, are known to be primary sources of selenium [64]. Some carcinogenic effects have been shown by the action of selenium, which includes the effects of selenoproteins in reducing DNA damage or inflammation in some cases or oxidative stress in most of the cases, along with the improved immune response, increase in tumor suppressor protein p53, alteration in DNA methylation, inactivating protein kinase (kinase C) activity, initiation of cancer cells apoptosis, cell cycle arrest, and angiogenesis inhibition [65]. Most selenocompounds show anticancer effects in various types of cancers, such as breast cancer, hepatocarcinoma, lymphoma, colon adenocarcinoma, esophageal cancer, glioma, ovarian cancer, and prostate cancer.

## 4. Conclusions

Selenoproteins are present in all three domains of life, such as bacteria, archaea, and eukaryotes, including humans. The human selenoproteome consists of 25 selenoproteins. Among these selenoproteins, about half are oxidoreductases, whereas the remaining selenoproteins are involved in other functions such as reduction of thioredoxins, glutathione-dependent hydroperoxide removal, selenophosphate synthesis, activation and inactivation of thyroid hormones, thioredoxin independent repair of oxidized methionine residues and ER-associated protein degradation. These selenoproteins are able to carry out various functions due to the presence of biologically active selenium in their structures. Thus, selenoproteins can be a thousand times more effective in catalysis than their cysteine homologs. There are some detrimental effects of selenium in the human body, but in spite of this, there is a need for selenium and its compounds in human health and in diseases. The increased selenium intake is helpful in decreasing the risk of breast, colon, lung, and prostate cancer. In addition to that, selenium is one of the sovereign treatments against cancer and cardiovascular diseases that protects cell membranes and prevents free radical generation, thereby decreasing the risk of cancer and heart and blood vessel disease. It also helps fight various infections since it stimulates increased antibody response to infections, promotes more energy in the body, and assists males in producing healthy sperm while it helps reduce menopausal symptoms in

women. It also preserves tissue elasticity and slows down the aging and hardening of tissues through oxidation. In the present review, we mainly focused on the role of selenium and its selenocompounds in the synthesis of different selenoproteins and their function as an important element in human health and diseases. In the near future, the use of selenium or selenocompounds in cancer prevention and treatment is going to be a major attraction for the medical and pharmaceutical world because of their high biocompatibility, distinct selectivity, and consistency.

### **Author Contributions**

All authors have read and agreed to the published version of the manuscript.

### **Institutional Review Board Statement**

Not applicable.

### **Informed Consent Statement**

Not applicable.

### **Data Availability Statement**

No new data were created or analyzed in this study. Data sharing is not applicable.

### **Funding**

This research received no external funding.

### **Acknowledgments**

The authors are thankful to Amity University Maharashtra for providing infrastructural facilities.

### **Conflict of Interest**

The authors declare no conflict of interest.

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