Review

Selenium and Selenoproteins, from Structure, Function to Food Resource and Nutrition

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Selenium, is an essential trace nutrient in the human diet. The health promoting properties of selenium and its compounds are due to its unique mechanism of incorporation into selenoproteins in which selenium is present as selenocysteine. This review presents the nutritional benefits of selenium by listing and linking selenoprotein function to evidence of health benefits. The classification, function, absorption, metabolism, and bioavailability of selenium and selenoprotein are elaborated. Particularly, the resource and nutrition of several common and selenium-enriched foods are discussed herein. Moreover, the future outlook of selenium and selenoproteins involved in selenium supplementation and food nutrition is also elucidated.

Keywords: selenium, selenoprotein, selenium-enriched foods, nutrition

Introduction

The trace element selenium, discovered in 1817 by the Swedish chemist Berzelius, was considered as an undesirable element in human body due to its toxicity initially (Pieczyńska and Grajeta, 2015). One hundred and forty years later, Schwarz and Foltz reported that selenium was an essential nutrient at very low dietary concentrations, which could protect against liver necrosis in vitamin E deficient rats (Brown and Arthur, 2001). Today, it is well recognized as an essential micronutrient of fundamental importance to human health.

In recent years, the metabolism, bioavailability, nutrition of selenium, and its compounds have attracted substantial attention, due to its multiple biological functions and beneficial effects on human health. In humans, at a moderate intake, selenium was shown to have a protective effect against Keshan disease, Kaschin-Beck disease, cardiomyopathy, muscular disorders and so on (Behne and Kyriakopoulos, 2001). Among three groups of selenium-containing proteins, selenoprotein is the main selenium-containing proteins in mammals, in which selenium is incorporated as selenocysteine (SeCys) at the active site and this process is mediated by the UGA codon. Selenoproteins are present in all lineages of life, bacteria, archaea and eukarya, and many of which act as a redox gatekeeper and play an important role in maintaining cellular antioxidant homeostasis (Papp et al., 2007). The activity of selenoproteins depends on an adequate selenium supply from the diet and there are a lot of food resources of selenium from plant and animal, such as onion, garlic, meat, sea foods and so on. However, it is not enough to meet the physiological needs of the population with low selenium by common food (Navarro-Alarcon and Cabrera-Vique, 2008). Therefore, selenium supplementation is necessary to improve selenium nutrition level of selenium deficiency population. At present, people have researched various selenium-enriched functional foods using plant or microorganism as carrier of selenium, such as yeast, ganoderma lucidum, wheat, tea, and Agaricus bisporus.

This article mainly expatiates the functional and nutritional
value of selenium and selenoprotein, including absorption, metabolism and bioavailability, especially three selenium supplements, selenium-enriched yeast, Brazil nuts, and Agaricus bisporus. This review is an attempt to combine the knowledge about selenium and selenoprotein and facilitates people a more comprehensive understanding of the development and utilization of selenium and selenoprotein in functional food.

Selenium

Selenium is an essential component of several major metabolic pathways, including thyroid hormone metabolism, antioxidant defence systems, reproductive system and immune function (Brown and Arthur, 2001). Although selenium is an element that can meet important physiological functions, there is a concentration limit between the beneficial effects and the toxic action on living organisms. Studies have generally shown that selenium deficiency is associated with a wide variety of diseases, such as reduced antioxidant protection, immune dysfunction, cancer, and neurological and endocrine function disorders, muscle and cardiovascular disorders, and may contribute to well-known Keshan and Kashin-Beck diseases (Heras et al., 2011). Besides, low selenium status in the body may also contribute to the increased risk of mortality, cognitive decline, and infertility in men (Pieczyńska and Grajeta, 2015). Prospective studies have indicated that adequate intakes of selenium can reduce the risk of heart disease, autoimmune thyroid disease, cardiovascular diseases (Rayman, 2012), and has the function of cancer prevention (bowel, lung, and prostate cancer) and anti-inflammatory activities (Navarro-Alarcón and López-Martínez, 2000). In addition, appropriate selenium can protect the body against detrimental effects of heavy metals and determine the proper functioning of the immunological system (Pieczyńska and Grajeta, 2015). Many researches have indicated that excessive selenium intake can cause selenosis including nail brittleness, hair loss, peripheral paresthesias, decreased cognitive function, lesions in the skin and nervous system (Nuttall, 2006; Navarro-Alarcon and Cabrera-Vique, 2008). Therefore, healthy individuals with a balanced and varied diet should have an appropriate selenium nutritional level and do not need a supranutritional intake of this element.

In nature, selenium exists predominantly in tissues of plants and animals in two chemical forms, organic and inorganic. Inorganic forms of selenium can be found with different minerals such as selenite (SeO$_3^{2-}$) (Fig.1A), selenate (SeO$_4^{2-}$) (Fig.1B) and selenide (HSe-) (Fig.1C), as well as in the metallic (SeO) form (Barcelo and Poschenrieder, 2011). Among which, SeO$_4^{2-}$ is the major inorganic selenocompound found in both animal and plant
Selenium and Selenoproteins from Food Resources

Selenium in foods is an integral part of various organic compounds including amino acids selenomethionine (SeMet), Se-methylselenocysteine (MeSeCys) (Fig. 1D) and SeCys (Sunde, 2010). SeMet (Fig. 1E) is the major selenocompound which was found initially in animals. Furthermore, SeMet accounts for a large proportion in selenocompounds from cereal grains, grassland legumes and green leafy vegetables. SeMet can also be the major selenocompound in selenium-enriched yeast, but the amount may vary markedly depending upon the growth conditions. SeCys (Fig. 1F) is the predominant selenoamino acid in tissues when inorganic selenium is given to animals. SeCys obtained directly from the diet or from the degradation of SeMet cannot be utilized, whereas it must be synthesized in the body from the amino acid serine and SeCys is required for Se-dependent enzyme functions. MeSeCys is the major selenocompound in some selenium-enriched plants such as garlic, onions, broccoli florets, sprouts and wild leeks (Whanger, 2002).

**Selenium-containing protein**

Generally, selenium-containing protein refers to those involved in the composition of the protein with Se atom. As a characteristic part of selenium-containing proteins, all of selenium forms (selenocystine, SeO\(^{3-}\), or SeO\(^{4-}\)) are transported via an intermediary pool. It is generally believed that selenium-protein complex is the main existing state of selenium in the body, and which known so far can be divided into three categories: noncovalent binding selenium-containing proteins, nonspecific covalent binding selenium-containing proteins, and specific covalent binding with selenocystine selenium-containing proteins. In addition, there are novel proteins in which selenium has been detected but no effective information is available on its binding form. The incorporation of dietary selenium into the different types of selenium-containing proteins is summarized in Fig. 2. At present, selenocystine-containing proteins are generally defined as selenoproteins, and the reason why SeMet-containing proteins are not regarded as selenoproteins is that selenium utilization in these proteins is nonspecific (Heras *et al*., 2011). Other proteins bound to selenium are called selenium-containing protein.

Studies have shown that most selenium in animal exists in selenoprotein form. Unlike other metal elements that interact with proteins in form of cofactors, selenium as metalloid is cotranslationally incorporated into the polypeptide chain as part of the amino acid SeCys (Papp *et al*., 2007). SeCys is a newly recognized twenty-first coded amino acid and the discovery of its genetic codon makes it known that the incorporation into the protein is mediated by codon UGA. UGA is also one of the three stop codons and this codon duality is circumvented by the presence of evolutionary conserved cis- and trans-acting elements and protein factors dedicated to decoding of UGA as SeCys (Behne and Kyriakopoulos, 2001).

Most selenoproteins identified so far are enzymes, with the SeCys residue responsible for their catalytic functions (Behne and Kyriakopoulos, 2001). In recent years, it has been suggested that up to 100 selenoproteins may exist in mammalian systems and about 25 identified mammalian selenoproteins have been functionally characterized so far (Brown and Arthur, 2001; Behne and Kyriakopoulos, 2001). These selenoproteins with clear function mainly include glutathione peroxidase family (cytosolic GPx1, gastrointestinal GPx2, plasma GPx3, phospholipid hydroperoxide GPx4), the iodothyronine deiodinases (ID1, ID2, ID3), the thioredoxin reductases (TrxR1, TrxR2, TrxR3), and selenophosphate synthetase (SPS2), which all have oxidoreductase functions and play an important role in organisms (Brown and Arthur, 2001). It is noteworthy that cytosolic glutathione peroxidase (GPx1) was the first identified selenoprotein in the selenoprotein family. This enzyme consists of four identical selenocysteine-containing subunits of about 22 kDa, catalyzing the reduction of hydrogen peroxide and various soluble organic...
The structure of the GPx1 based on PDB 2F8A, the active site SeCys is highlighted by globular rendering.

peroxides. And the SeCys of the active site is at the No. 49 location based on rendering of PDB 2F8A (Fig. 3). GPx1 can function as an antioxidant by directly reducing $H_2O_2$ and various soluble organic peroxides. It plays an important role in antioxidant activity and protection of the cell membrane and other organs of the body from oxidative damage. In addition, selenoprotein W, and selenoprotein P have also been described though many have roles that have not been elucidated. The remaining indentified selenoproteins have been annotated in alphabetic order and include the Sel15, SelH, SelI, SelK, SelM, SelN, SelO, SelR, SelS, SelT, SelU, SelV, SelX, and SelZ. Their functions may be less understood or even unknown (Behne and Kyriakopoulos, 2001). Table 1 shows the mainly selenoprotein species and the corresponding biological functions. The detailed information of selenoprotein species and function is summarized as follows.

3.1 Selenoprotein’ role in human related diseases As early as in 1979, selenoproteins fulfill vital physiological functions and play an irreplaceable role in human health. Dietary selenium, mainly through its incorporation into selenoproteins, plays an important role in inflammation and immunity and may affect various aspects of the optimal immune system including innate and adaptive immune responses (Navarro-Alarcon and Cabrera-Vique, 2008). The benefits and potential adverse effects of intervention with selenium supplementation for various inflammatory or immune disorders are reviewed as follows.

3.1.1 Selenoprotein and cancer As early as in 1979, the nutrition experts pointed out that the adult with daily intake of 100 to 200 $\mu$g of selenium, can reduce the occurrence of a variety of cancer (Huang, 2006). Medical research shows that the primary liver cancer incidence of the hepatitis B virus carriers was significantly decreased by continuous supplementation of selenium-enriched yeast in 4 years. Selenoproteins, in which main groups exert actions as antioxidants, are essential for protection against oxidative damage and cancer. It is reported that GPx, TrxR, and SelP are the main selenoproteins associated with cancer, which can reduce the risk of prostate cancer, lung cancer and colon cancer, and the incidence rates were reduced by 63%, 58% and 49% respectively (Liu et al., 2009). Gene coding GPx1 has the nature of anti oncogene, and its loss of heterozygosity is common in head and neck cancer, breast cancer and colon cancer. GPx1 gene mutation is positively correlated with the risk of cancer (Hu et al., 2005; Hu and Diamond, 2003). TrxRs, which are essential enzymes in cell growth, have a central role in Se’s anti-oxidative stress action. In addition, there are a few reports about the Sel15 and SelH involved in cancer (Hatfield et al., 2014); however, the precise mechanism is not clear. A possible mechanism may be related to its carcinogen effect which promotes apoptosis of cancer cells and GSH depletion (Hatfield et al., 2014; Liu et al., 2009).

3.1.2 Selenoprotein and thyroid diseases ID regulates the metabolism of thyroid hormone by catalyzing the conversion reaction of diverse thyroid hormone. The activation and inactivation of thyroid hormones can be controlled by the expression level of ID, suggesting that several related diseases can be treated by improving the activity of ID. Autoimmune thyroiditis is a common autoimmune thyroid disease caused by abnormal thyroid hormone metabolism or thyroid tissue damage. In the area of severe selenium deficiency, the incidence of this disease is very high mainly due to the decrease of Se-dependent GPx activity in thyroid cells (Wang and Lei, 2003). GPx is located in the thyrocytes and follicular tissues whose main function is to protect the thyroid against the deleterious effects of hydrogen peroxide and to control iodination (Schmutzler et al., 2007). Low selenium levels may indicate the impaired detoxifying capacity and the increased production of ROS, which may impair the antioxidant defense. Therefore, the reduction of selenium intake may affect several selenoprotein in the thyroid, thus potentially raising the risk of thyroid cancer (Liu et al., 2011).

3.1.3 Selenoprotein and low fertility Barrington et al. (1997) found that the serum selenium content of women who had either first-trimester or recurrent miscarriage was significantly lower. Selenium is also essential for male fertility which is required for testosterone biosynthesis and normal development of spermatozoa (Nicoll et al., 1999). Ursini and colleagues (1999) found that a form of GPx4 could protect developing sperm cells from oxidative damage. And low sperm GPx activity is associated with reduced viability and motility in men. Animal experimental studies indicated that mice lacking the SelP gene exhibited male infertility (Schomburg et al., 2003). Animals fed selenium-deficient diets show structural abnormalities in the sperm midpiece, causing decreased sperm motility and a tendency for the tail to break off, thus reducing the opportunity of fertilisation (Wu et al., 1973). Studies found that low fertility of adult males take a daily supplement of selenium 100 $\mu$g for 3 months, thus the sperm
<table>
<thead>
<tr>
<th>Selenoprotein</th>
<th>Abbreviation</th>
<th>Location</th>
<th>Functions</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutathione peroxidase (GPx)</td>
<td>GPx1</td>
<td>Cytosolic, tissues and cells</td>
<td>Antioxidant protection, reduce hydrogen peroxide and organic peroxides to water and alcohols</td>
<td>Hatfield et al., 2014; Hu et al., 2005</td>
</tr>
<tr>
<td></td>
<td>GPx2</td>
<td>Gastrointestinal tract, liver</td>
<td>Antioxidant, involved in metabolism of ingested peroxides of fats by reducing free hydroperoxides of fatty acid and hydrogen peroxide</td>
<td>Mehdi et al., 2013; Behne and Kyriakopoulos, 2001</td>
</tr>
<tr>
<td></td>
<td>GPx3</td>
<td>Plasma and extracellular fluid</td>
<td>Plasma antioxidant</td>
<td>Heras et al., 2011; Schmutzler et al., 2007</td>
</tr>
<tr>
<td>Phospholipid hydroperoxide glutathione peroxidase</td>
<td>GPx4</td>
<td>Testes, Cytosolic and membranes, various splice forms, many tissues and cells</td>
<td>Detoxification of lipid hydroperoxides, Involved in metabolism of lipids such as arachidonic and linoleic acids, cholesterol and its esters. Structural protein constitutive of the mitochondria that make up the midpiece sheath of the sperm tail</td>
<td>Fairweather-Tait et al., 2010; Behne and Kyriakopoulos, 2001</td>
</tr>
<tr>
<td>Thioredoxin reductase Type I (TRxR)</td>
<td>TRxR1</td>
<td>Liver, kidney, heart, bone, cytosolic</td>
<td>Antioxidant, catalyzing redox-reaction, cell signaling, decrease thioredoxin</td>
<td>Mehdi et al., 2013; Behne and Kyriakopoulos, 2001</td>
</tr>
<tr>
<td>Thioredoxin reductase Type II (TRxR)</td>
<td>TRxR2</td>
<td>Mitochondrial, testes</td>
<td>Antioxidant, catalyzing redox-reaction, decrease thioredoxin, cell signaling</td>
<td>Behne and Kyriakopoulos, 2001</td>
</tr>
<tr>
<td>Thioredoxin reductase Type III (TRxR)</td>
<td>TRxR3</td>
<td>Liver, kidney, heart, mitochondrial</td>
<td>Antioxidant, catalyzing redox-reaction, cell signaling</td>
<td>Mehdi et al., 2013; Fairweather-Tait et al., 2010</td>
</tr>
<tr>
<td>Iodothyronine deiodinase Type I (ID)</td>
<td>ID I</td>
<td>Liver, kidney, thyroid, adipose tissues and in many other tissues</td>
<td>Thyroid hormone metabolism, conversion of T4 to T3 and T4 to reverse T3</td>
<td>Mehdi et al., 2013; Fairweather-Tait et al., 2010</td>
</tr>
<tr>
<td>Iodothyronine deiodinase Type II (ID)</td>
<td>ID II</td>
<td>Liver, kidney, thyroid, brown adipose tissue, central nervous system, pituitary, skeletal muscle</td>
<td>Activation of thyroid hormones, deiodination of T4 to T3</td>
<td>Brown and Arthur 2001; Fairweather-Tait et al., 2010</td>
</tr>
<tr>
<td>Iodothyronine deiodinase Type III (ID)</td>
<td>ID III</td>
<td>Brain, placenta, skin, central nervous system, fetus (not in pituitary, thyroid, adult liver)</td>
<td>Inactivation of thyroid hormones, conversion T4 to reverse T3</td>
<td>EPODP Nutrition, 2013; Heras et al., 2011</td>
</tr>
<tr>
<td>Selenoprotein P</td>
<td>SelP</td>
<td>Plasma, extracellular glycoprotein and other tissues</td>
<td>Storage and transport of selenium from the liver via the plasma to other tissues, particularly the brain, the kidney and the testes. Has antioxidant properties and is involved in immune function. Forms heavy metal ion complexes</td>
<td>Mehdi et al., 2013; Pieczyńska and Grajeta, 2015; Schomburg et al., 2003</td>
</tr>
<tr>
<td>Selenophosphatase synthetase</td>
<td>SPS2</td>
<td>Testes, many other tissues</td>
<td>Synthesis of selenophosphate (Fig.1G)</td>
<td>Navarro-Alarcon and Cabrera-Vique, 2008</td>
</tr>
<tr>
<td>15-kDa selenoprotein</td>
<td>Sel 15</td>
<td>Brain, lung, testes, liver</td>
<td>Tumor suppression function</td>
<td>Papp et al., 2007; Heras et al., 2011</td>
</tr>
<tr>
<td>Selenoprotein W</td>
<td>SelW</td>
<td>Brain, colon, heart, skeletal muscles and prostate.</td>
<td>Skeletal and cardiac muscle growth and function, calcium binding</td>
<td>Huang, 2006; EPODP Nutrition, 2013</td>
</tr>
<tr>
<td>Selenoprotein S</td>
<td>SelS</td>
<td>Endoplasmic reticulum</td>
<td>Regulation of cellular redox balance</td>
<td>Papp et al., 2007; EPODP Nutrition, 2013</td>
</tr>
<tr>
<td>Selenoprotein M</td>
<td>SelM</td>
<td>Endoplasmic reticulum</td>
<td>Redox function, may be involved in cancer etiology</td>
<td>Papp et al., 2007</td>
</tr>
<tr>
<td>Selenoprotein T</td>
<td>SelT</td>
<td>Ubiquitous</td>
<td>Role in regulation of Ca(^{2+}) homeostasis and neuroendocrine secretion</td>
<td>Papp et al., 2007</td>
</tr>
</tbody>
</table>
motility was significantly enhanced and 1% of subfertile men restore fertility (Scott and MacPherson, 1998).

### 3.2 Absorption and Metabolism

The intestinal absorption and metabolism of selenium from diet may be greatly affected by the chemical form and concentration of this element as well as several other element or interactive substrates in the diet (Fox et al., 2005). In general, organic selenium has a higher absorption than inorganic selenium. Most proportion of selenium is absorbed when supplied as SeMet and presumably as SeCys. Selenium in inorganic compounds such as SeO$_4^{2-}$ or SeO$_3^{2-}$ also appears to be well absorbed, but retention is lower than organic compounds (Fairweather-Tait et al., 2010).

In addition, the element concentration also influences absorption efficiency of selenium. Van et al. (1991) have assessed absorption efficiency from bread or meat using three selenium doses (55, 135 and 215 μg/day) and corresponding absorption from bread and meat was 57 and 38%, 73 and 75%, 74 and 80%, respectively. Furthermore, the existence of other elements also has a certain impact on the selenium absorption. For instance, research experiments have suggested the Cu treatment significantly increased the amount of selenium retained in the gut wall compared with the control group.

About metabolism, there are different models describing mammalian selenium metabolism, and the overall idea is that all ingested selenium has to transverse a “HSe- pool” and then be utilized for the synthesis of SeCystRNA to meet to the SeCys codon for selenoprotein synthesis (Suzuki, 2005).

Inorganic and organic selenium compounds are usually metabolized into the common assumed intermediate, HSe$^-$. Inorganic selenium species, SeO$_4^{2-}$ and SeO$_3^{2-}$, can be reduced simply to HSe$^-$. Studies revealed that SeO$_4^{2-}$ and SeO$_3^{2-}$ are metabolized differently in the blood-stream. SeO$_4^{2-}$ is not readily reduced to HSe$^-$ by glutathione (GSH) which needs more rigorous reducing conditions while SeO$_3^{2-}$ is readily reduced by GSH to the assumed intermediate HSe$^-$ (Suzuki, 2005).

In fact, SeO$_3^{2-}$ are readily and selectively taken up by red blood cells (RBCs) in the bloodstream through band 3 protein instead of being excreted into urine, while SeO$_4^{2-}$ ions are directly taken up by hepatocytes through the transport system for phosphate, and partly excreted directly into urine without being processed in the bloodstream (Kobayashi et al., 2001). SeO$_3^{2-}$ taken up by RBCs is readily reduced to HSe$^-$, and then effluxed into the bloodstream in the presence of albumin and transferred to the liver in the form bound to albumin. The major portion of selenate was taken up by the liver, reduced and then utilized for the synthesis of selenoproteins or excreted into the urine after being methylated. Thus, HSe$^-$ of SeO$_3^{2-}$ and SeO$_4^{2-}$ origin are taken up differently by the liver and utilized for the synthesis of SelP and cellular GPx (Suzuki, 2005).

About the transformation of organic selenium compounds to HSe$, there is a relatively sophisticated pathway. Though organic selenium chemicals can be oxidized to SeO$_4^{2-}$ or SeO$_3^{2-}$, however, organic selenium compounds, mostly selenoamino acids, are usually transformed to HSe$^-$ through reductive cleavage of the C-Se bond by lyase reactions (Suzuki, 2005). SeCys, is converted to HSe$^-$ by β-lyase, which is thought to be the main route for the
transformation of selenoamino acids to selenide. In the case of SeMet, SeMet can transform to SeCys, then further degraded to selenide, on the other hand, the direct C-Se cleavage is at the γ-position of SeMet when excessive selenium intake (Suzuki, 2005; Navarro-Alarcon and Cabrera-Vique, 2008).

Once selenium is taken up by the body, it goes through a process of excretion. although significant losses occur via faeces, skin and respiration, and it is mainly eliminated from the body by urine (Burk and Levander, 2002). There are various selenocompounds present as Se metabolites and methylation is a major pathway for Se metabolism. Urinary metabolites are known to be monomethylated selenium (Fig.1H) and trimethylselenonium (TMeSe) (Fig.1I), while selenium in breath is exhaled in the form of dimethylselenide (Fig.1J). The ratio of the two major selenium metabolites responded rapidly to changes in Se intake, at a lower dose, selenium is excreted mostly in monomethylated form, while at a higher intake, excess selenium is eliminated through urine as the TMeSe (Suzuki, 2005).

When the body selenium status is low, urinary selenium excretion is diminished to keep element homeostasis in a narrow range. Intestinal excretion of selenium is a secondary path of elimination (Navarro et al., 2003). However, when large amounts have to be excreted, respiration can also contain volatile selenium compounds, usually in the form of dimethylselenide. On the other hand, around 30% of ingested selenium was excreted via the faeces when selenium was provided through controlled diets based on conventional foods (Holben et al., 2002; Hawkes et al., 2003).

The metabolism of selenium is dynamic and urinary excretion plays a central role in selenium homeostasis. Researchers remarked that urinary excretion rose rapidly when selenium is high, but decreased only with severe selenium restriction demonstrating a low adaptation to selenium excretion. Additionally, Hawkes et al. (2003) reported that fecal excretion decreased by half in the low selenium group, which indicates an underappreciated role in metabolic adaptation to low selenium.

3.3 Bioavailability Several researches showed that selenium bioavailability varies among different chemical forms found in the food. Normally, the bioavailability of selenium in organic compounds is significantly more bioavailable than that in inorganic forms (Thomson, 2004) and the bioavailability is also affected by certain dietary factors. For example, Vitamins E and A are reported to increase selenium bioavailability. In addition, source and species of selenium are also important factors. For example, data shows that the order of bioavailability for selenium species of Atlantic salmon is: SeMet > SeO₃²⁻ > SeCys > fish meal (Dumont et al., 2006b). Experimental results showed the selenium bioavailability of fish is not affected by processing, such as cooking or enzyme and salt treatment (Fox et al., 2004). Several studies have shown that selenium bioavailability in meat is high because selenium forms in foods of animal origin are mostly SeCys and SeMet (Van et al., 1991; Dumont et al., 2006a).

Food resources and nutritional supplements of selenium
As mentioned above, adequate dietary intakes of selenium are essential to reduce blood supply to tumours and kill several cancer cells in animals and humans and may prevent the development of AIDS in HIV-positive individuals (Rayman, 2002), therefore which has aroused people’s attention to selenium resources. For humans, a source of this microelement is of both plant and animal original foodstuff, and marginally–drinking water (Pieczyńska and Grajeta, 2015).

Plants origin may be classified as “selenium accumulators” or “non-accumulators”, depending on their ability to tolerate and accumulate selenium (Broadley et al., 2006). Brazil nuts, allium spices (onion and garlic), as well as Brassica species (rapeseed, broccoli, cabbage) with the ability of accumulating selenium from soil to significantly high levels, have been recognized as selenium accumulators. Whereas cereal crops such as wheat, oats, rye and barley are “non-accumulators” (Rayman, 2008).

The richest animal sources of selenium are organ meat and sea foods, followed by muscle meat, dairy products (egg, milk, etc.) (Moreda et al., 2013). Red meat such as pork and beef can accumulate high amounts of selenium when the animal is fed a selenium-rich diet, which is becoming a unique source of dietary selenium (Hintze et al., 2002). In the visceral organs such as kidney, liver and spleen, the selenium content was found to be considerably higher than that in the skeletal muscles (Liu et al., 2011). In Sweden, fish contains higher amounts of selenium than most of other foods and an increased intake of fish could be one way to raise the selenium intake taking the speciation and the bioavailability into account (Onning, 2000). Water may contain selenium but its content is relatively low and is usually less trivial compared to the content in food, thus water does not significantly contribute to selenium intake (WHO, 2011). The selenium content of plant food mainly depends on the soil-type in which the plant was grown, but also on the agricultural use of pesticide, manure and phosphate fertilizers, while the selenium content from animal sources is affected by the selenium levels in their consumed diet of the animals (Mehdi et al., 2013).

Although there are a lot of food resources of selenium, it is obviously not enough to achieve the purpose of providing adequate selenium to the population with low selenium, as well as the prevention or treatment of related diseases to ensure the health of the human body. Accordingly, extradietary selenium supplementation is increasingly recommended by health professionals.

4.1 Selenium-enriched yeast Selenized yeast is an attractive selenium supplement in human nutrition due to its low cost and the ability to serve as a precursor for selenoprotein synthesis. Moreover, selenium in selenized yeast is stable even at higher temperatures and the industrial production of yeast is more manageable than the selenium-enriched plants (Dumont et al., 2006b). Selenized yeast is the product of the aerobic fermentation of Saccharomyces cerevisiae which has a high protein content
related to the ability of incorporating selenium (Dumont et al., 2006b). Selenium-enriched medium use selenium salts (e.g. sodium SeO\(_2\)) as the selenium source, and is also added with vitamins and other nutritional growth factors (Rayman, 2004). Saccharomyces cerevisiae may assimilate during its growth up to 3,000 ppm as SeO\(_2\); and today’s commercial products typically contain from 1,000 to 2,000 ppm (Schrauzer et al., 2001).

Generally, the absorbability of dietary organic selenium is high even up to 80% (Navarro-Alarcon and Cabrera-Vique, 2008). Experiment measured the absorption and retention of selenium from selenized yeast with 12 volunteers fed \(^{77}\)Se-labeled SelenoPrecise yeast and results showed the absorbability is between 75% and 90%, but other selenized yeasts measured is between 50% and 60% (Sloth et al., 2003). The reason for different results is due to the form that selenium is consumed influencing the selenium bioavailability (Dumont et al., 2006b). According to the results obtained by HPLC–HG–AFS method, the principal selenium form in yeast is SeMet, which is a safer and highly bioactive species with improved nutritional properties (Dumont et al., 2005). SeMet of selenized yeast is more bioavailable than inorganic selenium and is well absorbed and stored within the human body (Levander, 1987). In fact, the actual selenium bioavailability would depend on the digestion of the selenized yeast, the absorption of selenium from the intestinal tract and finally, the transport and biotransformation of selenium into biological active forms (Reyes et al., 2006). Selenized yeast at the level of 0.3 ppm in feed dry matter was twice as effective as SeO\(_2\) in increasing the selenium content of the sirloin muscles in pigs (Mahan et al., 1994), and its ability of enhancing the selenium levels in serum and liver was significantly higher than that of the Na\(_2\)SeO\(_3\) (Suomi and Alaviuhkola, 1992). Studies showed that selenized yeast will eventually completely replace the inorganic selenium compounds as feed additives by SeMet or nutritional sources and is the preferable choice as the source of selenium for a large-scale cancer prevention trial (Schrauzer, 2001). Medical research showed that taking an extra 200 \(\mu\)g of Se per day could significantly reduce the risks of developing prostate, lung and colorectal cancer (Schrauzer, 2001). In addition to the application in the medical field, there is a possible trends that selenized yeast with better thermal stability can be used to replace conventional yeast for baking bread, which results in a growing intake of selenium in human due to the fact that conventional bread selenium content is generally low and bread is also a common product consumed by many individuals (Dumont et al., 2006b).

4.2 Brazil nuts Brazil nuts (Bertholletia excelsa) are known for their natively high concentrations of selenium, indicating that they could become a “new nutraceutical product” (Chunhieng et al., 2004; Chang et al., 1995). The concentration of selenium in Brazil nuts varies greatly ranging from 0.20 to 253 ppm (Chang et al., 1995), which reflects differences in soil content of selenium since the selenium content in the nuts is highly dependent on selenium amount present in the soil on which the tree grows. Research pointed that Brazil nuts originating from the central part (above 500 ppm) of Brazil contained up to ten times more selenium than the nuts harvested in the western part (30 ppm) (Chang et al., 1995). In addition, nuts coming from the same area may also show considerable differences in their selenium contents; in fact, the selenium content even varies among nuts from the same tree (Chunhieng et al., 2004). There are many substantial factors responsible for these variations, such as soil type, pH, and moisture content, maturity of the tree and root system and the position of the nut (Dumont et al., 2006b). It has been suggested that selenium from Brazil nuts is bioavailable for the restoration of tissue selenium and selenoprotein activity, which mainly depends on its chemical species (Ip and Lisk, 1994). The species of selenium in Brazil nuts were examined by HPLC–ICP-MS and the results obtained showed that the selenium-containing main compound identified was SeMet (Vonderheide et al., 2002) and the presence of these amino acids enhances the selenium absorption in the nut.

With high selenium content, Brazil nut is considered to be associated with protection against cancer development in laboratory animal studies. A study suggested that selenium retention from Brazil nuts in the liver, kidney, and mammary gland is beneficial for mammmary cancer protection (Dumont et al., 2006b). Daily consumption of only one Brazil nut per day could increase dietary selenium intakes to the recommended levels, thus it should be noted that the nuts should be reasonable intake to avoid excessive poisoning. With the deep research on the nuts, nutrition experts point out that the development of this nut as a new nutraceutical product can bring great economic benefits. And a standardized defatted cake powder made of nuts could be used as a natural selenium source in nutraceutic preparations (Chunhieng et al., 2004). Although Brazil nuts form a good source of selenium for the diet, it is not a commonly consumed foodstuff for the residents of non origin, which limits the supply of Brazil nuts to a great extent (Dumont et al., 2006b).
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stipe (Vetter and Lelley, 2004). The variable selenium concentrations of A. Bisporus reflect the difference of species and growing conditions. The cap/stalk selenium level ratio of cultivated A. Bisporus ranged from 0.75 – 3.05 depending on the selenium irrigation level (Maseko et al., 2013). Selenium speciation studies have identified that SeMet, SeCys and MeSeCys were the major seleno-compounds found by means of HPLC-HG-UV-AFS (Stefanca et al., 2001). Among them, SeCys was the main selenoamino acid assimilated into water soluble proteins by A. Bisporus, and SeMet is at a much lower level than SeCys. Moreover, further research shows that SeMet unbound with proteins in cultivated ordinary A. Bisporus was hot water (at 85°C) labile, while that bound to proteins was hot water stable (Diaz et al., 2006). MeSeCys is a non-protein selenoamino acid, which was precipitated with the protein fraction with acetone and also occurred at a lower level (Maseko et al., 2013). In addition, there are studies that also demonstrated that dietary selenium supplementation with the selenium-enriched A. Bisporus significantly up-regulated the expression of GPx1, GPx2, TrxR1 and SelP mRNA (Maseko et al., 2005).

As a high selenium accumulator, cultivated A. Bisporus is an attractive food source for residents in low selenium areas and it is easy to reach the recommended daily dose (RDD) (55 μg) with only a small amount of around 1 g of product (Cremades et al., 2012). Moreover, this product also plays an important role in prevention of diseases associated with low selenium concentrations, such as cancer, cardiovascular and neurological disorders, which need higher selenium amounts for prevention purpose (Neve, 1996; Rayman, 2005). Animal studies have revealed that dietary selenium supplementation with seleniumized A. Bisporus at 1 ppm Se fed to rats significantly reduced the incidence of 7,12-dimethylbenz (a) anthracene (DMBA) induced mammary epithelial cell DNA adducts (Spolar et al., 1999). The present study provided evidence that dietary selenium from selenium-enriched A. Bisporus protected the gastrointestinal tract in rats barrier dysfunction as indicated by reduced ileum permeability during hyperthermally induced oxidative stress in rat (Maseko et al., 2014). Therefore, the ability to accumulate selenium and its role in disease prevention would present cultivated A. Bisporus as a viable and efficient source of functional selenium supplement with demonstrated biological benefits.

Several food sources, both natural (Brazil nuts, onion and garlic, etc.) and selenium-enriched (yeast-based supplements, cultivated A. Bisporus, selenium-enriched tea, etc.) products are good selenium nutritional supplements because they are sustainable, less expensive, and present a lower risk of toxicity compared with other supplements. Dietary selenium supplementation with selenium-enriched foods is an effective means to achieve the purpose of supplementing selenium and prevention of related diseases. Therefore, their consumption should be encouraged.

**Conclusion and outlook**

As a necessary trace element for human body, selenium has been a hot research field in life science and a considerable progress has recently been made in terms of selenium and novel selenium-containing proteins in human health. Selenium has a very low therapeutic window, and both the decreased intake and high doses may have deleterious effect on the normal operation of the body function. Therefore, further studies are urgently required to evaluate the reasonable selenium intake to promote human health and prevent diseases. Knowledge of selenoprotein synthesis has also considerably increased attention and selenium is unique in its structural incorporation into proteins. Selenoprotein in species from all domains of life have been recently characterized. For example, TrxR and GPx are major components of the antioxidant defense, and IDs are enzymes involved in regulating thyroid hormone metabolism. Selenoproteins are implicated in a variety of diseases, which can prevent atherosclerosis, neurodegeneration, viral infections, promote healthy embryonic nervous, and improve fertility and the immune response. However, the biological function and structure of some selenoproteins remain unknown, such as SelO, SelV, and SelT. In addition, many challenges about selenoprotein still exist. It is necessary to improve the selenium level of selenium-deficiency population and to establish the efficiency of selenium supplementation in the prevention of cancer. With the in-depth research on various selenium and selenoproteins, efficient organic selenium supplements have been developed using the trace element selenium characteristics. And taking the advantages of various excellent selenium-enriched carriers, supplements organically combine selenium and the physiological active substances of carrier, giving full play to their biological activity. Therefore, the excellent selenium supplements from food sources will have a very broad application prospects.

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