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Organoselenium Compounds as Phytochemicals from the Natural Kingdom

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Selenium is naturally present in soils but it is also produced by pollution from human activities into the environment. Its incorporation into plants affords organoselenium metabolites that, depending on the nature of the molecules and the plant species, can be incorporated into proteins, stored or eliminated by volatilization. The possibility to use the selenium metabolism of some plants as a method for bioremediation and, at the main time, as a source of selenated phytochemicals is here discussed taking into consideration the growing interest in organic selenium derivatives as new potential therapeutic agents.

Keywords: Selenium, Metabolism, Phytoremediation.

Introduction

"Phytochemicals" can be defined, in the strictest sense, as chemicals produced by plants. However, the term is generally used to describe chemicals from plants that may affect health, but they can also be non-essential nutrients. There is ample evidence to support the health benefits of diets rich in fruits, vegetables, legumes, whole grains, and nuts. Because plant-based foods are complex mixtures of bioactive compounds, information on the potential health effects of individual phytochemicals is linked to information on the health effects of foods that contain those phytochemicals. Sometimes some of the compounds in plants with potent medicinal properties contain heteroatoms, metal or non-metals, such as selenium. As an example, selenomethionine was recently evaluated in a clinical trials aimed to assess the impact of selenium supplementation on thyroid autoimmunity and inflammation [1]. During the last decades the use of selenium derivatives as potential therapeutically useful agent has been deeply debated and some evidence was reported demonstrating that to organoselenium compounds can be ascribed a number of biological activities but more defined knowledge is required to define better its "Janus" characteristic. This review has been realized as a scholarly overview about the role of selenium in the Natural Kingdom focusing the attention on its incorporation in plants. The enrichment, either artificial or as consequence of a bioremediation process, affords natural derivatives that could be theoretically employed for either prevention of disease or as natural therapeutic agents. Data were collected also by means of Scifinder, Sciencedirect, Google Scholar and Scopus.

Selenium and human health

In 1818 the Swedish chemist Jacob Berzelius discovered selenium as a naturally present element able to form both soluble and insoluble derivatives. One hundred and forty years later, Schwarz and Foltz identified selenium as an essential element for animal health when they discovered that trace amounts protected against liver necrosis in vitamin E deficient rats [2]. Interest in the role of selenium in human health gathered momentum in the late 1960s, and investigations looked for human diseases similar to those of Se-responsive animal disorders [3]. Although it is nowadays well recognized that selenium is essential for human nutrition, a universal marker of daily requirements remains elusive. At low doses, selenium is an essential micronutrient for humans, animals and cyanobacteria [4], and for certain plants under drought conditions, selenium (Se) can intervene and settle the status of the water [5], prevent oxidative stress, delay senescence and promote growth [6-7].

Table 1: Mean selenium concentrations in various European food sources.

Food	Mean Selenium Concentration (µg/100 g)
Milk	1.5
Beef	7.6
Pork	14.0
Lamb	3.8
Fish	16.0
Fruit	1.0
Vegetables	2.0
Cereals	11.0
Bread	4.5

Selenium is present in soil and enters the food chain through plants. Humans obtain most of their dietary Se from bread, cereal, meat and poultry (main selenium concentrations in Table 1), but a direct intake from plants is also possible. Tissue levels of Se are readily influenced by dietary intake which itself is governed by geographical differences in available selenium in soil. In general, the Se available concentration in soil is low in Europe. To this end, the use of Se-containing or Se-enriched plants as a supplement is up to date accepted, e.g. US government mandates have initiated various Se supplementation schemes, and their use as herbal drugs would be foreseeable, as Se is involved in a number of metabolic and biological activities [8]. Selenium is a sulfur antagonist causing an inhibition of absorption of this element [9]. Because of large chemical similarities between selenium and sulfur there are some biochemical systems in which selenium replaced sulfur [10], as in the case of the aminoacids cysteine [11] and methionine that occur naturally also in the corresponding selenylated form, selenocysteine (Sec) and selenomethionine (SeMet), respectively.

The biological activity of organoselenium compounds has become of more and progressive interest in recent years as new research has revealed a hitherto unsuspected role for this element in areas of vital importance to human health as it has been recognized that a number of enzymes are Se-dependent, generally containing selenocysteine at the active site [12], where Se functions as a redox center. A list of these enzymes is listed in Table 2 [13].

The best-known example of this redox function is the reduction of hydrogen peroxide and damaging lipid and phospholipid hydroperoxides to harmless products (water and alcohols) by the family of selenium-dependent glutathione peroxidases [14-15], through a redox mechanism that uses glutathione as cofactor [16].

Around thirty-five selenoproteins have been identified up to date, though many have roles which have not yet been fully elucidated [17]. Selenium has additional important health effects, particularly in relation to the immune response and cancer prevention, which are almost certainly not exclusively linked to these enzymatic functions. The anti-carcinogenic activities of some Se forms against colon, lung, skin, and other types of cancer have been stated [18]. The role of Se in the detoxification of heavy metals such as mercury and lead are also important for the human body. Certain Se compounds have been claimed to prevent carcinoma, slow the aging process, and enhance sexual activities [19]. Beside the antioxidant activity, several other correlations between selenium concentration and human health have been described.

For example selenium can delay the progression of the AIDS disease inhibiting the proliferation of HIV virus [20], as in the case study of some African populations living in the sub-Saharan region for which the high proliferation of HIV virus has been correlated to the low concentration of selenium in the soil and, consequently, in plants and foodstuffs [21]. Selenium has also be proposed in the treatment of rheumatoid arthritis, asthma, pancreatitis, and in the prevention of atherosclerosis [22]. Recognition of the important role of selenoproteins in metabolism helps to explain the adverse consequences of selenium deficiency in human and animal health. Notably, there are several health conditions with a recognized selenium-deficiency etiology. There is evidence that less-overt selenium deficiency can have adverse consequences for disease susceptibility and the maintenance of optimal health [23].

It was also demonstrated that a significant deficiency in selenium causes Keshan disease, an endemic cardiomyopathy, mainly affecting children and women that is present in those countries where the level of selenium is low [24]. A study focused on pregnant women showed that the plasma selenium level is lower for women on a diet poor in selenium and / or fed with vegetal food grown in low selenium concentration soil, and this condition represents a potential risk for both the fetus and the newborn [25].

Nevertheless, selenium at high dosage may be toxic to animals and humans [26]. The concentration range from element requirement to toxicity and from the antioxidant and pro-oxidant activity is quite narrow: the minimal nutritional level for animals is about 0.05 to 0.10 mg Se Kg^{-1} dry forage feed, while exposure to levels 2 to 5 mg Se Kg^{-1} dry forage feed causes toxicity [27].

The first report of selenium poisoning is considered to be the description by Marco Polo of a necrotic hoof disease of horses that occurred in Western China in 1285 [28] as a consequence of grazing some plants particularly enriched with selenium.

In the case of human diet the suitable dose for this essential microelement depends on age, sex and body mass index (for a man, the range may vary between 0.2 and 1 µg per g of body mass) [29]. The recommended daily intake of selenium for an adult in good physiological condition is 55 µg / day for women, 70 µg / day for men, and lower for children under 14 [30]. Daily intakes lower that 30µg/day are classified as selenium deficiency [21a], whereas the upper recommended limit is established at 400 µg /day [31]. It is important to highlight that the values of the harmful dose of selenium for humans are still uncertain as the literature on selenium toxicity for humans is limited and incomplete and the cases of selenosis (*id est* the multiple organ toxicity by excess of selenium intake) are less common and documented than the effect produced by selenium deficiency. A recent study has demonstrated no adverse effect for consumption of 853 µg / day [32] and in general the toxicity seem to be mainly correlated to the chemical form: inorganic and organic, with the latter safer than the former. A good tolerance was demonstrated when methylselenocysteine was used as a tumor preventing agent [33]. Nevertheless, a recent study among indigenous communities along the Tapajós River (Amazon), whose local traditional diet includes important selenium sources such as Brazil nuts, chicken, game meat and certain fish species, highlighted no evidence of selenosis from a selenium-rich diet.[34].

The narrow margin between the beneficial and harmful levels of Se has important implications for human health. Plants can play a pivotal role in this respect: for example, a plant that accumulates Se may be useful as a “Selenium-Delivery-System” food supplement in the mammalian diet (animals or humans) in many areas that are deficient in Se, or be used as a phytotherapeutic agent in all the illnesses and circumstances that selenium and its biological activities could help. The first report of the nutritional benefit of selenium was published in 1957 [2]. From then to now, interest in selenium has escalated, especially because of its effect on human health and its potential beneficial effects.

Selenium in the environment

Selenium can also be considered as an environmental contaminant. A number of human activities produce selenium that can flow into the food chain via its accumulation in soils and/or its bio-accumulation in plants [35]. Plants having the characteristics of a hyper-accumulator can promote the organication of selenium transforming it into less toxic and/or volatile derivatives such as dimethylselenide (DMSe) and dimethyldiselenide (DMDSe). The use of plants for bioremediation represents an interesting alternative to recover the environmental damage of human activities [36] and an easy way to collect selenium enriched natural derivatives with a potential interest for human health as a food supplement [37].

Selenium is naturally present in the environment in four different oxidation states: Selenate (SeO_4^{2-}), Selenite (SeO_3^{2-}), elemental (Se) and Selenide (Se^{2-}). SeO_4^{2-} and SeO_3^{2-} are the most abundant inorganic forms; they are soluble in water and for this reason are characterized by a good mobility in soils. Selenium is generally associated with sulfur minerals in the composition of sedimentary rocks and the alterations of these rocks promote the release of the element in the soil from which mainly the soluble forms can be easily assimilated and organicated [38].

The biosphere enrichment factor (BEF) of selenium is 17, corresponding to a severe enrichment and indicating that the selenium cycle is strongly effected by anthropic activities. Selenium is a compound used in the manufacture of insecticides and fungicides; it is present in wastes associated with the operational cycle of nuclear power plants and in the effluents of some oil refineries and water treatment plants. As a long-living isotope, it is persistent in the environment and it continues to be variously present in the ecosystem: in the atmosphere, in water and the water cycle, in soil, and/or incorporated into farmland and bio-accumulated in food plants.

Selenium absorption by plants depends on a number of soil parameters, which influence its oxidation state and, consequently, its mobility and bioavailability. SeO_4^{2-} is the most bioavailable form and its formation is favored by alkaline soils, while SeO_3^{2-} is the principal ion normally present in the soil. The presence of cations such as Ca^{2+} promotes the absorption of selenium, whereas in the presence of anions such as Cl^- and SO_4^{2-} the absorption is inhibited and this inhibition is particularly evident in the presence of the antagonism between SO_4^{2-} and SeO_4^{2-} [39]. Also the oxidizing or reducing nature of the medium effects the distribution of selenium between the solid (soil) and the liquid mobile phase, generating species that are differently subjected to the adsorption and desorption processes [8].

Selenium in higher plants: Accumulators and Non-accumulators

Selenium has not been classified as an essential element for plants although its role has been considered to be beneficial in the

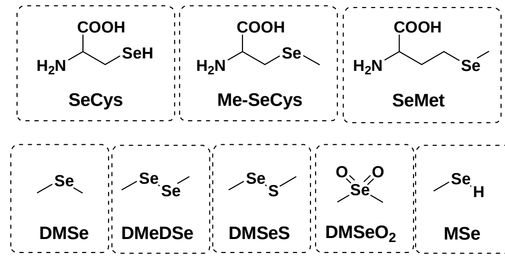

Figure 1: Organoselenium metabolites.

so-called Se-accumulator plants [40]. A number of studies evidenced the presence of GPx proteins specific for plants that, contrary to most of their counterparts in animal cells, contain cysteine instead of selenocysteine and, in addition, some of them have both glutathione peroxidase and thioredoxin peroxidase functions [41].

Selenium is absorbed through the root system, then, it can follow three different metabolic pathways: (i) translocation of selenate (SeO_4^{2-}) and selenite (SeO_3^{2-}) from roots to the aerial parts [42]; (ii) metabolic transformation of the inorganic forms to selenium containing aminoacids (SeMet, SeCys, MeSeCys); (iii) biomethylation with the formation of dimethylselenide (DMSe), dimethyldiselenide DMDSe, dimethyl selenone ($DMSeO_2$), methylselenol (MSe), and dimethyl selenyl-sulfide (DMSeS) [43]. Some microorganisms, such as *Alternaria* and *Penicillium corynbacterium* may also be involved in these processes [44].

Plants differ in their ability to accumulate selenium. Certain plants are able to hyperaccumulate selenium in their shoots when growing on seleniferous soils. These plants are called Selenium-accumulators and include a number of species of *Lecythidaceae*, *Astragalus*, *Stanleya*, *Morinda*, *Neptunia*, *Oonopsis,* and *Xyloriza* [45].

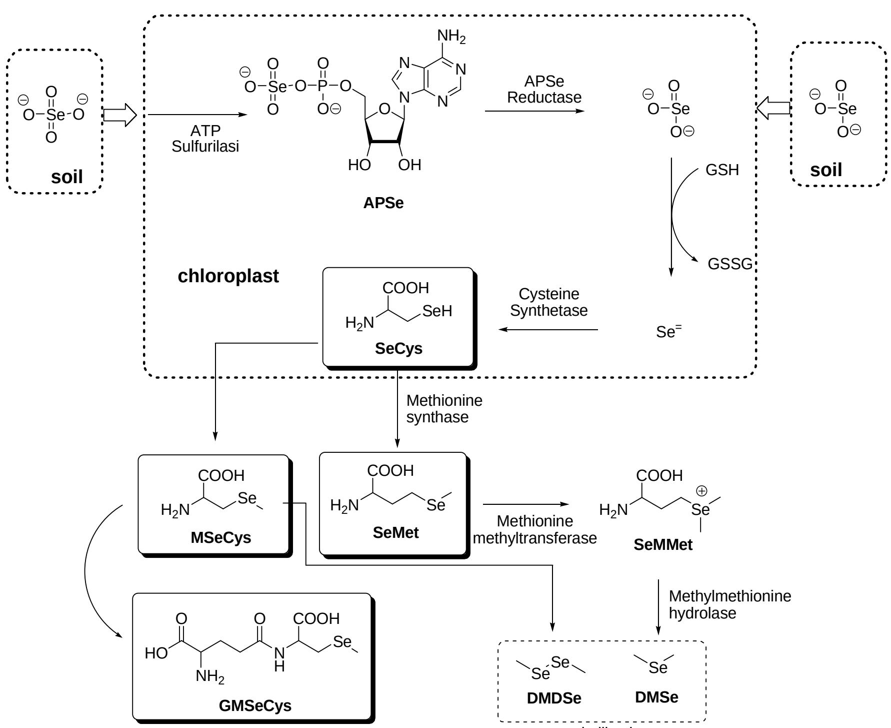

Figure 2: Selenium biosynthetic pathways from soil to metabolites and/or volatilization.

Table 2: Selenoproteins and their functions.

Selenoprotein	Function
Glutathione peroxidases (GPx1, GPx 2, GPx 3, GPx 4)	Antioxidant enzymes: remove hydrogen peroxide, lipid and phospholipid peroxides (thereby maintaining membrane integrity, modulating eicosanoid synthesis, modifying inflammation and the likelihood of propagation of further oxidative damage to biomolecules such as lipids, lipoproteins and DNA).
Mitochondrial capsule selenoprotein, (found in sperm)	Form of glutathione peroxidase (PHGPx): shields developing sperm cells from oxidative damage and later polymerizes into a structural protein required for stability/motility of mature sperm
Iodothyronine deiodinases	Production and regulation of level of active thyroid hormone, T3, from thyroxine, T4
Thioredoxin reductases	Reduction of nucleotides in DNA synthesis; maintenance of the intracellular redox state, critical for cell viability and proliferation; regulation of gene expression by redox control of binding of transcription factors to DNA
Selenophosphate synthetase, SPS2	Required for the biosynthesis of selenophosphate, the precursor of selenocysteine, and therefore for selenoprotein synthesis
Selenoprotein P	Found in plasma and associated with endothelial cells. Appears to protect endothelial cells against damage from peroxynitrite.
Selenoprotein W	Needed for muscle function
Prostate Epithelial Selenoprotein (15kDa)	Found in epithelial cells of the ventral prostate. Seems to have a redox function (resembles PHGPx), perhaps protecting secretory cells against development of carcinoma.
DNA-bound spermatid selenoprotein (34 kDa)	Glutathione peroxidase-like activity. Found in stomach and in nuclei of spermatozoa. May protect developing sperm.
18 kDa Selenoprotein	Important selenoprotein, found in kidney and large number of other tissues. Preserved in Se deficiency.

In 2015, El Mehdawi and coworkers investigated whether certain Se hyperaccumulators such as *Artemisia ludoviciana*, *Symphyotrichum ericoides*, and *Chenopodium album* would affect Se speciation and accumulation in neighboring plants without finding any correlation [46]. They can accumulate from hundreds to several thousands of milligrams of Se Kg^{-1} dry weight in their tissues. Conversely, most forage and crop plants, as well as grasses, contains less than 25 mg Se Kg^{-1} dry weight [47] and do not accumulate Se above the level of 100 mg Se Kg^{-1}. These plants are usually referred to as Se non-accumulators [48]. Although Se accumulators grow on seleniferous soil, not all the plants growing on such soils are Se-accumulators. For example, the genus *Astragalus* contains both Se-accumulating and non-accumulating species and they can grow next to each other on the same soil. For non-accumulating species, plants use the S uptake and assimilation pathway to metabolize Se, since it is chemically similar to sulphur, and the uptake transporter and enzymes cannot distinguish between these two chemical analogs [49]. A third category of plants, known as secondary Se accumulators, grow on soil of low to medium Se content and accumulate up to 1000 mg Se Kg^{-1} dry weight. Examples of plants in this group are species of *Aster*, *Astragalus*, *Atriplex*, *Castilleja*, *Comandra*, *Grayia*, *Grindelia*, *Gutierrezia* and *Machaeranthera* [50]. Some *Allium* and *Brassica* species are also included in the class of secondary Se accumulators with a typical concentration of several hundred milligrams of Se Kg^{-1} dry weight in their shoot tissues when growing on soils containing moderate levels of Se [51].

In crop studies where soils were supplied with selenate, garlic (*Allium sativum*), onion (*Allium cepa*), leek (*Allium ampeloprasum*), and broccoli (*Brassica oleracea*) accumulated some selenium as seleno-amino acid (selenomethylcysteine, SeMeCys), while *Arabidopsis thaliana* and *Brassica juncea* [52] accumulated Se primarily in the chemical form of selenite [53].

In 2013 Yuan and colleagues discovered *Cardamine hupingshanesis* (Brassicaceae), a novel selenocysteine accumulating plant in the Se-mine drainage area from China. Such a plant was able to accumulate 99% of total selenium as SeCys [54].

In view of the chemical similarities the metabolic process of selenium is similar to that of sulfur [55].

Selenium uptake by plants from the soil involves either selenate (SeO_4^{2-}) or selenite (SeO_3^{2-}). Selenate is in strict competition with the uptake of sulfate and the resistance to selenate showed by mutants of *Arabidopsis thaliana* that lack a functional sulfate transporter demonstrated it. Selenate is transported into the chloroplasts, where it is activated by ATP sulfurylase, forming adenosine 5'-phosphoselenate (APSe) as a rate limiting step of the entire selenium metabolism in plants. APSe is then reduced to selenite by adenosine 5' -phosphosulfate (APS) reductase. Worthy of mention is that, *in vitro*, selenate can be easily reduced to selenite in the presence of glutathione, but *in vivo* the first step needs ATP activation and a non–enzymatic reduction has been demonstrated in the transformation of selenite into selenide. This latter acts as a precursor for the synthesis of selenocystine (SeCys) and selenomethionine (SeMet). The presence of this non-enzymatic reduction has been proposed as an explanation for the evidence that selenite is more readily assimilated by plants than selenate. Selenomethionine, through a methylation catalyzed by L-methionine *S*-methyltransferase, is transformed into methylselenomethionine (SeMMet) that can be enzymatically hydrolyzed to afford the volatile dimethyl selenide (DMSe). In some cases the volatilization has been demonstrated to involve dimethyl selenopropionate as an intermediate and normally both mechanisms are present at the same time. The S-methyltransferase (SMT) using S-methylmethionine as a source of a methyl group promotes the conversion of the selenocysteine into the corresponding methylselenocysteine (MSeCys). The methylation prevents the incorporation of the selenoaminoacid into proteins enhancing the tolerance of the species toward selenium. MSeCys can be accumulated as it is conjugated in the form of gamma-glutamyl-methylselenocysteine (GMSeC). It has been proposed also that MSeCys can be decomposed affording the dimethyl diselenide (DMDSe), contributing to the volatilization of selenium [56].

Phytoremediation

Plants have been shown to be highly effective in phytoremediation in contaminated soils. Selenium phytoremediation is a green biotechnology to clean up Se-contaminated environments, primarily through phytoextraction and phytovolatilization. With their copious root systems, plants can scavenge large areas and volumes of soils, removing selenium as selenite, selenite and organic forms of selenium such as selenomethionine (SeMet). Once absorbed by the plant roots, Se is transolcated to the shoot where it may be harvested and removed from the site, a process called phytoextraction [57]. Many species have been evaluated for their efficacy in phytoremediation. Certain species of *Astragalus* were found to accumulate the most selenium, which led some researchers to suggest the use of the Se-accumulators *A. bisculatus* and *A. racemosus* [48]. However, these are slow growing plants and Se accumulated in *Astragalus* roots is mostly soluble, thus leading to the leaching of selenium from plant tissues back to the soil [58].

Phytovolatilization, on the other hand, circumvents this problem because it removes Se completely from the local ecosystem into the atmosphere. This minimize the entry of selenium into the food chain, particularly as selenium is volatilized by roots [59].

Biofortification is a biotechnological strategy, which aims to increase micronutrient contents, e.g., Se, in the edible parts of plants, animals, or mushrooms, via breeding, biotechnology, or application of Se fertilizers. Phytoremediation strategies commonly attempt to select plant species that accumulate more pollutants in shoots to increase the phytoremediation efficiency, while biofortification focuses on increasing a specific micronutrient content in edible plant tissues. These strategies are considered to be safe and effective in alleviating micronutrient malnutrition in many areas or countries [60]. By integrating Se phytoremediation and biofortification technologies, Se-enriched plant materials harvested from Se phytoremediation can be used as Se-enriched green manures or other supplementary sources of Se for producing Se-biofortified agricultural products.

However, one of the difficulties associated with Se phytoremediation management is how to utilize/dispose of Se-contaminated plant waste materials harvested from phytoremediation sites. Different management options have been discussed by researchers regarding the disposal of plant waste materials, including landfill and incineration, but none of these options are considered sustainable or environmentally-friendly [61]. Generally, the plant materials harvested from phytoremediation sites can contain high concentrations of Se, which if not properly managed can be potentially toxic to waterfowl and wildlife via biomagnification. One alternative disposal option is to utilize Se-enriched plant materials for Se biofortification of agricultural products [62]. Thus, it is critically important to screen and select the appropriate plant species and to use toxic metal-free phytoremediation field sites for integrating Se phytoremediation and biofortification strategies. In general, there are two very basic requirements to meet this goal: firstly, the selected plant tissues should be edible or convertible into food, and secondly, the edible part of the plant should accumulate higher and safe concentrations of Se, but not other toxic compounds [63] .

Selenium-containing plants showing potential benefits for human health

The success of functional foods in the marketplace has led to intense interest in the discovery and the characterization of plant-based bioactive compounds. Synergism between bioactive components of a plant may result in unexpected metabolic outcomes within the plant and within an animal that consumes it. Foods that contain Se as a functional ingredient must be enriched naturally, because Se is not on the FDA's GRAS (generally recognized as safe) list and therefore cannot be directly added to food products. Consequently, dietary supplementation of Se requires enriched food sources, but the Se content of most plants is variable and reflective of the amount available from the soil. In the past decade the possibility of developing either Se-rich or Se-biofortified agricultural products as nutritional supplement for human health has come to the fore. This was supported not only by the evidence of the strong connection between Se levels and human health, but also by the biological activities that some Se-containing plants have been shown to have. Such seleno-accumulating plants provide a rich genetic resource that we are beginning to exploit to develop food crops enriched with antioxidant and anticarcinogenic [64] Se compounds for improved public health [65]. Moreover, Se plays a role in the prevention of atherosclerosis, arthritis, and altered immunological functions [66]. In general, all the beneficial effects of selenium, and thus the potential beneficial effects of Se-rich plants as food supplements and/or phytotherapeutic agents, are strongly related to the high antioxidant potential of selenium-containing compounds. Moreover, Se-supplementation could be used in any case of selenium deficiency [67] as selenium has two main levels of biological activity: in trace concentrations it is required for normal growth and development, while in moderate concentrations it can be stored to maintain homeostatic functions; nevertheless elevated concentrations can result in toxic effects [68]. Selenium deficiency and low Se daily dietary intake can cause either endemic diseases or other significant environmental health problems, such as Keshan disease (a degenerative heart disease observed in Keshan, China) and Kaschin–Beck disease (an osteoarthropathy that causes deformity of affected joints [69]. The beneficial effects of Se are dependent on its chemical form, selenomethionine (SeMet) being the most readily assimilated [70].

Recently, a glasshouse experiment was carried out to investigate the effect of selenium on the antioxidant activity of *Ficus deltoidea* (Mas cotek). The influence of Se on the antioxidant ability was determined by measuring the free radical scavenging effect with the 2,2-diphenyl-1-picrylhydrazyl radical (DPPH) in the extracts from the dried leaf samples. It was concluded that Se uptake by Mas cotek significantly increased when selenite was supplied to the soils. In terms of antioxidant activity, Se in general augments antioxidant compounds in Mas cotek leaves. These compounds were more effectively induced by higher Se concentration in the soils [71]. Another interesting research project was carried out on green tea leaves. As widely known, some species of tea have strong antioxidant properties and much attention has been focused on the antioxidant and antimutagenic activities [72], and anticancer effects of green tea [73]. Most of these effects have been attributed to the antioxidative and free radical scavenging properties of tea, particularly to its high polyphenolic compound content and microelements. The study was aimed at determining the effect of foliar application of selenium on increasing the antioxidant activity of green tea (*Camellia sinensis*) leaves harvested during the early spring using a (DPPH) radical scavenging method and the linoleic acid system. Se-enriched tea obtained by fertilization with selenate exhibited the highest inhibition percentage of 84.3% at 30 min when BHT showed 78.1% inhibition under the same conditions. Se-enriched tea extracts provided higher hydrogen-donating capabilities than regular tea. As a result, with human consumption of this Se-enriched tea, both the Se intake and the antioxidant activity and thus the beneficial effect of green tea can be increased [74].

An earlier but interesting study was carried out on the determination of the bioactivity of selenium from Brazil nut for cancer prevention and selenoenzyme maintenance. Brazil nut (*Bertholletia excelsa*) is one of very few consumable products with exceptionally high levels of selenium. The mean selenium concentrations of two shipments of Brazil nuts used in the study were 16 and 30 μg/g. In contrast, most common foods contain much less selenium, from 0.01 to 1 μg/g. This study clearly demonstrates that Brazil nut has potent activities with respect to maintenance of selenoenzymes and cancer protection. Brazil nut is unique in the sense that it is one of very few consumable products which is a rich source of selenium. Because in these experiments ground Brazil nuts were used, it could reasonably be assessed that the reported biological activities are likely to be attributable to the high selenium content of Brazil nuts. This research also provided several interesting lines of evidence to suggest strongly that the models under investigation are responding to the selenium rather than to the other components of Brazil nut. First, the dose-response profiles to selenium in Brazil nut and to selenite selenium are very similar regarding the ability to maintain selenoenzymes at nutritional levels and to protect against mammary carcinogenesis at supranutritional levels of selenium intake. It would therefore not be unreasonable to argue that the modulation of these biological effects after ingestion of Brazil nut is due to the indigenous selenium. Moreover, the study showing the repletion of glutathione peroxidase and type I 5'-deiodinase by Brazil nut is conclusive proof that the selenium contained in these nuts is bioavailable. Finally, mammary cancer prevention by Brazil nut was associated with increased tissue selenium retention in a dose-dependent manner. It is important to highlight that any bulk effect due to the consumption of a large amount of nut material would have to be discounted, because the consumption of a comparable amount of English walnut did not elicit any beneficial response in cancer protection [75].

Studies were conducted to determine whether enhancement of broccoli (*Brassica oleracea*) with Se would produce a plant with superior health benefits. Broccoli can accumulate selenium, and Se has been demonstrated to reduce the risk of cancer. In particular, it was investigated whether enhancement of broccoli with Se would produce a plant with superior health benefits. Although increasing the concentration of Se in broccoli from <1.0 to >800 µg/g resulted in inhibition of colon cancer in rats, it also decreased sulforaphane content by <80% and inhibited production of most phenolic acids. The inclusion of Se-enriched broccoli in the diet of rats induced the activity of the selenoprotein thioredoxin reductase beyond the maximum activity induced by Se alone. These results emphasize the complex interactions of bioactive chemicals in a food; attempts to maximize one component may affect accumulation of another, and consumption of high amounts of multiple bioactive compounds may result in unexpected metabolic interactions within the body [76]. Numerous studies have reported low selenium status in HIV-infected individuals, and serum selenium concentration declines with disease progression. Some cohort studies have shown an association between selenium deficiency and progression to AIDS or mortality. In particular, plasma Se is a strong predictor of HIV-progression, and it has been suggested that low plasma Se is a greater risk factor for mortality than other antioxidants or a low $CD4^+$ count. Several studies and trials are ongoing to elucidate the effect of selenium supplementation on opportunistic infections, and other HIV disease-related comorbidities in the context of highly active antiretroviral therapy in both developing and developed countries [77].

Conclusions – By analysis of the literature it appears evident that some natural species in the presence of a high level of selenium can metabolize and accumulate some organic derivatives, reducing the potential toxicity for plants and representing a natural supplement for animal and humans that consumed it. A connection between Se levels and human health, as well as the biological activities of some Se-containing plants has been observed even if defined utilization as a nutraceutical element is still an open debate but, in our opinion, needs to be more deeply investigated.

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