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CHEMISTRY AND BIOLOGY OF SELENIUM

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ABSTRACT
Selenium is a trace dietary metal serve as a antioxidant after insertion into aminoacids such as selenocysteine, selenomethionine and these selenoaminoacids insertion into various types of proteins. The selenoamino acids and selenoproteins have potential free radical scavenging properties as vitamin E and vitamin C. These molecules protect all tisssues of animals from free radicals and induce defence to systems of body at 5ppm level. This manuscript is narrated based on research work of many scientists.

Selenium (Se) exists in free state as five allotropic forms, two of which are amorphous, and another three are crystalline (Fernandez-Martinez, 2009). Se can form a ring structure molecule, consisting of eight atoms (Se_8) chain by a considerable length. Crystalline forms exhibit alpha and beta structures, which characterises a red colour. These are obtained from the condensation of selenium vapor (Fernandez-Martinez, 2009). It has low electrical conductivity and thermal stability at 470K. Most isotopic Se is ^{75}Se radioactive and emits α and γ radiations (Fordyce, 2005). The physicochemical properties of Selenium are listed in Table 1.

Table 1: Physico - chemical properties of selenium.

Properties	Selenium (Se)
1. Electronic configuration	[Ar] $3d^{10}$ $4s^2$ $4p^4$
2. Atomic number (Z)	34
3. Atomic weight	78.96
4. Density (g/cm^3)	4.808
5. Melting temperature (^oC)	220
6. Boiling temperature (^oC)	685
7. Thermal stability	470K
8. Electron affinity	-4.2 Ev
9. Ionization potential	9.75 Ev

(Source: adapted from Kieliszek, 2019)

Occurrence of Selenium

Selenium, a commonly occurring element of nature, is found in the atmosphere, lithosphere, biosphere, and hydrosphere of the earth (Reich, 2016) and is released into the atmosphere through volcanic gases and bio methylation process by micro-organisms. Moreover, a higher selenium level, 34 mg/kg, is present in the soil (humus) area of Olkiluoto Nuclear Power Plant in Japan (Soduerlund, 2016) and very low selenium content in the soil of China (< 0.1 mg/kg). Selenium associated with many minerals including, berzelianite (Cu_2Se), Klaustalite (PbSe), and Naumanite (Ag_2Se) is into drinking water and according toWHO recommended dietary value is 10 µg/L (He, 2018).

Selenium sources

Selenium in diet

Selenium is found in different food sources including dairy products, vegetables, meat, fish, seafood and nuts (Table 2). The selenium content in the various foods in descending order is as follows, Animal-based foods products > vegetables > cereals > fruits. In addition, the Se content in foods mainly depends upon content of soil where plants and animals live and grow (Dinh, 2018).

Several studies suggest that the order of selenium content in the different vegetables is cruciferous vegetables > liliaceous vegetables > legumes > solanaceous vegetables > leafy vegetables (Dinh, 2018). In general the selenium concentration is ranges from < 0.5 mg/kg to 140-300 mg/kg and is present in the high Se-accumulating vegetables such as cruciferous vegetables,

garlic, and onions (Dinh, 2018). Likewise, the selenium content in cereals and animal foods such as eggs, meat, milk, and fish ranges from 0.0021-2.11 mg/kg (Fairweather-Tait *et al.*, 2011). The dietary selenium forms are divided into inorganic selenium (eg: selenite, selenite), and organic selenium (eg. selenomethionine (SeMet), selenocysteine (SeCys), and Se-methylselenocysteine (MSeC). For example, Se-methylselenocysteine is the main Se form present in Selenium-enriched broccoli, garlic, and onions. The chemical structures of these dietary compounds and their percent composition in Se-enriched foods are given in Figure2.

Table 2: The selenium content in various foods and food products.

Food	Selenium Content (range in µg/g)	Reference
1. Yeast	500-4000	Kieliszek, (2016)
2. Liver	0.3-0.4	Pilarczyk *et al.*, (2019)
3. Pork	0.27-0.35	Skalny *et al.*,(2019)
4. Brazil nuts	0.2-512	Junior *et al.*, (2017)
5. Chicken	0.15	Skalny *et al.*, (2009)
6. Eggs	0.09-0.25	Pilarczyk *et al.*, (2019)
7. Bread	0.09-0.20	Dos santos *et al.*, (2017)
8. Fish	0.06-0.63	Skalny *et al.*, (2019)
9. Chocolate	0.04	Reilly, (1998)
10. Broccoli	0.012	Pappa *et al.*, (2006)
11. Beef	0.01-0.73	Pappa *et al.*, (2006)
12. Milk	0.01-0.06	Klapec *et al.*, (2004)

Selenium nutrition in poultry

Selenium is an essential element for poultry and animal nutrition that was discovered by Swedish chemist Berzelius 200 years ago. However, in 1974, the FDA has approved selenium for poultry and swine in the form of sodium selenite or selenite as an essential nutrients (Surai, 2017). Compared with inorganic selenium, organic sources of selenium appear to meet the needs of modern poultry based on its easy availability to protein synthesis. Moreover, different organic selenium sources are found at world market (Table 3).

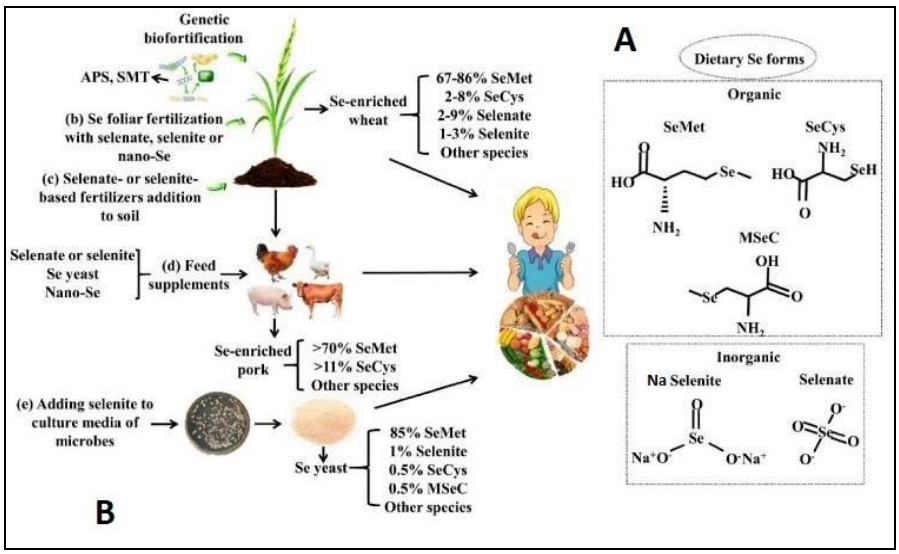


Figure 1. List of different dietary selenium compounds (A) and their percent composition in selenium-enriched foods (B).

Table 3: Different sources of organic selenium availability in the market.

Source	SeMet	References
1. Se-yeast	50-70% SeMet	Schrauzer, (2006)
2. Se-Met	> 95% SeMet	Liu *et al.*, (2017)
3. Zn-SeMet	> 95% SeMet	Geraert *et al.*, (2017)
4. OH-SeMet	> 95% OH-SeMet	Liu *et al.*, (2017)
5. Se-proteinates	No SeMet	Liu *et al.*,(2017)

6. Se-glycinates	No SeMet	Liu *et al*.,(2017)
7. Se-Chelates	No SeMet	Kubachka *et al*.,(2017)
8. Se-homolanthionine	No SeMet	Anan *et al.,* (2011)
9. Nano-Se	No SeMet	Sarkar *et al*.,(2015)
10. Selenized glucose	No SeMet	Zhao *et al*.,(2021)
11. Se-Met and Se-Cyst	>95% SeMet	Surai, (2017)

(Source is adapted from Surai, 2018)

Selenium-enriched yeast (Se-yeast)

The selenium-enriched yeast (Se-yeast) manufacturing technology was developed more than four decades ago (Schrauzer, 2006). Se-yeast is produced by many companies worldwide and is widely used in the poultry industry and has been reported to contain more than 60 selenium compounds (Arnaudguilhem *et al.,* 2012), and is well established that Selenomethionine (SeMet) is the primary selenocompound. Several of the selenium-enriched yeast supplements, and their percentage of Selenomethionine supplement values were 58-65% of total Se in LALMINe (Lallemand, Montreal, Canada); 60-70% of total Se in Seleno Excelle (Cypress Systems, Fresno, CA, USA); 54-60% of total Se in Seleno Precise (Pharma Nord, Vejle, Denmark) and 62-74% in SelPlex (Alltech, Nicholasville, KY, USA), 95% in Selsaf (France). In general, selenium-enriched yeast industrial use is less than 60% selenomethionine (SeMet), and 2% could indicate a low-quality selenium-enriched yeast (Surai, 2000b).Recently, Bierla *et al* (2013) have reported the incorporation of selenocysteine (SeCys) in proteins and also stated that they have developed yeast proteasome that contained selenium as dietary source.

Selenomethionine (SeMet) and Zinc-Selenomethionine (Zn-SeMet)

The pure form of selenomethionine (SeMet) is used as a dietary supplement (Surai, 2007). Previous studies showed theboth L-SeMet and D-SeMet can be used for poultry nutrition, and shown better efficacy than sodium selenite (Wang *et al.,* 2011). Recent findings suggest that L-SeMet is more effectively improved antioxidant defenses in chickens and average daily feed intake, feed conversion ratio (FCR) than D-SeMet (Jiang, 2009, Ambati PR, 1988).

One study showed that DL-SeMet in the chicken diet increased glutathione peroxidase activity (GSH-Px) and total antioxidant activity in the liver and muscle than sodium selenite (Bakhshalinejad*et al.,* 2018). On the other side, scientific information regarding on the Zn-SeMet is quite limited, and is not registered in the European Union (EU) and other markets such as Asian countries (Geraert, 2017).

2-Hydroxy-4-Methylselenobutanoic acid (OH-SeMet)

A new organic selenium source, OH-SeMet (2-Hydroxy-4-Methylselenobutanoic acid or HMSeBA) developed (Briens *et al.,* 2013). It is converted into selenomethionine (SeMet) and metabolized in the same way as selenomethionine(Geraert, 2017).

Se-homolanthionine (SeHLan)

Formula: (OH-CO-CH (NH2)-CH2-CH2-Se-CH2-CH2-CH-(NH2)-COOH)

A specific selenium-enriched yeast is produced based on *Torula* yeast. Se-HLan can be metabolized in animals similar to selenomethionine, but it cannot build selenium reserves in the body (Anan, 2011).

Chelated Se products (Se-CH (NH2)-COOH)

Many chelated seleniummolecules such as Se-glycinates, Se-proteinates, and Se-amino acid complexes are available in the market. Moreover, cows supplemented with a Se-amino acid complex diet has resulted in improved milk production (Givens *et al.,* 2004).

Selenium Nanoparticle (Nano-Se product)

Recently, nano-selenium has received over attention as a potential novel nutritional supplementnano-Se products have low toxicity, greater specific surface area with high surface activity, and high catalytic efficiency (Skalickova *et al.,*2017).Many researchers successfully tested nano-Se in poultry nutrition (Wang, 2009; Zhou, 2011).

Selenium requirement for humans and animals

According tothe World Health Organization,the recommended doses of Se was 50-55 µg per day for adult men (Strand, 2018). The Food and Nutrition Board at the Institute of Medicine of the National Academies, US has recommended as shown in Table 4. The recommended reference nutrient intake (RNI) of selenium for adults in the UK (United Kingdom) is given in Table 4. European Food Safety Authority (EFSA), in the European Union (EU), has recently set a daily selenium intake as 70 µg / day (EFSA, 2014). The recommended daily dose of selenium varies depending on the geographical are shown in Table 4.

Table 4: Recommended Dietary Allowances Selenium to humans.

Humans (in general)	µg/day	Year
Country:		
China, Keshan disease area	2-36	1985, 2002
UK	12-43	1995
India	27	1997

Food and Nutrition Board: Aged Men and Women (EAR) Adult Women Lactating women and Adult men (UK)	45-55 60 75	- - -

(Source: Adapted from Surai *et al.,* 2007)

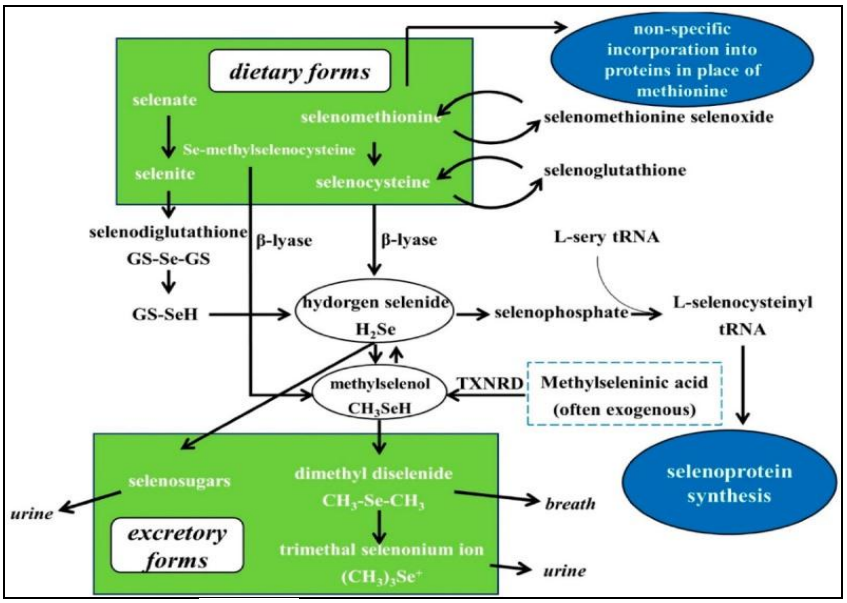
Table 5: Recommended dietary allowance (RDA) of selenium for humans and different animal's species.

Species	RDA
Human	50 µg/day for Male
	55 µg/day for Female
	60 µg/day for Female during pregnancy
Sheep	100-200 µg/kg DM of feed/day
Horse	100 µg/kg DM of feed/day
Donkey	150 µg/100kg DM of feed/day
Cow	100 µg/kg DM of feed/day
Camel	400-800 µg/day

Note: The information regarding RDA of selenium obtained from Rayman et al., 2004. (DM = Dry matter)

In corporation of selenium into selenoproteins

The metabolism of selenium in humans is illustrated in Figure 3. The dietary selenium can be divided into inorganic selenium, selenite, and selenite, and organic selenium as selenomethionine (SeMet) and selenocysteine (SeCys). All these selenium forms can be metabolized to hydrogen selenide (H_2Se), which is involved in the selenoprotein synthesis and methylation excretion of selenium (Lu, 2016; Nicastro, 2013). Interestingly, selenomethionine (SeMet) can synthesize general proteins instead of methionine amino acid or be converted into selenocysteine (SeCys) by trans-sulfurization. Furthermore, selenocysteine (SeCys) can be converted into hydrogen selenide (H_2Se) by β-lyase, whereas inorganic selenium can be converted to H_2Se through reductive metabolism. Furthermore, it can be converted into Selenocysteinyl-tRNA, a crucial transport RNA, to synthesize selenoproteins. However, selenium intake exceeds selenoprotein synthesis, i.e. higher than the nutritional requirement then it became toxic. Hydrogen selenide is methylated to methylselenol to dimethyl selenide and trimethylselonium ion, excreted via respiration and urine (Hu, 2021, Li et al., 1990).



(Source: adapted from Nicastro, 2013; Scortecci, 2020)

Figure 2. The selenium metabolism in humans.

Selenoproteins and their classification

The selenium after its in corporation into proteins, that may serve as functional moiety to express the enzymatic activities, binding proteins, and some other proteins to show the antioxidant activity, reduction properties, Deiodinase, immunity enhancement and also acts as an agent in regulations of many biological disorders as given Table 8. Their families are Glutathione peroxidases, thioredoxinases, Deiodinases, oxido reductases, and other nonspecific families.

Glutathione peroxidases

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Glutathione peroxidases I

GPxs family consists of eight isoforms, but only five members have selenocysteine (SeCys) residue. They reduce hydrogen peroxide (H_2O_2) and lipid hydroperoxides using glutathione content (GSH) as a reducing cofactor (Gromer, 2005). Glutathione peroxidase family comprises of the ubiquitous cytosolic GPx (cGPX, GPx1), gastrointestinal GPx (GI-GPx; GPx2), plasma GPx (pGPX; GPx3), phospholipid hydroperoxides GPx (PHGPx, GPx4) and the olfactory epithelium GPx (GPx6). However, the order of the relative biological importance of glutathione peroxidase family as follows as GPx2 > GPx4 > GPx3 = GPx1 (Brigelius-Flohe, 2009).

Glutathione peroxidase 1 (hydrogen-peroxide oxidoreductase; EC 1.11.1.9; GPx1) is a ubiquitous homotetrameric protein synthesized in the cytosol and mitochondria. GPx1 utilizes GSH as a substrate to reduce hydrogen peroxide and organic hydroperoxides, including cumene hydroperoxide and tert-butyl hydroperoxides (Gromer, 2005). Some studies suggest that GPx1 playsa significant role in cytokine signaling and apoptosis. Glutathione peroxidase-1 is one of the most highly sensitive to change in both selenium status and oxidative stress conditions. However, glutathione peroxidase-1 recovers rapidly under stress conditionsthan the other selenoproteins (Sunde, 2009).

Table 6: Overview of mammalian selenoproteins and their expression.

Symbol	Selenoproteins	Expression / Location
Glutathione (GPX) peroxidase family		
GPX1	Glutathione peroxidase 1	Ubiquitous ; cytosol
GPX2	Glutathione peroxidase 2	Gastrointestional tract ; cytosol
GPX3	Glutathione peroxidase 3	Extracellular, Plasma
GPX4	Glutathione peroxidase 4	Ubiquitous; cytosol, mitochondria, Nucleus
GPX5	Glutathione peroxidase 5	Uniquitous, non selenium protein for sperm protection
GPX6	Glutathione peroxidase 6	Embryos, Olfactory epithelium
Thioredoxin reductase (TXNRD) family		
TR1	Thioredoxin reductase 1	Ubiquitous, cytosol, nucleus
TR2	Thioredoxin reductase 2	Mitochondria
TR3	Thioredoxin-glutathione	Cytosol, endoplasmic reticulum, mitochondria
	Reductase	
Deiodinase family		
DIO1	Iodothyronine deiodinase 1	Livery, Thyroid,plasma membrane
DIO2	Iodothyronine deiodinase 2	CNS, Brain,Thyriod, Adipose tissue, Skeletal muscle
DIO3	Iodothyronine deiodinase 3	CNS, Brain, Placenta, Uterus, Skin
Putative oxidoreductases		
SELH	Selenoprotein H	Ubiquitous; nucleus
SELM	Selenoprotein M	Brain, Endoplasmic reticulum, Golgi apparatus
SELO	Selenoprotein O	Ubiquitous; Mitochondria
SELT	Selenoprotein T	Brain, Endoplasmic reticulum
SELV	Selenoprotein V	Testis
SELW	Selenoprotein W	Ubiquitous, highly expressed in muscle, heart, spleen
Others		
SELI	Selenoprotein I	Ubiquitous, highly expressed in cerebellum
SELK	Selenoprotein K	Ubiquitous, highly expressed in immune cells
SELN	Selenoprotein N	Ubiquitous, Endoplasmic reticulum
SELS	Selenoprotein S	Endoplasmic reticulum
SELENOF	Selenoprotein F	Endoplasmic reticulum
SELP	Selenoprotein P	Extracellular
MSRB1	Methionine sulfoxide	Cytoskeleton, Cytoplasm, Nucleus
SEPHS2	Selenophosphate synthetase	Cytosol

(Data from Labunsky *et al.*, 2014; Davis *et al.*, 2012; Avery, 2018).

Glutathione peroxidase 2

Glutathione peroxidase 2 is a secreted homotetrameric enzyme and is highly expressed in the gastrointestinal system (GI-GPx), such as the squamous epithelium of the esophagus, liver, and humans. The function of GPx2 may exert a protective effect on oxidative stress from the intestinal epithelium. Its substrate specificity is similar to GPx1, which includes hydroperoxide, but not phosphatidylcholine hydroperoxide (Wingler, 2000). More interestingly, GPx2 serves as the first line of defence in exposure to oxidative stress induced by ingested gut microbiota (Florian, 2001).

Glutathione peroxidase 3

An extracellular enzyme, GPx-3, is a glycosylated homotetrameric protein, produced in the proximal tubular epithelium and parietal cells of the Bowman's capsule of the kidney (Malinouski, 2012). However, part of GPx3 is then secreted into the plasma, where it constitutes approximately 15-20% of the total selenium, but a significant fraction remains bound to the basement membrane of the kidneys (Malinouski, 2012). However, compared with GPx1, GPx3 has restricted hydroperoxide substrate specificity. In addition, alow concentration of facilitated thiol groups in human plasma has been proposed that binding of glutathione peroxidase-3 to the basement membrane exposes the enzyme to higher levels of secreted glutathione. Thus, increasedactivity of GPx3 was observed at the basal extracellular epithelial cells (Burk, 2008).

Glutathione Peroxidase 4

Another selenoprotein, GPx 4, is relevant to the process of spermatogenesis. Ursini and collaborators (1982) identified GPx4 in the mid-piece tail structure of sperm. GPx4 protects cells against membrane lipid peroxidation. It was previously known as PHGPx (Phospholipid hydroperoxides GSH Px). This protein exists in three different isoforms, with different N-terminal amino acid sequences (Ursini*et al.*, 1982). It was found explicitly in cytosolic (cGPx4) (Maiorino *et al.*, 2003), a mitochondrial protein (mGPx4) (Puglisi *et al.*, 2003), and a nuclear protein (nGPx4), respectively (Chabory *et al.*, 2010). Nuclear GPx4 was identified as a sperm nucleus-specific glutathione peroxidase selenoprotein (snGPx). Mitochondrial (mGPx4) and nuclear forms (nGPx4) are expressed in testis during spermatogenesis (Puglisi *et al.*, 2003).

Notably, the phenotype of gene Sepp1 -/-, Gpx4 -/-, ApoER2 -/- under the selenium-deficient diet results in a decrease in their expression and has male infertility in mice and humans (Chabory *et al.*, 2010)**.** However, dietary Se deficiency causes oxidative stress due to diminished antioxidant property of Se as part of GSH-Px in testis.Oxidative stress can arise from an overproduction of ROS by redox imbalance. In addition, spermatozoa are more susceptible to oxidative damage because of the high content of PUFA (polyunsaturated fatty acid) and low cytoplasmic antioxidants. ROS promotes protein oxidation lipid peroxidation. As a result, it loses membrane integrity with increased permeability, impaired sperm motility, reduced viability, altered head shape of spermatozoa, sperm DNA damage, and apoptosis (Ueta, 2012).

Glutathione peroxidase 5

Glutathione peroxidase 5 [Homosapiens (humans)] this is known as EGLP, GPx5, GSH Px-5, HEL-S-75p. It is expressed in epididymis of male reproductive tract and is an androgenic regulated. As stated earlier enzymes it is a non-selenium proteins and lack the Se content. It is selenium independent and a play role in protection of membrane of spermatozoa from lipid peroxidation and prevents damage of premature acrosome of sperm. It is located on chromosome 6 an p arm at 22.1, exists with six exons (6p22.1) (HGNC, 2022).

Glutathione peroxidase 6

GPx6 is a similar homolog of plasma GPx3 compared with other glutathione peroxide families. However, it is located precisely in embryos and olfactory epithelium, and its specification remains unknown (Kryukov, 2003).

Thioredoxin reductases (TrxR)

These are three types. The thioredoxin reductases belong to the flavoprotein family, and three isoforms identified in mammals namely were cytosolic, mitochondrial, and thioredoxin glutathione reductase. They are involved in many physiological processes such as antioxidant defense, regulation of transcription factors, and apoptosis, and act as an electron donor in the redox-active enzymes, including ribonucleotide reductase, peroxiredoxins, and methionine sulfoxide reductase (Arner, 2009). TrxR1 and TrxR2 are known to be important for embryogenesis. TrxR2 involves the protection from mitochondrial-mediated oxidative stress and apoptosis during embryogenesis (Arner, 2009). TrxR3 (thioredoxin glutathione reductase) contains two 65 kDa subunits with an additional glutathione redoxin domain. It is mainly expressed in male germ cells and play an important role in sperm maturation (Su, 2005).

Deiodinases

The iodothyronine deiodinase (DIOs) are a family of three integral membrane proteins with similar structures. **DIO1** are plasma membrane proteins and highly expressed in the liver, kidney, thyroid, and pituitary gland (Baqui, 2003). **DIO2** in the thyroid, the expression pattern as it is mainly present in the embryonic and neonatal tissues (Baqui, 2003). **DIO3** is involved in the local regulation of deiodination processes, and it is considered a fetal enzyme and responsible for circulating T3 levels (Arrojoe Drigo, 2011).

Selenoprotein H (SelH)

Selenoprotein H (SelH) was primarily identified in fruit files as BthD proteins, and subsequently, its homologs were observed in mouse and human genomes (Panee *et al.*, 2007). Moreover, it is a 14-kDa selenoprotein that

contains a Sec residue within the Cys-x-x-Se motif. In addition, it has a conserved nuclear targeting RKRK motif in the N-terminal sequences. More interestingly is relatively low in adult mouse tissues but is elevated during embryonic development. Selenoprotein W (SelW) and selenoprotein H (Sel H) are sensitive to dietary selenium intake (Panee *et al.*, 2007). Although previous studies suggested that SelH was found in subcellular localization, it contains an AT-hook motif, present in the DNA-binding protein of the AT-hook family (Novoselov, 2007). However, *invitro* chromatin immunoprecipitation assay, it was observed that SelH mainly binds to a sequence containing heat shock and stress response elements. One study by (Mehta, 2013) reported that SelH exhibited glutathione peroxidase activity and has been implicated in regulating transcription of a group of genes involved in *De novo* glutathione synthesis and phase II detoxification enzymes.

Selenoprotein M (SelM)

SelM and Sep15 are thioredoxin-like fold ER-resident proteins that form a different selenoprotein family (Korotkov, 2002). SelM is mainly expressed in the brain, and many studies investigated the possible role of selenoprotein M in neuroprotection (Korotkov, 2002). This protein overexpression in neuronal cells prevented oxidative damage induced by hydrogen peroxidase treatment. In contrast, knockdown SelM using shRNA resulted in a decreased cell viability and inhibition of apoptotic cell death (Korotkov, 2002).

Some studies demonstrate that overexpression of SelM inhibited aggregation of amyloid peptide (A42) (Labunskyy, 2005). When A42 cells were co-transfected with SelM in HEK293T cells, suggesting a possible role of selenoprotein M in preventing Alzheimer's disease (Labunskyy, 2007). Recently findings showed that SelM knockout mice had been developed. Their phenotypic characterization of $SelM^{-/-}$ animals (deletion of SelM) proved that it does not affect neuronal and cognitive function and increases body weight, leading to obese mice (Labunskyy, 2005).

Selenoprotein O (SelO)

SelO is the least characterized human selenoproteins. However, homologs have been detected in various species, including bacteria, yeast, animals, and plants (Dudkiewicz, 2012). SelO contains a single Sec residue located at the C-terminal domain of the protein (Dudkiewicz, 2012). Interestingly, most selenoprotein O homologs contain a cysteine (Cys) residue in place of Sec. The function of SelO is mainly involved in the mitochondrial targeting peptide (Dudkiewicz, 2012).

Selenoprotein T (SelT)

Sel T is a member of the thioredoxin-like family, and it is a glycosylated transmembrane protein. (Moustafa, 2012). Sel T is present in mouse and rat cells. It localizes in Golgi, ER, and possibly the plasma membrane. Moreover, it is ubiquitously distributed mainly in the testes (Hoffman, 2007). In addition, elevated expression was found in embryonic tissues, pituitary gland, thyroid, and testis (Hoffman, 2007). Altogether these observations demonstrated an essential role for SelT in ontogenesis, tissue regeneration, and cellular metabolism of nervous, endocrine tissue, redox action in Ca^{2+} homeostasis (Sengupta, 2009).

Selenoprotein V (SelV)

Selenoprotein V is one of the least characterized selenoproteins. Recent studies suggest that SelV is most likely duplicated from SelW and mainly found in placental mammals (Varlamova, 2012). Many authors showed a comparison with SelV with SelW, and they concluded that the N-terminal domain was not found in SelW (Varlamova, 2012). However, the function of this N-terminal sequence is unknown. On the other side, SelW, SelV expression is detected only in testes and thus may be involved in male reproduction, but its particular function is unknown.

Selenoprotein W (SelW)

It, SelW, is one of the first identified Se-containing proteins, and it is one of the most abundant selenoproteins in mammals (Dikiy, 2007). This selenoprotein high expressed in muscles and brains and localized in the cytosol. SelW is related to the stress of selenoproteins, and their expression is highly regulated by the availability of selenium in the diet (Dikiy, 2007). Earlier studies reported that SelW was found to form a complex with glutathione in rat muscle. However, the NMR structure of mouse SelW, the active-site Sec, was mutated cysteine (Cys) (Jeong, 2002).

Selenoprotein I (SelI)

SelI is a recently evolved selenoprotein observed only in vertebrates (Horibata, 2007). SelI is a seven-transmembrane domain and has three conserved aspartic residues that are important for catalytic activity in DG(X)2AR(X)8G(X)3D motif (Vance, 2013). SelI from CHPT1 and CEPT1 is the C-terminal domain containing Sec residue, and their function is unknown. However, truncated SelI protein recombinant expressed in *E.coli*, which lacks the Sec residue, has been shown to possess ethanolamine phosphotransferase activity (Vance, 2013). Furthermore, Horibata, (2007) reported that CHPT1 synthesizes phosphatidylcholine from CDP-choline, whereas CEPT1 has a dual-specificity for CDP-choline and CDP-ethanolamine synthesis.

Selenoprotein K (SelK)

Selenoprotein K is mainly expressed in the spleen, immune cells, brain, and heart (Lu, 2006). SelS and SelK are involved in the ER-related degradation of unfolded and misfolded proteins (Shchedrina, 2011).

Selenoprotein N (SelN)

Selenoprotein N was among the first selenoproteins that were identified through bioinformatics approaches. SelN

is also known as SEPN1 and linked with a group of early-onset muscle disorders known as SEPN1-related myopathies (Petit, 2003). It is an ER-resident transmembrane glycoprotein mainly expressed during embryonic development and to a lesser extent in adult tissues, including skeletal muscle (Petit, 2003). Recent findings suggest that the zebrafish animal model revealed that SelN is required for early muscle development and differentiation in this organism. However, $SelN^{-/-}$ mice were developed and compared with zebrafish. They observed that no abnormalities were found in the structure and the size of muscle fibers in SelN knockout mice (Jurynec, 2008). Collectively, these findings suggest that SelN plays a significant role in the maintenance of satellite cells and is required for the regeneration of skeletal muscle tissue following stress or damage (Arbogast, 2010).

Selenoprotein S (SelS)

Their upregulation confirms the role of SelS in ER-associated degradation (ERAD) under glucose deprivation, Ca^{2+} depletion (Huang, 2011).

Selenoprotein F (SelF)

In 1998, Sep15 was identified experimentally, and their function was unknown. However, later this protein was mainly involved in regulating redox homeostasis in the ER (Korotkov, 2002). SelM is a distant homolog of Sep15, identified by bioinformatics approaches (Korotkov, 2002). Sep15 and SelM similar 31% sequence identity present from green algae to humans (Korotkov, 2002). Sep15 observed the highest expression level in the liver, kidney, prostate, and testis, whereas SelM is mainly expressed in the brain (Korotkov, 2002). More interestingly, Sep15-like protein was identified in fish and designated as Fep15. It is an ER-resident selenoprotein of unknown function found only in the fish.

Sep15 is subject to the regulation of dietary selenium, and it belongs to the group of stress-related selenoproteins (Labunskyy, 2007). However, under selenium-deficient conditions, the decreased expression of Sep15 in the brain and testis. Moreover, it has been implicated in preventing liver, prostate, breast, and lung cancers (Labunskyy, 2007).

Selenoprotein P (SelP)

Selenoprotein P (SelP, SePP, SEPP1, SELENOP) is a selenium-rich plasma protein, and the "P" denotes that it presences in plasma. SelP exerts various functions such as antioxidative defense, Se haemostasis, Se-transport to Leydig cells in the testis, and testosterone production (Pappa, 2007). SelP comprises two functional domains: N-terminal fragment possesses redox function while C-terminal parts contain 10 Se atom per one selenocysteine; hence it is regarded as Se-P_{10}or Functional biomarker of Se intake and Se status (Meplan, 2009). Furthermore, the dose-response relationship between Se intake and plasma SEPP1 concentrations in humans was studied. According to Hurst *et al*(2013) who reported that dropper off of plasma SEPP1 concentration is related to hydroperoxide of Se requirement. Therefore consider this criterion for establishing RDA for Se in humans. Consequently, it regards as an index of human Se nutritional status.More interestingly, Se bind to a specific region of a Se-rich C-terminal segment in SelP. The receptor of the lipoprotein receptor-related protein (LRP 8) family has been identified as the SEPP1 receptor. However, SePP1 supplies Se for spermatogenesis through apoER2-mediated endocytosis in Sertoli cells. *In situ* hybridization of testis shows that Gpx4 mRNA is abundantly and preferentially expressed in spermatids and released Se transferred to spermatogenic cells for GPx4 synthesis (Maiorino, 1998).

Methionine sulfoxide (Selenoprotein R)

Methionine-R-sulfoxide reductase 1 is a zinc-containing selenoprotein that was initially identified as Selenoprotein R (SelR) and Selenoprotein X (SelX) by searching for putative Selenocysteine Insertion Sequences (SECIS) element structures in expressed sequence tag (EST) databases using bioinformatics tools. Later, this protein functioned as stereospecific methionine-R-sulfoxide reductase, which catalyzes repair of the R-enantiomer of oxidized methionine residues in proteins (Kim, 2007). Therefore, based on its functional similarity to methionine-S-sulfoxide reductase A (MsrA), which catalyzes the reduction of another isomer, this selenoprotein was named MsrB1. MsrB1 exhibited an age-related decline in immune function, leading to weakened immune response-related and concomitant with selenium deficiency (Kim, 2007).

Selenophosphate synthetase (SPS2)

SPS2 were found in all vertebrates containing Sec-residues, whereas, in lower eukaryotes, the active site Sec residue in SPS2 is replaced with cysteine (Cys). SPS2 is a selenoprotein in vertebrates, and it has an autoregulatory role in selenoprotein biosynthesis (Suzuki *et al.,* 2007). Several reports suggested that comparative genomics analyses between vertebrates and invertebrates revealed that the SPS2 gene was duplicated from the original multiexon gene (SPS2a) was replaced with an intron less gene (SPS2b) in placental mammals (Tamura, 2004).

Selenium deficiency

Selenium deficiency is affected 500 million to 1 billion people and is also widespread in some parts of China, New Zealand, and Europe (Khatiwada, 2021). The common diseases resulting from its deficiency include Keshan and Kashin-Beck diseases (Fairweather, 2011).

Signaling Pathways

Nrf2 Pathway

The Nrf2 pathway is an essential channel in maintaining redox balance in the body and eliminating the damage caused by toxic and harmful substances (Hoang, 2019).

This pathway is activated by the specific stimulation of defense mechanisms like oxidative stress and exogenous substance. Nrf2 binds to the areas in the promoter regions of cytoprotective genes to activate the transcription of cytoprotective genes, which are essential to resist oxidative stress (Zhang, 2017). Several reporters suggested that the NRF2/Keap1 complex is directed to the CuLE3 ligase for ubiquitination under resting conditions. It is degraded by the proteasome, which maintains a low level of NRFE2 (Schwarz, 2019).

On the other hand, in an active condition, Nrf2 induces the transcription of many genes similar to oxidative stress defense and detoxification. More importantly, under oxidative stress, the cysteine residues of Keap1 are oxidized, and Nrf2 is allowed to cleavage from the inhibitory complex (Schwarz, 2019).

Furthermore, the activated Nrf2 protein is then transferred to the nucleus, where it is bound to Maf proteins and other complementary proteins such as Jun heterodimers to help promote gene transcription. The NRF2 transcription complex then binds to the cis-acting enhancer of ARE in the promoter region of the NRF2 target gene. The Nrf2 phosphorylation mediated by the kinase helps dissociate Nrf2 from the inhibitory complex with Keap1 proteins.

Additionally, Nrf2 can induce its own transcription through the ARE in its promoter regions, which leads to the rapid induction of Nrf2 in response to cellular stress. Recent findings suggest that selenium deficiency can increase the overexpression of TLR2 and aggravate the inflammatory reaction (Gao, 2019).

Several studies suggested that selenium deficiency-induced many enzymes through Nrf2-ARE and other stress response pathways to protect the body from oxidative stress and alter the exogenous metabolism (Burk, 2008).

However, selenium deficiency leads to oxidative stress response in the body, which activates Nrf2-Keap1 and Nrf2 in the nucleus, binds to the ARE, promotes the expression of antioxidant stress kinase genes, and reduces the damage caused by oxidative stress, as shown in Figure 4.

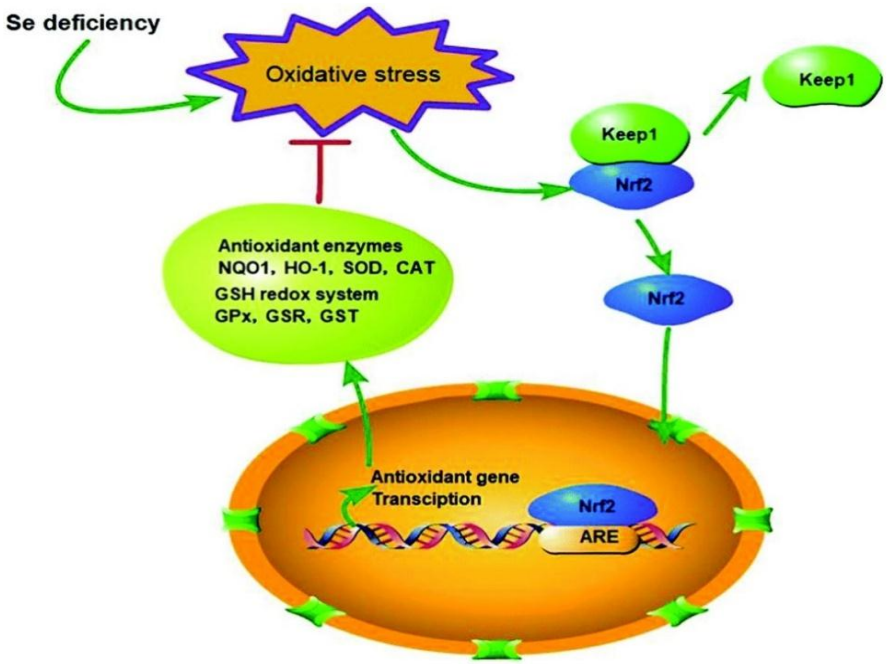


Figure 3. The interaction between selenium deficiency and the Nrf2 pathway.

1.7.3. NF-kB Pathway

The NF-kB single transduction pathway mainly mediates the immune response and plays an essential role in cell differentiation, proliferation, and survival (Oeckinghaus, 2009). In brief, NF-kB could translocate to the nucleus, bind to DNA molecules, and initiate the transcription of target genes (Hoffmann, 2003). The transcription of the NF-kB family is mainly regulated by two pathways: the standard pathway and the nonstandard pathway. IB suppressor protein degradation occurs in both pathways through the NF-kB activation expression (Xia, 2021).

However, earlier studies have shown that selenium supplementation inhibits the NF-kB activation by inhibiting the MyD and TRIF signaling pathways. In addition, some studies suggest that selenium supplementation inhibits the binding of NF-kB to DNA

and then modifies the cysteine residue of NF-kB (Gao, 2015) (Figure 5).

Experimental studies have shown that selenium-rich feed can reduce the relative secretion of pro-inflammatory factors and increase the secretion of anti-inflammatory factors. Furthermore, the overexpression of TLR2 after inflammation inhibits the initiation of downstream NF-kB and MAPK inflammatory signalling pathways and reduces inflammatory injury. On the other side, selenium deficiency can increase the overexpression of TLR2 and increase the inflammatory reaction. In addition, selenium can regulate the phosphorylation level of p53, Bax, Bcl-2 expression, and cleavage of caspase-3, 6, and 7, which leads to the execution of apoptosis (Gao, 2015).

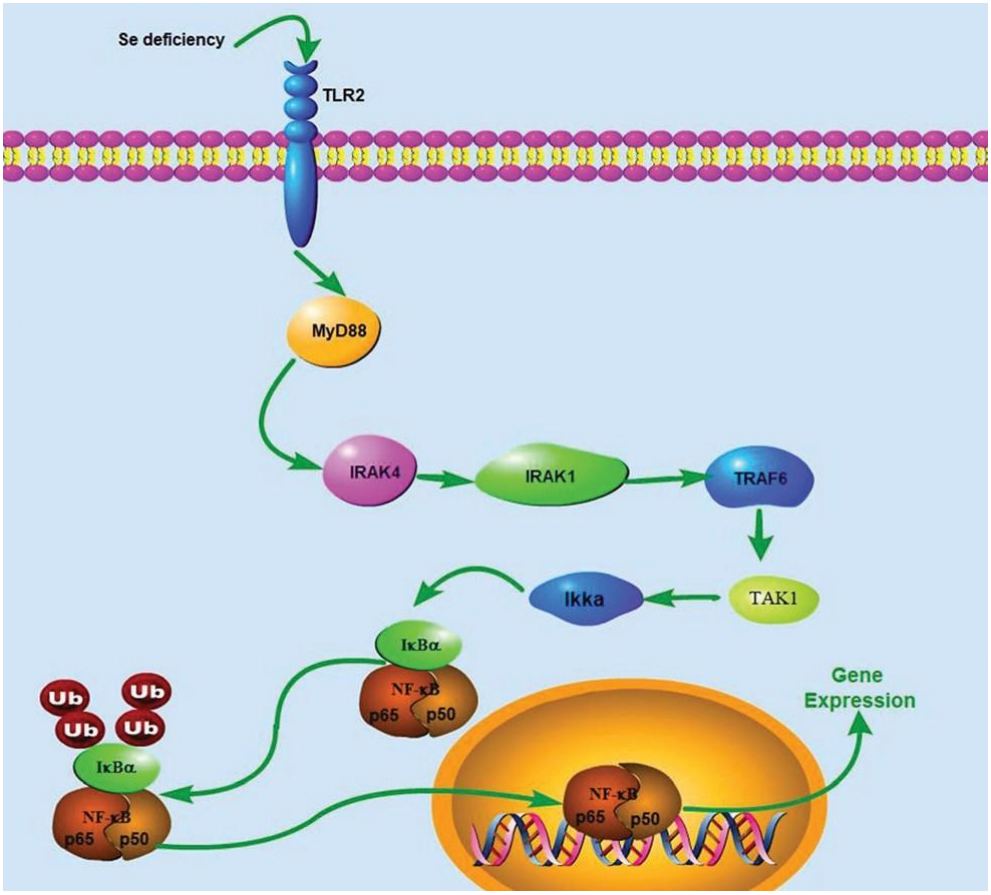


Figure 4. The interaction between selenium deficiency and the NF-KB pathway.

Ferroptosis

Ferroptosis is a nonapoptotic form of regulated cell death, mainly involving two components, glutathione and the selenoprotein GPx4 (Stockwell, 2017). Erastin can inactivate glutathione peroxidase 4, and glutathione depletion, which leads to overwhelming lipid peroxidation to cause cell death. It cannot be inhibited by cell death or autophagy inhibitors but can be inhibited by iron-chelating agents and antioxidants, and ferroptosis is iron-dependent and also characterized by an increased in lipid ROS. Many studies showed that selenium protects neurons by coordinating the activation of the Sp1 and transcription factor activator protein 2C (TFAP2C) and thereby enhanced transcription of GPx4 and other genes. The results show that selenium supplementation effectively suppresses GPx4-dependent Ferroptosis as well as cell death caused by ER-stress or excitotoxicity (Figure 6).

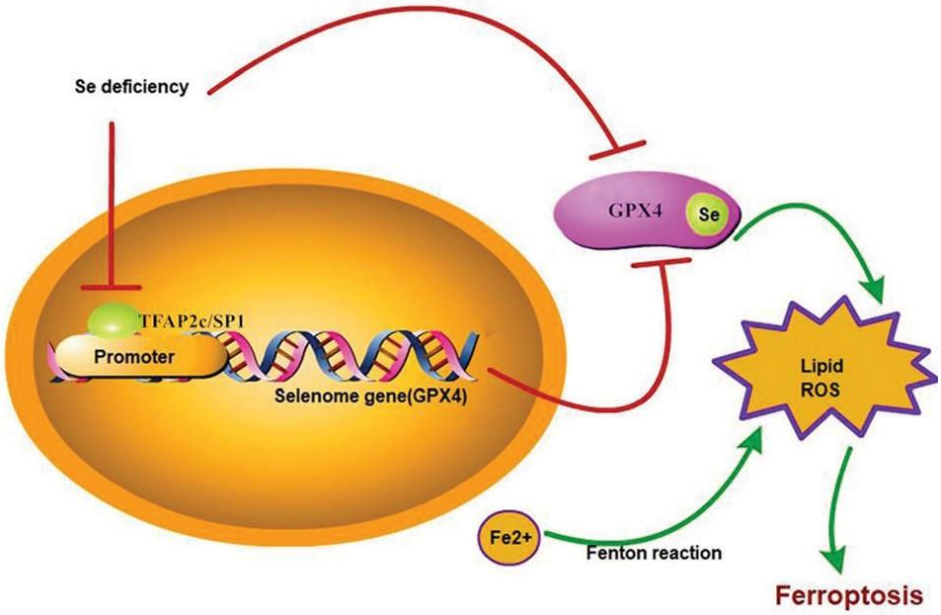


Figure 5. Selenium deficiency induces Ferroptosis.

Selenium deficiency in chicks

Nutritional muscular dystrophy is mainly due to deficiencies of vitamin E and Selenium. It is characterized by degeneration of muscle fibers in poultry with noticeable in the breast and thigh muscles and myopathy of the gizzard and heart (Surai, 2006). In addition, nutritional encephalomalacia is associated with peroxidative dysfunction in poultry characterized by ataxia, head twisting, and uncontrollable muscle spasms (Furhmann and Sallmann, 1995; Surai, 2006). Furthermore, many studies have shown that selenium could play a positive role in improving the antioxidant system by optimizing the selenium supply in the avian body (Surai, 2006).

Nutritional Pancreatic atrophy (NPA) is defined as a disease due to selenium deficiency alone or any other nutrients (Combs and Combs, 1984; Whitacre *et al.*, 1987). This disease is characterized by pancreatic lesions and atrophy, followed by very low glutathione peroxidase activity (GSH-Px) in the liver (Whitacre *et al.*, 1987). However, in most selenium-deficiency syndromes, deficiency symptoms can be prevented by administering Vitamin E through the nutritional sparing of selenium (Whitacre *et al.*, 1987).

Exudative diathesis(ED) is a common problem in chickens deficient in selenium and vitamin E. The sign of ED were increased capillary permeability due to endothelial cell failure in skeletal muscle (Combs and Scott, 1974). This disease characterized by low levels of muscle selenium, liver GSH-Px and an increase in liver non-selenium dependent GSH-Px (Hassan *et al.*, 1990). Some studies showed that inflammatory response associated with selenium deficiency (Bartholomew *et al.*, 1998).

Selenium deficiency in humans

In early 1930, KD was identified in China, mainly affecting women, childbearing age, and children living in selenium poor soil areas. In addition, some epidemiological studies have shown a relationship between low Se cereal grains concentrations and low Se status of local residents (Yang, 1988; Chen, 2012).

Keshan disease KD- patients showed acute to chronic infections such as cardiac enlargement and congestive heart failure. Moreover, histopathological studies include multifocal myocardial necrosis inflammatory cells. Dystrophic mineralization of necrotic muscle fibers and fibrous replacement of damaged myocardium (Ren, 2004 and Kim, 2000). Kaschin-Beck diseaseis also associated with severe selenium deficiency with clinical features of osteoarthropathy, necrosis of joints, epiphyseal plate cartilage. This disease occurs during preadolescent years in rural areas of China (Sunde, 2006).

One study by Bai*et al*(1980) showed that mice treated grains from Keshan disease areas developed a deficiency in selenium. These mice were infected with a strain of coxsackievirus B4 that was isolated from a Keshan disease victim. Similarly, mice treated grains from non-Keshan endemic areas developed only mild heart pathology when infected with the virus, demonstrating that selenium deficiency, an infection with coxsackievirus, was required to develop Keshan diseases.

Selenium-enriched eggs

Among animal-derived products, eggs are ideally suitable to meet the requirements. Moreover, eggs are considered traditional, and affordable food in most countries and are consumed by people of all ages more or less regularly.

Eggs enrichment is simultaneous with many essential nutrients, including Omega-3-fatty acids, vitamin E, and carotenoids (Surai, 2002, Surai, 2001). As a result, a single egg can deliver around 50% of the human recommended dietary allowance for selenium. It is also enriched with pork, beef and chicken meat, and milk.

The idea of producing Selenium-enriched eggs first originated at the Scottish Agricultural College in 1998 (Surai, 2000). Selenomethionine form the feed is effectively transferred to egg yolks and albumin, allowing to produce of Selenium-enriched eggs.

Table 7: Selenium-enriched eggs and recommended dietary allowance.

Organic Selenium added to the feed (ppm)	Selenium in egg yolk (ng/g)	Selenium in egg white (ng/g)	Selenium per egg (µg/g)	RDA from one egg
0	298.3	50.7	7.1	11.4
0.2	605.3	193.7	18.04	28.9
0.4	854	403.7	30.67	49.1
0.8	1087.3	621.7	43.35	69.4

Source: Adapted from (Surai, 2000b)

The recent development of several types of designer eggs could make an essential contribution to functional food science development with a consequent improvement of the human diet was shown in Table 9. In this regard, organic selenium in Sel-Plex can be added to diets for broiler chickens and other animals. Moreover, it produces selenium-enriched meats and their products. For instance, selected groups of people supplemented with designer eggs named Columbus eggs from UK products. It was observed that improved the circulating cell membrane fatty acid composition by altering the ω-6: ω-3 ratio (Surai, 2001).

Recently, Columbus eggs were modified with selenium, and it is delivered with a single egg more than 50% recommended dietary allowance (RDA; 35 µg) of these trace elements with 10 mg of vitamin E. These eggs improve selenium deficiency and also selenium status of the significant part of UK population (Surai, 2001).

Addressing Se deficiency in humans via Selenium-enriched eggs

Selenium-enriched eggs as a functional food

Many scientists suggested six significant reasons for the increased interest in functional foods sciences (Milner, 2000). They have been identified as proper gastrointestinal function, metabolism of the macronutrients, development in foetal and early life, redox and antioxidant system, mood and behaviour or cognition, and physical performance. Therefore, functional foods must remain foods, and they consider be achieve their effects in amount regular consumption in a diet (Cantor, 2003). However, eggs have not been regarded as traditionally functional food, mainly due to concerns about their adverse effects on serum cholesterol levels (Hasler, 2000). More recently, described above demonstrated little if any connection between dietary cholesterol and blood cholesterol levels as linked to moderate egg consumption and heart diseases, which could help change a bad image of eggs. Hence, to avoid improving the diet by eggs enriched with selenium as the combination of vitamin E, DHA, lutein (Surai, 2001; Surai *et al.*, 2000b). It clearly shows great public interest in improving egg quality and creating "healthy eggs".

Selenium-enriched eggs in the global context

Selenium-enriched eggs are produced in more than twenty-five countries worldwide. Russia is the most advanced country in this business, generating around 38 billion eggs. These eggs are modified with increased selenium levels, vitamins PUFAs, and other functional compounds (Fisinin, 2007). These eggs are sold with different names and brands like 'Universal', 'Healthy selenium', and 'Strong eggs'. Russia and Ukraine do not need to comply with European Union (EU) feed additive legislation for local use. However, they have to follow their local regulations and have strong marketing support (Surai, 2000b). Today, selenium-enriched eggs are produced globally for selenium deficiencies in humans (Table 10).

Selenium and Health: Role Selenium in the reproductive system

Male fertility

Selenium is essential for normal testicular development, spermatogenesis, and sperm motility (Isidori, 2006). Experimental studies suggested that the intraperitoneal injection of radiolabelled Se (^{75}Se) in the form of sodium selenite to different male and female rat models has shown the testicular tissue contains a high amount of selenium than ovaries. These studies concluded a higher selenium retention rate was observed in testes than ovaries, and also, male gonads actively uptake up and store selenium in the rats model (Brown, 1973). Many studies suggest that selenium and selenoproteins have an essential role in male fertility, as shown in Table 11.

Table 8: Some examples of Selenium-enriched eggs produced in different countries.

Trade name	Countries
Origin	Northern Ireland
Vita-eggs	UK
NutriPlus	Malaysia
Organic Selenium eggs	Singapore
Selen egg	Thailand
Tavas Yumurta	Turkey
Heart Beat eggs	New Zealand
Nutriplus	Portugal
Bag of Life (Koshik zhitja)	Ukraine
Universal (vSELENskoye)	Russia

(Source is adapted from Surai, 2018)

Animal studies

Many studies in male animal models have supported the hypothesis that selenium deficiency affects male reproductive capacity by oxidative stress and that dietary selenium replacement is beneficial for testes. However, sperm from selenium-deficient mice found chromatin condensation, reduced fertilization capacity, and increased lipid peroxidation in testis and sperm cells, indicating that selenium-deficiency induces oxidative stress.

Dietary selenium deficiency caused harmful effects on the male reproductive organ, intrinsic and extrinsic pathways, and protein expression of p53, Bax, and Bcl-2 in Hy-line cockerels (Huang *et al.*, 2016).

Table 9: List of selenoproteins associated with male reproduction, their locations, and functions.

Selenoproteins	Locations	Functions	References
Phospholipid hydroperoxide glutathione peroxidase (GPx4)	Intracellular Membranes mainly in testis	Intracellular antioxidant	Ursini*et al* (1982)
Sperm nucleus GPx4 (snGPx4)	Sperm nucleus	Condensation of chromatin during spermatogenesis	Chabory *et al*(2010)
Cytosolic GPx4 cGPx4	Testis, epididymal epithelium	Antioxidant	Maiorino *et al* (2003)
Mitochondrial GPx4 mGPx4	Mitochondrial capsule at midpiece	Antioxidant defense during spermatogenesis and structural component of mature sperm	Puglisi *et al* (2003)
Secreted enzyme (GPx)	Epididymal lumen	H_2O_2 scavenger	Chabory *et al* (2009)
Cytosolic GPx (GPx3)	Epididymal epithelium cells	Protect epithelium	Noblanc *et al* (2011)
Cytosolic GPx (GPx1)	Epididymal epithelium	Antioxidant	Noblanc *et al* (2011)
Selenoprotein P (SelP)	Blood	Transport Se to testis	Olson *et al* (2007)
Apolipoprotein E receptor -2 (ApoER2)	Sertoli cells of testis	Uptakes selenoprotein P in testis within the Sertoli cells	Imai *et al* (2009)

Sobolev, (2018) reported that dietary selenium supplementation influences the development of chicken testis and the expression of SelW and GSH-Px4. On the other hand, seleniumdeficiency in roosters is related to damages to the neck of spermatozoa was shown in Figure 7.

Figure 6. The microscope analysis of normal and selenium-deficient chicken spermatozoa.

(source: adapted from Surai, 2002).

Humans studies

Severalstudies have demonstrated that oxidative stress plays a vital role in male fertility in humans (Gianfrilli, 2009). Ideally, the reference range for selenium deficiency should be defined before investigating whether or not supplementation could be used to improve male fertility in humans. For example, the concentration of selenium in serum was < 60 µg/L could be considered as "Low selenium status" (Iwanier, 1995). More importantly, values between 60 - 80 µg/L can be regarded as selenium replacement that can benefit humans (Scott, 1998).

Table 10: Animal studies showed the effects of selenium supplementation on male reproductive efficiency.

Model	Treatment	Key Observations	References
SD rats	Se-nano particles	Improved sperm parameters were observed	Liu *et al*(2017)
	supranutritional levels		
	(0.2, 04, or 0.8 mg Se/kg bodyweight)		
Mouse	Se-deficient diet	Increased lipid peroxidation	Ibrahim *et al* (2012)
	Se-sufficient (0.2 ppm)	(LPO) in both testes and sperm	
	Organic Selenium		
Aged	Inorganic Se	Improved sperm parameters was observed	Mohammadi *et al* (2009)
Mice	0.2 mg/kg B.wt		
Rabbit	Se nanoparticles	Improved serum testosterone levels were recorded in Se-treated group	Abdel-Wareth *et al* (2019)
	(400 g/kg) for 60 days	compared to the control	
Ram	Organic Se (0.5 ppm) Organic Se (0.2 ppm)	Improved sperm quality was observed in seminal plasma of rams	Baiomy *et al*(2009)
Boar	Organic Se Inorganic Se	Ejaculate quality and sperm parameters were significantly improved in boars	Jacyno *et al* (2002)
Buffalo bulls	Organic Se (10 mg/animal twice a week)	Three months long Se supplementation significantly improved the sperm quality parameters	El-Sharawy *et al* (2017)

Female fertility and Pregnancy

There are comparatively few studies of the role of selenium in female fertility, and only recently has some light been shed on its possible role in ovarian physiology (Mistry, 2012). However, several encouraging studies have found a beneficial effect on pregnancy outcomes.

Experimental evidence for the role of selenium in ovarian function comes from Grazul-Bilska *et al*(2009) who noticed that dietary selenium intake could regulate early folliculogenesis, the cellular proliferation of the follicles, and stromal tissues of fetal ovaries in sheep.

Table 11: Selenium supplementation to improved male fertility in humans.

Condition	Type and Duration of Treatment	Results	References
Men with varicocele	Oral supplementation of Selenium (200 ug) for 6 months	Sperm parameters were improved compared to the control group	Zadeh *et al* (2019)
Men with male factor infertility	Oral supplementation of Selenium (200 ug) for 3 months	improvements in sperm quality parameters	Steiner *et al*(2018)
Infertile men	Oral supplementation of Selenium (50 ug) for 3 months	Improved sperm count motility, viability, sperm morphology	Morbat*et al*(2018)
Infertile Men with Idiopathic Astenoteratozoospermia	Oral supplementation of Selenium (50 ug) for 4 months	Improvements in sperm quality parameters	Busetto *et al* (2012)
Chronic prostatis	Oral supplementation of Selenium (82.3 ug) for 6 months	Improvements in sperm quality parameters and improved leucoytospermia	Lombardo *et al*(2012)

Rat and human models suggest that free radicals have a crucial role in polycystic ovary syndrome (PCOS) (Gonzalez, 2006). Recently, evidence has proven that a selenium-based herbal medicine prevents biochemical ovarian alterations induced by hyperandrogenism in rats with letrozole-induced PCOS (Coskun, 2013). Dickerson *et al*(2011) reported that selenium positively affected follicle number and oocyte yield after ovarian stimulation.Negro *et al* (2007) reported that selenium administration of 200 µg/d during pregnancy reduced thyroperoxidase antibody titers and decreased the incidence of persistent hypothyroidism. Zeng *et al*(2012)

showed that a high-selenium diet induced moderate gestational diabetes mellitus and prevented insulin resistance in gestating rats.

Role Selenium in the cardioprotection

Selenium is an essential role in anti-oxidant that protects cells against exposure to ROS and RNS (Tinggi, 2008). Recent studies showed increased cardiovascular disease risk linked with low selenium intake and glutathione peroxidase activity in the blood (Blankenberg, 2003). In addition, glutathione peroxidase (GPx) and other selenoproteins prevent LDL oxidation, leading to atherosclerosis (Zhu, 2019). Table 14 summarizes recent studies on the protective effect of selenium linked to cell survival, such as an antioxidant and anti-apoptotic agent.

Table 12: Recent research on the cardioprotective effect of selenium related to cell survival.

Authors	Methodology	Effect of selenium treatment
Kalishwaralal *et al* (2015)	Animal study and In vitro test zebrafish embryos and H9C2 cells; ethanol	Decreased ROS and apotosis
Gunes *et al* (2016)	Animal study with rats; Blood and Heart tissue; Cyclophosphate	Decreased MDA and increased GSH
Ren *et al*(2016)	*In vitro* test and endothelial cell; Homocysteine	Decreased Caspase-3, Bax and Increased BCL-2, NO, and p-AKT
Zhang *et al*(2017)	*In vitro* test ; Cardiomyocytes Low selenium treatment	Decreased Apoptosis, Bax, and Increased BCL-2, STAT3
Yang *et al*(2017)	Animal study with chicks; Blood and Heart tissue; Low selenium treatment	Decreased Caspase-3, Caspase-8, Caspase-9 and Bax
Liu *et al (*2018)	Animal study; myocardial tissue Low selenium treatment	Decreased Cyt-C, Caspase-3, Caspase-8, Caspase-9 and Bax
Cai *et al*(2019)	Animal study with chicks and In vitro test; myocardium from chicken; Se-deficient	Decreased ATP synthesis PGC1-α

Selenium deficiency in rat myocardial tissue caused increased ROS levels and decreased total antioxidant capacity, thus denoting that oxidative damage in cardiomyocytes (Benstoem, 2015). More interestingly, levels of antioxidant enzymes like paraoxonase and myeloperoxidase in cardiovascular diseases were significantly increased and decreased antioxidant capacity However, under the selenium deficiency condition, there was a significant increase of paraoxonase expression but without effect on myeloperoxidase in rat myocardial tissue in the rat model.

In a rodent model of myocardial infarction, administration with selenium reduced the expression of cleaved caspase-3 and decreased inflammatory markers such as TNF-α and IL-6. Furthermore, it directly inhibits the anti-apoptotic factor, Bcl-2 (Dallak, 2017). Likewise, chicks embryo myocardial cells treated with hydrogen peroxide selenium pretreatment decreased the expression of inflammatory genes such as NF-kB TNF-α. Hence, selenium preserves cellular functions by regulating the inflammatory response (Liu, 2016).

Selenium deficiency alters the cell's survival. For instance, selenium deficiency affects ATP synthesis, which leads to decreased mitochondria function (Cai, 2019), while the addition of selenium improves mitochondrial structures (Laird-Frick, 2020). On the other side, selenium also affects the mitogen-activated protein kinase pathway (Yang, 2019) and other regulatory factor-like calcium channel activation (Yang, 2019) and the Na+/K+-ATPase pump (Elwej, 2017).

Role Selenium in the Immune system

T-helper differentiation

On T-cell receptor stimulation of naïve CD4+ T-helper cell, these cells differentiate into effector T-cells such as Th1, Th2, Th17, Treg, or other T-helper subtypes (Stockinger, 2007). Consistent with this notion, glutathione depletion in mice caused decreased Th1 responses and the antigen-presenting cells (Sakaguchi, 2007). Like-wise, a higher reductive state induced through increased dietary selenium intake (0.086-1.0 ppm) had similar effects on activation of naïve CD+-T cells. In addition, higher selenium intake led to increased production of IFN- on TCR-stimulation, whereas the low dietary selenium led to increased IL-4. However, adequate selenium intake appears to produce a more flexible differentiation state of T-cells (Huang, 2012).

B-cell functions and antibody production

In one study,numbers of B-cells in the spleen of female mice responded to dietary selenium with low (0.02 ppm), adequate (0.2 ppm), or above adequate selenomethionine (SeMet) (2 ppm) for 50 days. In this study, a low SeMet diet reduced the number of B-cells in the spleen compared to adequate Se diets, whereas an above-adequate SeMet intake reduced B-cell numbers. The memory B-cells is sensitive to levels of ROS such as superoxide and hydrogen peroxidase, and selenium has been shown to influence levels of both in B-cells. In addition, some studies report that B-cell activation and differentiation is controlled by oxidatively sensitive NF-kb and involve leukotriene formation (Vega, 2007).

Prevention of viral infections

Coxsackievirus

In early 1930 an endemic cardiomyopathy, namely Keshan disease, was first described in Heilongijang province of Northeast China (Li, 1972). However, the Coxsackie virus is a nonenveloped, linear, positive-sense single-stranded RNA virus that belongs to the family of Picornaviridae and the genus of Enterovirus. These coxsackie viruses, group A infected mainly through the skin and mucous membranes, while group B infects the heart, pleura, pancreas, and liver (Li, 1972; Jubelt, 2014).

In 2005, Beck and co-workers showed that the non-virulent strain of CVB3 that does not cause myocarditis, although replicating, can evolve in a virulent strain when inoculated in selenium-deficient mice as illustrated in Table 15. They concluded that host nutritional status and its antioxidant defense system are essential for virulence factors. It significantly contributes to the evolution of benign viral genomes into more virulent viruses.

Table 13: The pathogenicity of Coxsackie virus in knock mice.

	Selenium adequate mice	**Selenium deficient mice**	**Selenium mice**	**$Gpx1^{-/-}$ mice**
Myocardial Disease	None	Severe	Severe	Moderate
Viral titer	Normal	Higher	Higher	Normal
Viral genome mutation	No mutation	6 mutations including 4 resulting in amino acid substitution	ND	7 mutations, including 4 resulting in amino acid substitution
Antibody titer	Normal	Normal	ND	Lower

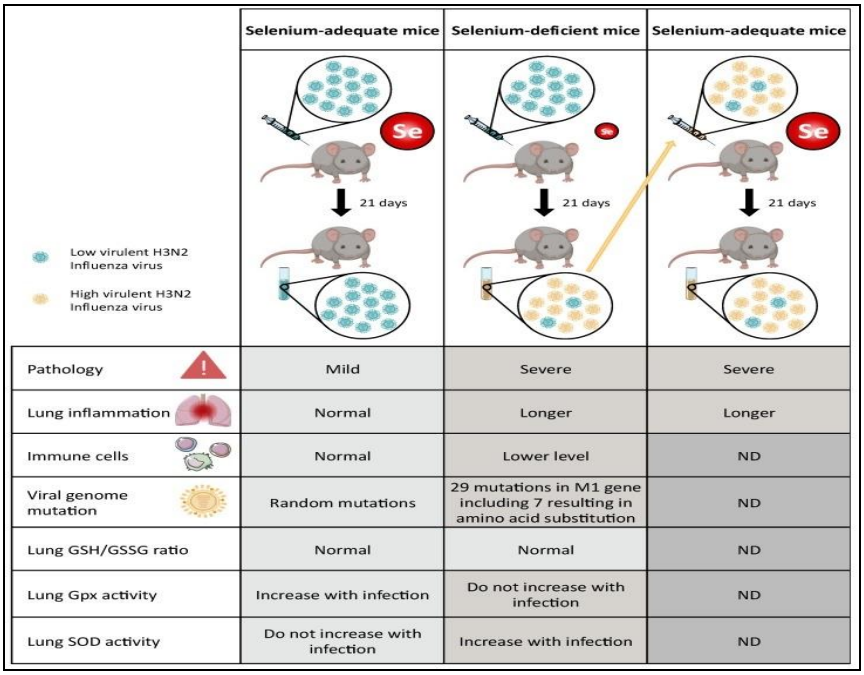
(Source: obtained from Beck, 2003)

Influenza viruses

Influenza viruses are known to cause the flu, and it is enveloped, single-stranded RNA viruses belonging to the Orthomyxoviridae family (Pleschka, 2012). Many studies showed that selenium deficiency had been linked with low expression of selenoproteins and altered antioxidant response. Beck *et al.,* 2003 established the first time demonstrating the detrimental effect of selenium-deficiency in influenza A virulence which occurred due to changes in the viral genome (Beck, 2001). Mice infected with a highly virulent influenza virus A strain (Influenza A/PR/8/34) combined with selenium-deficiency resulted in higher IL-2 and IL-4 expressed in the lung than in Se-adequate mice. These findings suggest the critical role of selenium on the immune response to influenza A by changing its virulence and altering the host's immune responses (Styblo, 2007).

Figure. 8 depicts that Coxsackievirus B3 infection of mice like myocarditis, similar to that found in human diseases. However, in this study, a non-virulent strain of CVB3 does not lead to myocarditis in this animal model, although replicating the mice heart fed with adequate selenium diet. A group of animals, Selenium deficient mice, was provided with a selenium-deficient diet for four weeks before infection with the benign stain CVB3/0 was shown in the second column from the left. On the other side, a control group of animals was fed with an adequate-selenium diet and infected in parallel. Results showed that selenium-deficient mice developed severe myocarditis (Guilian, 2019).

The mutation in the viral genome increased the virus's cardio-virulence, which results in severe myocarditis even in selenium adequate mice. Furthermore, this experiment confirmed that GPx1, which expression with Se intake, is involved in the virulence of CVB3. A similar study was conducted with $Gpx1^{-/-}$ mice. These findings demonstrate that benign strain CVB3/0 developed myocarditis, and nucleotide mutations of the viral genome isolated from their heart were shown in selenium-deficient mice. (Guilian, 2019).



	Selenium-adequate mice	Selenium-deficient mice	Selenium-adequate mice
Pathology	Mild	Severe	Severe
Lung inflammation	Normal	Longer	Longer
Immune cells	Normal	Lower level	ND
Viral genome mutation	Random mutations	29 mutations in M1 gene including 7 resulting in amino acid substitution	ND
Lung GSH/GSSG ratio	Normal	Normal	ND
Lung Gpx activity	Increase with infection	Do not increase with infection	ND
Lung SOD activity	Do not increase with infection	Increase with infection	ND

Figure 7. The pathogenicity of influenza virus in knout mic.
(Source: obtained from Beck, 2003; Guilian, 2019)

Human immunodeficiency virus

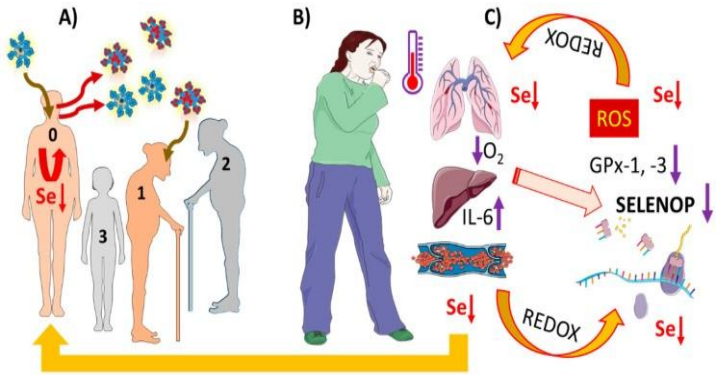
HIV is an enveloped, single-stranded RNA virus, and it is estimated that over 37 million people worldwide are living with HIV (Nyamweya, 2013). Experimental studies showed that HIV had been characterized into HIV-1 and HIV-2. HIV-1 is more virulent and infective than HIV-2. The epidemiology studies showed that HIV-1 had spread globally while HIV-2 is mainly confined to West Africa (Ferguson, 2002).

The nutritional deficiency of the HIV-infected patient can alter the immune system and the progression to AIDS. Nowadays, selenium is considered a micronutrient for antioxidant defense and proper immune function (Hoffmann, 2010). HIV infection increased the demand for micronutrients. Some studies showed that low selenium levels are associated with a lower number of CD4+ T-cells, higher progression of AIDS, and increased risk the death (Pitney, 2009). On the other side, selenium supplementation effectively slows HIV progression (Hurwitz, 2007).

COVID-19

The novel COVID-19 is caused by SARS-CoV-2, a single-stranded RNA coronavirus. This disease has been related to ageing and comorbidities like hypertension, diabetes, obesity, cardiovascular disease, cancer, and pulmonary diseases (Wang, 2020). In addition, many studies proved that people who test positive for COVID-19 develop no mild symptoms. In contrast, others develop acute respiratory distress syndrome (ARDS), heart failure, blood clots, neurological disorders, and increased inflammatory response (Braunstein, 2020).

Greaney *et al.*, 2021 observed the effect of dietary selenium deficiency in the development of COVID-19 in selenium-deficient areas, particularly in light of the recent occurrence of SARS-CoV-2 mutation.



(Sources: adapted from Arash Moghaddam *et al.*, 2020)
Figure 8. The mechanism of the pathophysiology of low selenium status in severe COVID-19 patients (A) People with more inadequate immune systems and low baseline selenium status may spread the virus efficiently and

allow viral replication. (B) COVID-19 patient is characterized by inflammation, hypoxia, and high cytokine concentration, and IL-6 suppresses selenoprotein expression. (C) Lower selenoprotein expression selenium concentration leads to COVID-19 progression.

Pathological studies proved that increased immune response leads to a release of cytokines, chemokines also called "cytokine storm", and increased inflammatory markers like D-dimer and ferritin (Song, 2020). In addition, hyperactive inflammatory response resulted in systemic inflammation in the brain of COVID-19 patients (Moghaddam, 2020).

Previously studied that selenium acts on RNA viruses and SARS-CoV-2 virus by restoration of glutathione peroxidase and thioredoxin reductase thus reducing oxidative stress and reducing viral-induced cell apoptosis, provision of selenium for host antioxidant needs, and reduced blood platelet aggregation (Fakhrolmobasheri, 2020).

On the other hand, normal levels of selenoprotein P, combined with zinc, indicated high chances of survival in COVID-19 patients (Heller *et al.*, 2021).

Recently, Taylor, (2020) reported that SARS-CoV-2 cysteine protease cleavage by different selenoproteins such as selenoprotein-F, thio-reductase-1and glutathione peroxidase.

Selenium and Human diseases

Muscle disorders

Keshan disease is endemic juvenile cardiomyopathy and primarily affects children between 2 -10 years old (Hartikainen, 2005). This disease is characterized by cardiac enlargement, abnormal electrocardiogram (ECG) patterns, cardiogenic shock, and congestive heart failure. Selenium deficiency was first identified only in the 1970s as the leading cause of Keshan Disease (Hartikainen, 2005). This disease was endemic based on extensive observational epidemiological studies conducted in china's northeast and southwest areas (Li, 2007). Many reporters observed a relation between the geographic distribution of the disease with low selenium intake and blood Se status, glutathione peroxidase activity in the patient (Roman, 2014). Moreover, biochemical and clinical studies demonstrate that a decreased activity of glutathione peroxidase 1 linked to selenium deficiency may impair the protection of mitochondria against membrane peroxides-induced damage. Furthermore, infection by the enterovirus coxsackie combined with selenium deficiency impairs the antioxidant action of selenoproteins, so viral DNA is caused oxidative damage, which increases its virulence (Roman, 2014).

Another pathology condition of Keshan disease is muscular dystrophy involving the slow degeneration of muscle tissue. However, these clinical features are multimnicore myopathy and are linked to mutations of the SelN gene (SEPN1) (Lescure, 2009)

Neurological disorders

Damage from ROS occurs in many neurodegenerative disorders like Alzheimer's disease, Parkinson's disease, and exposure to environmental toxins, brain tumors, multiple sclerosis, Batten's disease, and epilepsy (Ozdemir, 2011). Considering the antioxidant action carried out by several selenoproteins, these proteins are of potential interest as disease biomarkers in neurological disorders.

However, in Alzheimer's disease (AD), patients are characterized by intercellular neurofibrillary tangles, and extracellular plaques contain the protein amyloid β. These clinical features have been observed in mice with genetic deletion of selenoprotein P, together with impairment of synaptic function in the hippocampus region involved in memory and the reduction of spatial learning (Peters, 2006).

Parkinson's disease (PD) is another neurodegenerative disorder characterized by serve loss of dopamine-releasing neurons in the substantia nigra, where mainly high selenium levels were observed under normal conditions. On the other side, under selenium-deficiency condition caused that exacerbate the chemical lesions of dopaminergic terminals and neurons in Parkinson disease mouse model, whereas selenium supplementation and over-expression of glutathione peroxidase-1 have a protective action (Peters, 2006).

Male infertility

Selenium-deficiency leads to impaired sperm motility, and morphological alteration results in disconnections of heads and tails, while serve selenium-deficiency spermatogenesis is completely abrogated (Qazi, 2019). Selenium is an essential component of glutathione peroxidase-4 (GPx4) and plays a vital role in human spermatozoa. Furthermore, a decrease in the expression level of GPx4 in the spermatozoa caused in defected morphology of sperm (Qazi, 2019).

Cancers

Selenium has become primarily known in recent years due to its assumed prevention against certain types of cancers. However, the ability of selenium to reduce carcinogen-induced and spontaneous cancer incidence has been widely investigated over the last 20 years in animal and human models, in most organs, and against a broad range of cancer forms (Roman, 2014).

Ageing related disorders

The relationship of selenium with ageing is generally indirect because most of the biological processes involved in selenium change with age. However, many studies have shown that ageing cells accumulate oxidative damage. Furthermore, ageing-related oxidative

stress influence several of the processes such as damage of both mitochondrial and nuclear DNA, lymphocyte population fall, telomere length decreases in peripheral leukocytes and thyroid hormones alterations. In this relation, an inadequate Se intake should be considered a risk factor for several ageing-related diseases such as cancer, cardiovascular diseases, and immune disorders (Persson, 2000).

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