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Selenium as a Mineral with Anti-Cancer Properties

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Abstract

Selenium (Se) is a trace element necessary for the proper functioning of organisms that have recently gained substantial attention due to its promising chemotherapeutic potential in cancer prevention and treatment. Besides providing routine anticancer treatments, Se supplementation has been shown to enhance the suitability of standard chemotherapeutic approaches with limited side effects and without reducing the treatment effectiveness, thus improving the patients' general conditions. The smallest changes in the Se content may cause its deficiency or excess. Therefore, a supplementation has to be carefully and cautiously administered.

Nevertheless, Se mechanisms of potentially anticancer properties are not fully understood. The relevant research has shown that its properties may correlate with its antioxidant protection, enhanced immune surveillance, augmented carcinogen detoxification, modulation of cell proliferation (cell cycle and apoptosis), and inhibitions of angiogenesis and tumor cell invasion and migration.

It is worthy to mention that Se biological activity, potential anticancer properties, and compounds are highly dependent on its speciation, chemical form, and specific metabolic pathways of the target cells and tissues.

Elucidating and deepening our knowledge of Se and its properties will help in designing and optimizing its compounds with more specific antitumor properties for their possible future applications in the treatment of cancer. This review surveys the global cancer status and provides progress in the current understanding of the molecular mechanisms that clarify the potential anticancer effects of Se and its compounds.

Keywords: Selenium, Trace element, Neoplasm.

Introduction

There is a wide and fast growing research on the critical role of nutrition in the cancer process. It has been estimated by the World Cancer Research Fund and American Institute for Cancer Research that 30%-40% of any types of cancers can be prevented by physical activity, appropriate diet, and appropriate body weight maintenance.[1] Healthy and appropriate diets associated with an intake of micronutrients, such as vitamins, trace elements, and antioxidants would greatly improve the general health. Trace elements are the chemical micronutrients significantly required in minute quantities to maintain the integrity of various metabolic and physiological processes occurring within living cells and tissues.[2]

Selenium (Se) is a dietary trace element substantial for health and growth maintenance. It is mainly found in the seafood, egg products, animal liver, kidney, nuts, and other foods.[3] In 1817, the discovery of Se by the Swedish chemist, Jöns Jacob Berzelius, triggered investigations of the effects of Se inorganic forms on living organisms. In 1957, Schwarz and Folz unexpectedly discovered some protective effects of Se on organisms. Following these studies, Se was classified in a group of trace elements whose deficiencies in the diet may cause numerous diseases.[4] Currently, Se is insufficiently consumed in many countries, while its dietary deficiency has affected 0.5–1 billion people in the world.[5]

Se plays a significant role in the antioxidant defense

systems, immune function, and thyroid hormone metabolism.[6] Several epidemiological studies revealed an inverse association between Se intake and the risks of some cancers, including prostate,[7] lung[8] and bladder[9] cancers although the results were not consistent.[10] Nonetheless, a distinctive finding of almost 50% reduction in the overall cancer morbidities by providing free-living people with a supplementation of Se-enriched brewer's yeast predominantly associated with selenomethionine has provoked much interest in this field.[11] Recent advances have led to suggesting several mechanisms for Se anticancer properties, including antioxidant protection, incremented immune surveillance, altered carcinogen metabolism, inhibition of neoangiogenesis and tumor cell invasion, and regulation of cell proliferation.[11-14]

Se cellular function is mediated by its incorporation into selenoproteins, mainly in the form of selenocysteine, which is known as the 21st amino acid. The human genome harbors 25 selenoprotein genes, including thioredoxin reductases, selenophosphate synthetase 2, methionine-R-sulfoxide reductase (MsrB), thyroid hormone deiodinases, glutathione peroxidases, etc.[15] Some of these proteins are essential enzymes integrating Se in the form of selenocysteine that requires selenoproteins for an appropriate enzymatic activity in their active site.[16] Se antioxidant function is involved by some of these selenoproteins providing a direct protection against oxidative stress. Additionally, the indirect antioxidant function of Se is mediated by selenoproteins, which make regeneration and activation of the antioxidants of low molecular weights like Q10 and Vitamins C and E when provided at low nutritional levels.[17]

However, at extra doses, Se typically turns into a pro-oxidant of high cytotoxic activities with well-established growth inhibiting properties. Importantly, Se beneficial and toxic effects have been reported to be strictly dependent on its chemical form and concentration. Additionally, there is a relatively narrow window between Se deficiency and toxicity, while the growing evidence suggests that the health effects of Se as a micronutrient greatly depend on its baseline level. Thus, Se supplementation is not an easy task and requires a precisely individualized approach.[6]

Since there exists a very broad and incongruent literature on Se anticancer properties and compounds, further research is incumbent to better characterize Se compounds and mechanisms of action, which could be crucial for cancer prevention and treatment. This review focused on the details of the molucular mechanisms of Se anticancer effects and aimed at describing the proposed mechanisms and targets of Se compounds and their effects on cancer treatment together with cancer pathogenesis and epidemiology.

Cancer epidemiology

Approximately 12.7 million cases of cancer and 7.6 million deaths related to it existed throughout the world in 2008 when 56% of the cases and 64% of the deaths were found to increasingly occur in the developing countries. Part of this outcome is related to population aging though it is strongly affected by the lifestyle risk factors like poor diet and physical activity and smoking as well.[18,19]

23% of the total cases of cancer are most commonly related to breast cancer among women, which accounts for 14% of cancer deaths both in the developing and developed countries. Cervical cancer had been previously known as the most frequent cause of cancer-related deaths among women. In recent years, 11% of cancer deaths among women have been related to cervical and lung cancers with almost equal mortality rates. Also, colorectal cancer has been commonly diagnosed in the developing countries.[20,21]

Generally, lung cancer has been most commonly known to be the cause of cancer cases (17%) and deaths (23%) among men. In addition, prostate cancer as a most frequent types of cancer has been diagnosed in the developed countries. Liver and stomach cancers stand on the next places.

In the developed countries, the mortality rates of

cancer in males and females are 21% and 2% higher than those of the developing countries. Moreover, the incidence rates are nearly twice as high in the developed countries. Female breast, lung, prostate, and colorectal cancers are the most frequent types (with the incidence rates of 2-5 times higher in the developed compared to the developing countries. The reasons for this inconsistency are related to the different prevalence and distributions of the major risk factors, detection practices, and treatment availabilities and uses in different regions. Yet, the highest incidence in the developing countries can be due to the infectious cancers, which may lead to liver, stomach, and cervical cancers.[20,21]

Reduced access to suitable drugs and facilities can be another cause for the higher case-fatality rate in the developing countries. For instance, the 5-year survival rates of breast cancer in parts of Africa, India, and the Phillipines have been less than 50% compared to those of Singapore, South Korea, and parts of China (more than 75%).[20,21]

Still, many options, including tobacco control, vaccination for infectious cancers, early detection and treatment, and dietary and physical activity promotions through public health programs, exist for reducing cancer burden worldwide. Of course, coordinated efforts of public and private health centers, pharmaceutical industries, and individual and governmental donors are required for such programs. Besides, dedicated funding is incumbent to provide continuous progress against cancer. An integrated health care system consisting of clinicians, nutritionists, health professionals, and policy-makers can play an active role in these efforts. In addition, both basic and clinical research is essential in the campaign against cancer. Also, the disadvantaged groups must not be withdrawn from our special attention in these efforts.

Molecular Pathogenesis of Cancer

Cancer is a complex group of diseases with some possible etiologies, including genetic and lifestyle factors, environmental exposures to different types of chemicals and radiation, and certain types of infections. Various types of carcinogenesis, including chemical (asbestos, benzpyrene, and over 800 other chemicals), physical (ultraviolet and ionizing radiations, etc.), and biological (bacteria, viruses, and fungi) carcinogens have been already confirmed.[22] However, there are no clinical and practical possibilities of determining the etiological causes of cancer.

In the modern oncology, the cellular damage to the genetic apparatus, including mutation, disturbance of gene expression, inactivation of tumor suppressor genes, activation of tumor promoter gene, etc. is considered as the potential cause of cancer. Recently deep fundamental research on living organisms at cellular, molecular, and genetic levels has defined cancer as a pathological process of transformation of a normal cell into a tumor cell.[23,24] These processes can be caused by metastasis (invasion factors, cell products, impaired intercellular interactions, permanent reproduction of tumor cells under the influence of autocrine and paracrine stimulations of cell division, etc.), angiogenesis (growth factor production by the cells of blood vessels, endothelial cell proliferation, etc.), oxidative nitrosative stress (cell productions of reactive oxygen and nitrogen species), disruption of the immune system (violation effects or functions of NK cells, macrophages, cytotoxic lymphocytes, emergence of T-regulatory cells, imbalance of Th1/Th2, etc.), and inflammation (cell productions of pro-inflammatory cytokines, growth factors, etc.).[25-28]

Current Therapeutic Strategy for Cancer Management

In the clinical practices, it there is no possibility of determining the exact etiological cause of cancer so as prescribing an appropriate etiotropic cancer therapy in each case. Therefore, no causal treatment of cancer exists. For a better outcome, therapeutic strategies should take into consideration some necessary

elements, including assessment of the extension of a tumor process, histological nature of the lesion, and evaluation of the general state of the disease.[29]

The treatment of cancer has been based and still relies almost exclusively on a surgical therapy although some associated therapies have been developed over the past decades: surgery and/or chemotherapy and/or radiotherapy, with the development of cryotherapy, hormonal therapy, virotherapy, multimodality and adjuvant chemotherapy, bone marrow/stem cell transplantation, vaccines, targeted therapy (including immunotherapy, such as monoclonal antibody therapy) and gene therapy (RNAi approaches, hematopoietic progenitor cell gene transfer, biology of cancer stem cells, homologous recombination, antisense technology, ribozyme technology, tumor suppressors, drug resistance, viral and non-viral gene delivery systems, anti-gene therapy, antisense technology, siRNA & ribozyme therapeutics, and apoptosis and DNA synthesis and repair). However, some of these anticancer therapies are being developed and their uses in clinical practices raise a subject matter for the future.[30,31]

Since cancer incidence is multifactorial, it is unlikely that there will be ever a single efficient cure for cancer. Over the last decade, considerable advances in the combinatorial approaches have emerged to improve cancer treatment outcomes. Combinatorial approaches are the result of an improved understanding of the molecular mechanisms that mediate cancer progression and its resistance to a single therapy.[32]

Through a deep understanding of the underlying biological processes in cancer, anticancer therapy has undergone evolutionary changes. Tumor removal surgeries have been recorded in ancient Egypt, while radiation and hormone therapies are some achievements of the late 19th century. Developments of chemotherapy, immunotherapy, and newer targeted therapies occurred in the 20th century. By the emergence of new information about cancer biology, treatments are developed and modified to increase effectiveness, precision, survivability, and life quality in this field. Since each possible pathological process becomes a target for the development of different methods of anti-cancer therapeutic effects, such as the various methods of antioxidant therapy,[33] cell therapy, targeted therapy,[34] cytokine therapy,[33] vaccine therapy (DNA vaccines),[35] methods of blocking neoangiogenesis[36] and some other relevant approaches have been presented.

The ideal and practical goal of treatment in is accomplished by completely diminishing a cancer without damage to the rest of the body, i.e., achieving a cure with near-zero adverse effects. Sometimes, this can be achieved by surgery; however, since cancers have a tendency to invade their adjacent tissues or spread to distant sites through microscopic metastasis, the effectiveness of surgical interventions is often limited. Besides, radiotherapy and chemotherapy leave some negative effects on normal cells.[24] These negatives effects may differ between people, even among those receiving the same treatments. The type(s) of treatment(s), as well as the frequency or amount of treatment, patient's age, and other health conditions may influence on the side effects of cancer treatments. The common side effects caused by cancer treatments are as follows: anemia, appetite loss, bleeding and bruising (thrombocytopenia), constipation, delirium, diarrhea, fatigue, edema, lymphedema, hair loss (alopecia), infection, and neutropenia, memory or concentration problems, mouth and throat problems, nausea and vomiting, nerve problems (peripheral neuropathy), pain, sexual and fertility problems (men and women), sleep problems, skin and nail changes, urinary and bladder problems, lethargy, mucositis, dermatologic manifestations (erythema, pruritus, desquamation), esophagitis, pneumonitis, hepatitis, tenesmus, and cytopenias. Additional late complications have included hypopituitarism, xerostomia, hypothyroidism, keratitis, cataract and retinal damage, pericarditis, pneumonitis, esophageal stricture, ulcer, hepatitis, gastritis, nephritis, sterility,

and muscular contracture.[37-41]

Therefore, treatment without negligible adverse effects may be accepted as a practical goal in some cases. Besides curative intents, practical goals of therapy can include suppressing cancer to a subclinical state and maintaining that state for years of good life quality i.e., treating cancer as a chronic disease, as well as providing a palliative care without a curative intent for advanced-stage metastatic cancers. However, in spite of recent advances in cancer therapy, some types of resistance to therapeutic methods have still remained as a major obstacle for anticancer therapies. Hence, to overcome the resistance mechanisms resulting in recurrence of the disease, some strategies involving the combinatorial approaches have been extensively investigated. For an effective cancer management, nutritional factors and trace elements should remove part of the puzzle found in the combinatorial approaches.

A Need for Anticancer Agents

Despite recent developments in cancer treatment, 14% (from 50% to 64%) of survivals for cancer patients in the past 30 years would provide strong evidence of the insufficient efficiency of the existing approaches to cancer therapy.[32] In addition, cancer incidence has globally increased from 12.7 million in 2008 to 14.1 million new cases in 2012 with 8.2 million deaths. Over the next 20 years, it is expected that the cases of cancer reach 25 million (a 75% increase).[42] Despite the availability of the important basic knowledge about the process of cancer, some obstacles have been faced in the creation of effective cancer treatments in humans.

Currently, there are some eminent strategies of treating cancer, which include surgery, using cytotoxic drugs, and radiation therapy. All these have significant limitations, but drugs been have administered as the only approach for treatment in the cases that cancer has spread (metastasized) throughout the body. Other less well-established options include the drugs that can stimulate the immune system to assist the body itself to fight the disease, as well as non-cytotoxic drugs that can prevent multiplication of cancer cells.[31]

Thus, the search for novel anticancer drugs is still a priority objective for cancer treatment since rapid resistance to chemotherapeutic drugs has been developed. Nevertheless, new agents have been steadily less approved for cancer treatment over the past decade. In addition, the high toxicity usually associated with some cancer chemotherapy drugs and their undesirable side-effects has increased the demand for novel anti-tumor drugs active against untreatable tumors with fewer side-effects and/or greater therapeutic efficiency.[43]

Until the 1990s, the development of anticancer drugs was largely based on testing the compounds derived from a variety of sources, including natural products, substrate analogues, combinatorial syntheses, typically in vitro cytotoxicity assays followed by the in vivo assessment of toxicity and efficacy. Since then, particularly following the determination of the human genome and the emergence of increasing insights into the genetic changes associated with cancer, drug development has moved into an era of cellular and molecular targets.[44]

Unfortunately, despite the scientific substantiation and efficiency of the developed methods of treating cancer in preclinical studies, the degree of success expected in clinical practices has not been achieved yet. Thus, there is always a constant need to develop alternative or synergistic anticancer drugs with minimal side-effects. One important strategy to develop effective anticancer agents is to study the anticancer agents derived from natural sources. Recently, many studies have been conducted about dietary interventions aimed at preventing or treating cancer. Also, cancer survivors are often highly motivated to seek information about food choices, physical activity, and dietary supplement used to improve their treatment outcomes, life qualities, and survivals.[45]

Se as a trace element has been used alone and in combination with therapeutic agents for the treatment

of various types of cancers for a long time. Since indication, the probable direct or indirect influences of trace elements on the development and prevention of cancers have been under scrutiny. Trace elements are micronutrients that are part of daily diets required in minute quantities, but are extremely important in many different biological and physiological processes, such as the functions of structural nutrients, normal healing, protection against oxidative damage, metabolism of genetic materials for growth and differentiation, programmed cell death and necrosis, and anti-inflammatory and anti-carcinogenic effects. The in vivo utilization of trace elements is complex and not completely understood. Because of the multiplicity of functions and the varying roles depending on balance and concentration, the impacts of trace elements on cancer management are still to be fully elucidated.[3, 46-50]

Natural Sources of Se

Se as a trace element existing in the environment in several organic and inorganic forms, while its content in foods is characterized by great diversity. Se contents of animal products are influenced by Se levels in their consumed diets,[47] whereas the Se contents of plants reflect its levels in the soil, in which they are grown, as well as their abilities to accumulate it. Yet, most plants cannot accumulate large amounts of Se Since some other factors, such as geographical area, climatic conditions, cultivation and breeding methods, and methods of preparing food products influence on Se levels in plants.[51]

Se most frequently exists in combination with proteins in food products and can replace sulphur in the amino acids as selenocysteine (Se-Cys), selenomethionine (Se-Met), and selenocystathionine due to their physicochemical similarities. Furthermore, selenocompounds would be used in the synthesis of Se-amino acids (mainly, Se-Met and Se-Cys) and finally incorporated into vegetable proteins. Thus, the Se forms included in the vegetable proteins of animal feeds would be ultimately employed in the synthesis of the animals' own proteins facilitating their accumulations in the livestock. Thus, the products with high protein contents are typically characterized by a higher Se content.[52]

Meat, chicken, fish, and eggs which are protein-rich foods are known as high Se-content products.[53] In these food groups, fish of both marine and freshwater origins and eggs have shown the highest Se concentrations.[54] Other good sources of Se are animal meats, but Se content in the livestock is dependent on diets and the region, in which the animals feed.[55] Animal meat mostly contains selenomethionine (up to 60%) and Sec (up to 50%). The remaining Se species are small Se-containing molecules. These ratios can vary depending on what form of Se is consumed. Selenate and selenite in food are converted into Sec. Animals fed by selenomethionine-containing food increase the contents of selenomethionine and Sec in their meats.[56]

Milk and dairy products are other groups thatinclude Se. It has been found that Se concentrations in milk change in different animal species like goat and sheep, as well as humans. Cow milk has been observed to have the most Se content. It has been reported that Se concentrations in milk and cheese as dairy products are negatively correlated with its fat content. Also, it has been determined that season is an important factor in the Se content of cow milk indicating higher levels of milk in the summer than in the winter. It is noteworthy to say that milk and dairy products contribute to a considerable part of the total dietary intake of Se for humans, particularly infants.[47,54]

Vegetables and fruits contain small amounts of Se because of their low contents of protein and high contents of water.[53] However, it is known that vegetables, such as broccoli, brussel, sprouts, cauliflower, cabbage, collards, mustards, kohlrabi, kale, garlic, chives, and onions tend to have higher Se concentrations, while the extent to which they are consumed is reflected in the Se content of human tissue and body fluids.[57,58] Additionally, these plants have a

greater fraction of sulphur containing amino acids and their derivatives, as well as other sulphur compounds like glycosinolates or sulfoxides. Adequate analogues of these can be formed by the substitution of sulphur with Se resulting in higher Se levels. Garlic and onions seem to be good dietary sources of Se, both of which are valuable to decrease the risk of cancer development. Furthermore, the intakes of these vegetables by humans do not result in excess accumulation of Se in tissues nor can any perturbation in Se enzymatic actions be observed even at high Se intakes.[57] This is mainly due to the reduction of the intracellular Se concentration of Se-Cys and Se-Met, which are normally incorporated into proteins. When consumed in appropriate amounts, these foods can be a significant food source of Se.[57] Legumes, especially lentils, present Se contents. Pistachios have proven to be the richest in Se concentrations, whereas almonds have shown the poorest Se sources. The proteins found in nuts are very high in Se-containing amino acids, mainly Se-Met.[57,59] Grains, wheat, and corn used for bread and other food products contain selenomethionine as a bioavailable Se source.[60] Sec and selenate/selenite are also detectable in substantial amounts in wheat. Also, Se content is detected in other plant products like turmeric and sweet neem, olive, marc oil, Indian spices, and condiments.[61] Plants that accumulate Se may be used as a natural source of mineral supplements for both animals and human beings, especially in areas with Se deficiencies.

Se yeasts in comparison with the preparations containing inorganic Se constitute valuable sources of easily assimilable Se.[62] Similarly, mushrooms contain substantial amounts of protein, while their protein fractions exhibit high levels of organic Se.[63] Drinking water contains very low amounts of water-soluble inorganic forms of Se [64] and this Se contribution as a dietary source is very minor.

Finally, regardless of Se sources, food processing, such as cooking (boiling, baking, or grilling) can decrease food Se content through volatilization.[57,65] For example, Se losses in asparagus and mushrooms were observed when boiled for some minutes.[52,57] Some Se losses have been also noted when roasting chicken and fish.[66] However, other researchers have not found any decreases and have even reported that processes like cooking, aeration, or lyophilization significantly increase Se contents in all foods.[67]

Therefore, food Se content of varies from sample to sample, even in cases of the same products. Also, the content of Se in food should not be exclusively based on food tables, but the losses during food processing and preparation, variations due to seasonal changes or geographical location, and food habits should be taken into account as well.

Physiochemical Characteristics of Se

Selenium with the symbol "Se" and atomic number of 34 is a non-metal element, but is sometimes considered metalloid. Se is located between sulphur and tellurium in Group VIA and between arsenic and bromine in Period 4 of the periodic tables. It was first described by the Swedish chemist, Jöns Jacob Berzelius in 1817 (1779–1848). He named this element "selenium" (Greek σελήνη selene meaning Moon) after the Greek moon goddess Selene. During investigations of the cause of illness among workers at a sulfuric acid manufacturing plant, Berzelius found Se in the bottom sludge of a sulfuric acid preparation. He noted that Se had similarities with the previously known element "tellurium" (named after the Earth) and chemical properties, such a valence shells, electronic structures, and atomic radii, which were similar to those of arsenic. He also reported Se to have the atomic size, bond energies, ionisation potentials, and electron affinities of a close resemblance to sulphur. Although Se forms the same type of compounds similar to sulfur (occurring in the oxidation states of −II, 0, +II, +IV, and +VI), its chemistry cannot be simply compared.[68,69]

The major difference between Se and sulfur is that Se exists as a reduced quadrivalent form, whereas sulphur occurs as an oxidized quadrivalent form. Se compounds tend to be less stable than the corresponding

compounds of sulfur, especially the form with the oxidation state of +VI. This significant difference is caused by the strongest attraction of the 4s orbital to the nuclei due to the poor shielding of the nuclei by the fully occupied d orbitals (the so-called "inert electron pair effect"). For this reason, unlike sulfur, Se resists reaching the maximum possible oxidation state of +VI, which can be attained using very strong oxidizing agents, i.e., only potassium permanganate, fluorine, and concentrated hydrogen peroxide). Se compounds in the oxidation state of +VI are unstable in the presence of organic materials and are thus as potent oxidizing agents. Generally, the most stable compounds are selenides M2– formed with the most electropositive metals and compounds of oxide, chloride, and fluoride with Se in positive oxidation states.[70]

In addition, there is a difference between Se and sulfur based on acid strength. For instance, selenium hydride (H2Se) is a stronger acid (pKa=3.7) than sulphur hydride (H2S, pKa=6.9). Due to its greater acid strength, Se as a selenol compound (R SeH) is readily dissociated at the physiological pH, which is required for its role in catalytic reactions. Se can also exist in various oxidation states, which allow it to form into several organic Se compounds (dimethylselenide, trimethyselenium) and amino acids (selenomethionine, selenocysteine) in place of Sulphur.[69]

A wide range of Se compounds can be found in the environment and living organisms ranging from simple inorganic forms (e.g., selenides, halides, oxyhalides, acids, oxides, and oxyacid salts) to complex biogenic compounds, such as selenoenzymes and selenium nucleic acids.[70] Huge families of Se biogenic compounds consist of simple organic and methylated species, selenoamino acids, selenoproteins, Se peptides, selenoenzymes, selenoaminocarboxylic acids, as well as Se derivates of pyrimidine, purine, steroids, cholines, coenzyme A, and many others. Most of these forms play a role in living organisms and have biological functions by contributing to the reduction of oxidative stress.[4]

Available Formulations of Se

Se exists in the two organic (selenocysteine and selenomethionine) and inorganic (selenate and selenite) forms. Both forms can be good dietary sources of Se. Soils contain inorganic selenites and selenates, which plants accumulate and convert into organic forms, mostly selenomethionine and selenocysteine and their methylated derivatives. Most Se is in the form of selenomethionine in animal and human tissues where it can be nonspecifically incorporated with the amino acid methionine to make body proteins.[46]

The most pertinent example of inorganic Se compounds evaluated as a therapeutic agent for the treatment of cancer can be found in Se (IV) selenite. In several studies, it has exhibited a significant cytotoxicity against malignant cells, such as lung,[71] prostate,[72] cervical,[73] ovarian,[74] and colon[75] cancer cells within a low micromolar range in the primary human acute myeloid[76] and lymphoblastic [77] leukemia cells, as well as hepatoma,[78] melanoma,[79] and mesothelioma cells.[80] Among other inorganic Se forms, Se (IV) dioxide (SeO_2) has been found to exert a discrete in vitro cancer cell killing activity, whereas the compounds of higher Se oxidation states, such as Se (VI) selenate (SeO42–), have been hardly effective against mammalian cancer cells.[81]

Selenoproteins are the major forms of organic and functional Se, thus providing an assessment of Se nutritional requirements through selenoprotein optimization.[82] Mammalian Se-containing proteins can currently be divided into the following categories, including specific enzymatic proteins with selenocysteine incorporated into their active centers, proteins containing nonspecifically incorporated Se, and Se-Binding Proteins (SBPs).[83,84]

Dietary Se acts principally through selenoproteins, which are proteins with enzymatic activities incorporating Se in the form of Sec, a Se-containing homolog of cysteine (Cys). In addition, incorporating as Sec, Se can replace sulfur in methionine (Met), forming selenomethionine (Se-Met). Since cells do not

distinguish between Met and Se-Met during protein synthesis, Se-Met that is not immediately metabolized is randomly incorporated into proteins in place of Met.[85] When needed, Se-Met is reversibly released, which may be converted into Sec via the trans-selenation pathway and then used for selenoprotein synthesis. This nonspecific incorporation of Se-Met into the general body proteins allows Se to be stored in the organism, thus offering Se-Met an advantage over other Se compounds used for dietary supplementation. The organs with high rates of protein synthesis, such as skeletal muscles, liver, pancreas, or kidney have been found to serve as a rich source of Se-Met.[6,85]

Se occurs in the composition of active selenoproteins that play an important role in many physiological processes. The biosynthesis of the selenoproteins is a complex process of many steps that involve a cadre of specialized reactions leading to Sec insertion by ribosomes. The synthesis of selenoproteins has been demonstrated to be sensitive to the supply of Se, but not all selenoproteins are affected in the same way.[86] So far, 25 selenoproteins have been identified in humans.[83]

Selenoprotein P is involved in defending an organism against the damaging effects of free radicals. It actively participates in the storage and transport of Se; moreover, it is a good indicator of Se resources in the organism.[83] Se is also an essential component of selenophosphate synthetase that plays an important role in the synthesis of selenophosphate and catalyzes selenocysteine binding to selenoproteins. Selenoprotein W (having a probable function in muscle metabolism), selenoprotein R (having a probable antioxidant function), selenoprotein S (controlling redox balance in cells), and selenoproteins N and M are other distinguished selenoproteins. The functions of numerous selenoproteins are still poorly understood due to scarce research in this field.[87,88]

Se constitutes an integral part of selenoproteins and some antioxidant enzymes, such as glutathioneperoxidase (GPx), and thioredoxin reductase, which protect cells from the damaging effects of free radicals produced during oxidation. Se is also a component of other enzymes, particularly iodothyronine deiodinase, which catalyzes the deiodonization of thyroxine (T4) to triiodothyronine (T3). Deiodinases play a key role in the regulation of thyroid hormones. Like iodine, Se is an essential element for the proper thyroid function. Consequently, these enzymes are involved in the synthesis of thyroid sulphated hormones. An association between Se status and low plasma T3 levels showing a diminished IDI function has been reported by several researchers.[89] Thioredoxin reductase is also a Se-dependent enzyme involved in the reduction of intracellular substrates. When rats were administered considerably higher Se amounts than the Recommended Dietary Allowance (RDA), their thioredoxin reductase activity was directly enhanced. With some forms of Se, thioredoxin reductase enzyme has been associated with anticancer effects at very high doses.[70,83]

Another group of Se-containing proteins are Se-Binding Proteins (SBPs) that covalently bind to Se, while their functions have not been fully characterized. SBP1 is the best SBPs studied, the exact physiological function of which is unknown though it has been suggested to be involved in intra-Golgi transport and ubiquitination-mediated protein degradation pathways. Additionally, SBP1 has been proposed to play a role in a malignant transformation and cancer progression as markedly reduced SBP1 levels have been detected in multiple epithelial tumors and low SBP1 expression has been found to correlate with a poor prognosis in various human cancers.[90,91]

Se concentrations in plasma and serum provide the most commonly used measures of human Se status. Se concentrations in blood and urine reflect a recent selenium intake. Analyses of Se contents in nail or hair can be used to monitor longer-term intakes during months or years. Quantification of one or more selenoproteins (e.g., selenoprotein P and glutathione peroxidase) is also used as a functional measure of Se status. 8 micrograms (mcg)/dL of Se concentrations in

the plasmas or serums of healthy people or higher typically meet the needs of selenoprotein synthesis.[92] More than 60% of plasma Se is carried by selenoprotein P, which is known as the main plasma Se carrier. It is a plasma protein whose source is in the liver and kidney. Besides, it is known that protein levels depend on the body's Se status in a way that it is used as a biomarker of body Se content. Particularly, selenoprotein P acts as an extra cellular antioxidant associated with the vascular endothelium, which diminishes peroxinitrile (ONOO−) level that represents a reactive nitrogen species.[93]

Bioavailability of Se

Se is a micronutrient whose safe concentration range between the deficiency and toxic level is very narrow.[83] Therefore, it is important to know its deficiency or abundance in food and diet and determine its appropriate balance in human beings. In general, the bioavailability of the nutrient must be taken into account due to the unreliable estimation of its total content in a given food. It is a priority to find out the element bioavailability or amount absorbed and used by the organism since only a fraction is usually absorbed and transformed into a biologically available form.[94]

Therefore, for a complete bioavailability assessment, measurements of the total nutrient content, absorbable fraction, amount actually absorbed, and percent utilized by the organism should be regarded. The in vivo bioaccessibility studies are arduous and expensive and the possibility of measuring certain parameters during the experiments is often limited.[94] The in vitro bioaccessibility methods of simulated digestion represent an interesting alternative to the in vivo bioavailability procedures for calculating the percentage of an element that is transformed into absorbable forms in the digestive tract. The results of such bioaccessibility studies are usually expressed as the soluble fraction of the element under the given experimental conditions of pH, temperature, enzyme addition, and duration of contact.[94] These bioaccessibility methods comprise a two-phase simulation of gastrointestinal physiology, including the stomach and intestinal phases. The in vitro bioaccessibility analytical procedures are often useful because they are simple, inexpensive, and quick, while allowing the individual experimental variables to be easily controlled.[94]

Se bioavailability varies depending on several factors, including Se chemical form, physiological status, solubility, status in the organism, and other dietary components.[83] The soluble Se forms are mainly absorbed at the lower part of the small intestine through different mechanisms based on its form. Se bioavailability is the lowest in the inorganic selenite. Selenite (SeO32−) is absorbed by the passive diffusion to non-enzymatically react with the reduced glutathione to form selenodiglutathine (GS-Se-SG).[6] Selenate (SeO42−) is absorbed paracellularly via a passive diffusion and is subsequently reduced to selenite in the presence of NADPH, which is able to react with GSH in the same way.[95] Se amino acids l-selenocysteine (SeCys) and l-selenomethionine (SeMet) are absorbed by the transporters like Na+ through transcellular pathways. Also, SeMet could be nonspecifically bound to transport proteins, such as serum albumin or hemoglobin or alternatively transformed into SeCys.[96] It is believed that the absorbed Se is bound to albumin and transported to the liver where it can be used for selenoprotein synthesis. Most Se proteins either play a role in the defense against antioxidants where they participate in the redox state regulation or are employed for the metabolism of thyroid hormones.[97]

As mentioned, Se bioavailability is strongly affected by its chemical form (generally, Se organic compounds are more bioavailable than its inorganic forms).[98] For instance, because of its non-specifically incorporation into proteins (e.g., albumin, haemoglobin) in place of methionine, selenomethionine is more effective on increasing the apparent Se status. However, before

entering the available Se pool, it must be catabolized to an inorganic precursor. Selenomethionine is a less available metabolic source of Se than selenite or selenate since these need only be reduced to selenide to provide selenophosphate as a selenocysteine precursor, which is an active form of Se in selenoproteins.[99] Despite this, the organic forms (e.g., high-selenium yeast) are often preferred in the interventions, partly because they are less acutely toxic. Such organic forms may, however, be more toxic during a long-term consumption owing to Se non-specific retention (selenomethionine) in the body proteins rather than its excretion.[83]

Se solubility is an important local factor influencing on the distribution of unused or metabolized Se by the used nutrients. The oluble forms are readily distributed, but natural Se levels can be also quickly restored. In the case of insoluble Se forms, the problem may gradually emerge. The influences of other dietary factors, such as total fat, protein, and heavy metals have been also described in Se bioavailability. Se interacts with several trace elements in the additive, synergistic or antagonistic ways, while they reverse the interaction in some cases, i.e. changing synergism into antagonism.[100] Perhaps, one of the most reported interactions between inorganic elements is the antagonistic interaction between Se and Hg. Se is recognized to decrease Hg toxicity when both elements are simultaneously administrated.[94]

Approximately 80% of the dietary Se is absorbed although this figure depends on the food types consumed. The overall absorption of all forms of Se is relatively high (70–95%), but varies according to its source and status in a subject. Several studies have revealed the high bioavailability of Se in meat because Se forms in the foods of animal origins are mostly Se-Cys and Se-Met.[57,101] Se-Met is an essential selenoaminoacid, which is the major nutritional source of Se for animals and is known to be highly bioavailable. It is absorbed in the small intestine to be then incorporated into the long-term body reserves. Se content in fish is high though fish is sometimes a poor source of available Se due in part to its high Hg content and other heavy metals, which bind to Se and form insoluble inorganic complexes.[54,101] Se absorption from fish by humans is comparable to that from plants. Se in fish is a highly bioavailable dietary source, while cooking fish does not affect Se absorption or retention.[102] However Se from yeast is less bioavailable. It is reported that Se bioavailability from yeast is mixed. In a study, it has been reported that Se from yeast is effective on increasing Se concentration in red blood cells, but compared with selenate and selenite, it is ineffective on the enhancement of GPx activity. Contrarily, another research reported that Se from yeast was almost twice as bioavailable as Se from selenate and selenite for restoration of depleted GPx activity. These discrepancies may reflect differences in the study populations as well as a difference in the chemical speciation of Se in yeast.[50] A high absorbable fraction of Se has been reported to exist in dairy products, such as yogurt, cream cheese, custard, curd, ice-cream, crème caramel, and condensed milk. As previously mentioned, the chemical forms of Se species differ among foods. For example, broccoli as a Se-accumulating plant that contains many methylated forms of Se has a less bioavailability for Se, while Se from meats has been reported to be highly bioavailable for selenoprotein synthesis.[50]

Several pharmacological factors of human Se supplements influence on Se bioavailability, such as its physicochemical form, interaction with other medications or micronutrients being taken, consumption of the supplements in meal or fasting conditions, and finally timing, dosing, and scheduling of supplementation. These factors are very interesting because most studies focus on the influence of dietary factors on Se bioavailability from supplements, such as fiber content and the presence of oxalate, phytate, polysaccharides, protein, and amino acids, etc. In general, animal trials and human studies have demonstrated that the bioavailability of organic Se (Se-

Met and Se-yeast) has been higher than its inorganic forms (selenite and selenate).[57]

Recommended Doses and Safety of Se

In 1980, the National Research Council (NRC) established an estimated sufficient and safe daily dietary intake for Se in humans. The daily dose recommended for adults was set between 50 and 200 µg/d based on the research on animals.[103] As a trace element, an RDA for Se was established in 1989 (70 µg/d for men and 55 µg/d for women) and revised in 2000 (55 µg/d).[104] The WHO recommends a daily dose of Se to be 30-40 µg for adult individuals emphasizing that its doses of up to 400 µg/day are safe. According to the Food and Nutrition Board of the National Academy of Science, the daily requirement for Se was depending on age varies between 40-70 µg and 45-55 µg in men and women, respectively.[62,105] Nevertheless, Se intake should be established at 60–70 µg/day during pregnancy and lactation.[106] The recommended daily dose for adults is 55 µg/d in the United States and ranges from 55 to 70 µg/day in Europe.[107] A review of the literature data reveals that the recommended intake for Se varies depending on the geographical region as well. Residents of Venezuela (200–350 µg/day) and some selected areas of China (7–4990 µg/day) consume the highest doses, while the least Se (10–25 µg/day) is consumed by those of the Czech Republic.[108,109] Ideally, the recommended dose of Se should adequately reflect both the current local Se level with regard to its bioavailability and knowledge of the amount received from the imported sources. Naturally, the received content of Se in the body is driven by a number of factors already mentioned, but the local concentrations do not always need to correspond to the average, which is set for a country or even larger areas. Apparently, the ideal nutritional dose can be still insufficient if the natural Se intake is below an average level. In the worst case, the recommended nutritional dose can be too high with a natural Se intake and can cause a number of serious problems. Its efficacy and optimum dosing should be subjected to sufficiently frequent and efficient control mechanisms to prevent the adverse effects primarily stemming from its high intake. Thus, Se homeostasis needs to be tightly regulated for a healthy life. The range of Se intake for optimal health in humans and animals is narrow in a way that its low and high intakes are associated with the states of deficiency and toxicity, respectively.

Most of the early studies on Se have been done with the goal of addressing its toxicity. In the 1930s, Se was found to cause the poisoning of livestock feed in areas with a high Se content in the soil. In the mid-20th century, Se was recognized as a micronutrient and its biological function was studied with regard to its importance in human nutrition.[110] In 1957, a pioneering research by Schwarz et al. showed that liver necrosis in rats could be prevented by a supplementation with low doses of Se, thus shedding a new light on this microelement and leading to the recognition of Se as an essential micronutrient.[111] In 1973, it was discovered that Se is an integral component required for the activity of glutathione peroxidase (GPx) as an enzyme that plays a major role in the protection against oxidative stress. Since then, numerous scientific investigations have been carried out on the substantial role of Se in human health and illness.[112] Food supplementation with Se should be performed in a careful and controlled way to avoid the opposite of what has been intended because Se in relatively small quantities can be both a most toxic element and an essential micronutrient with an important biological role. The range between the necessary quantity of Se and toxic dose is very narrow.[4]

Se deficiency is a critical problem worldwide with a negative impact on health and lifespan. Particularly, patients with phenylketonuria[113] or the individuals suffering from diet-related diseases are vulnerable to the adverse effects of Se deficiency. Moreover, individuals exposed to specialized chemotherapy and those who have already undergone radiotherapy are vulnerable to the decreased levels of this trace

element.[114] Se deficiency in humans and animals inhabiting in the geographical regions with the soils of low Se contents has been confirmed. Se deficiency primarily leads to the degeneration of many organs and tissues, which is resulted from the decreased expression of selenoproteins and subsequent changes in the biological processes, in which it participates.[115] The symptoms of Se deficiency found in humans and animals have been primarily the kinds of disorders related to heart muscle and joints. Moderate deficiencies of this trace element may have negative impacts on human health like increasing the risks of infertility in men, nephropathy, prostate cancer, and occurrence of neurological diseases.[116]

The first reported cases of diseases related to Se deficiency in human population have been in China. The Se-responsive disease known as Keshan's disease is cardiomyopathy, which mainly affects young children and women of child-bearing ages. This has been found to occur in some areas of China where the soil is characterized by low Se contents.[117] Another Se-responsive disease, also reported in some areas of China, is Kaschin–Beck disease, which is osteoarthropathy, a generative articular disease caused by oxidative damage to cartilage that leads to bone structure deformation.[118] Also, Myxedematous endemic cretinism induced by thyroid atrophy and resulting in mental retardation has been associated with severe Se deficiency due to its occurrence in areas characterized by poor Se soils. Although Se may be only a cofactor in these diseases with other factors contributing to its incidence or severity, Se supplementation provides significant therapeutic benefits in all of these conditions.[49] Se deficiency may lead to the occurrence of other diseases, such as asthma associated with the impaired activity of glutathione peroxidase, promoted development of HIV infection leading to its significant progression and a reduced survival, impaired circulation, stroke, cardiac arrhythmia, epilepsy, age-associated neurological disorders, and sudden infant death syndrome.[49,119]

On the other hand, exposure to unusually high doses of dietary Se leads to some adverse effects. Many people take the dietary supplements of Se due to massive advertising campaigns and are unaware of the potential risk of Se overdose. Se compounds are characterized by different degrees of toxicity. Inorganic sources of Se exhibit a higher toxicity as compared to the organic forms.[120] Elemental Se and metallic selenides have relatively low toxicities because of their low bioavailability. Selenites and Selenates are very toxic. Organic Se compounds, which occur in metabolic processes, such as selenomethionine, Sec, and methylated Se compounds, are toxic when used in large doses. An excess of Se in the diet causes chronic food poisoning symptoms, such as vomiting, nausea, and diarrhea. Acute exposure to high amounts of Se leads to a general weakness of the organism, as well as neurological disorders. In any case, Se toxicity is determined by many factors, including the occurrence form of this element, the organism's physiological condition, ingested dose, and Se interaction with other diet components.[121] The chronic toxicity caused by an excess of Se in living organisms leads to the symptoms of selenosis, which vary depending on the poisoning severity and include garlic odor on the breath, a metallic taste in the mouth, poor dental health, hair and nail loss, brittleness, infertility, lesions of the skin and nervous system, nausea, diarrhea, fatigue, and even pulmonary oedema. Selenosis in humans is a rare event except in the areas with very high Se contents. Extreme cases of selenosis can be fatal due to cirrhosis of the liver.[122] Among other effects related to Se toxic doses, the presence of endocrine disruption in the synthesis of thyroid hormones, Growth Hormone (GH), and Insulin-like Growth Factor (IGF-I) can be noted. Excessive Se amounts in the serum and liver are a symptom of severe toxicity. Particularly noteworthy is the occurrence of hematological abnormalities of blood. Inhalation of Se compounds, especially highly toxic hydrogen selenide causes commonly observed symptoms of respiratory diseases, such as chemical

pneumonia and bronchitis among others. Other symptoms include inflammation of pulmonary alveoli with pulmonary edema and hemorrhage, nausea, eye irritation, and headache.[123] Some toxic effects of Se on the organisms are related to the production of free radicals causing DNA damage. Se toxic effects are also associated with an affinity towards thiol groups affecting the integrity of protein functions responsible for DNA repair, as well as natural killer cells to be lost.[3]

Se Metabolism and pharmacokinetics

Though our understanding of the details of Se metabolism in the body is not complete, the majority of Se compounds, organic and inorganic, are easily absorbed from the diet and then transported to the liver. The absorption of Se species mainly occurs in the small intestine and involves various mechanisms often shared with their sulfur analogues although identities of the specific transporters responsible for the absorption of dietary Se remain uncertain.[124] In the intestine, about 85%–95% of Se quantity supplied with food is absorbed. As already mentioned, bioavailability depends on Se form. Organic Se compounds are absorbed in a level of 90%–95%, while inorganic compounds are less accessible (10% on the average). Little is known about Se transport, which is the first step in Se metabolism including reduction, methylation, and incorporation into selenoenzymes. Selenate is the major inorganic selenocompound found in both animal and plant tissues.[125] Selenate is absorbed paracellularly through a passive diffusional process. Following an absorption, it is reduced to selenite by ATP sulfurylase via an uncharacterized Se-isologue of 3-phosphoadenosine 5-phosphosulfate.[124] However, eukaryotic selenite transporters have not been identified on the molecular level. The kinetics of selenite uptake in yeast suggests the existence of two transport systems including low and high affinity systems, both of which are inhibited by glucose.[126] On the other hand, Se-amino acids, SeMet and Sec, are absorbed through transcellular mechanisms, but the identities and affinities of the transporter proteins are still to be determined. Se-Cys is not absorbed through an active transport and its capture is not inhibited by similar sulphur compounds or body Se status. Se-Met is absorbed by the same active transport mechanism used by methionine because Se can substitute with sulphide atoms due to their similar ionic radii.[124,125]

Immediately after entering into the bloodstream, Se is bound to red blood cells, albumins, and globulins of serum. In this form, it can be transported to many tissues and penetrate into the placenta. Also, two selenoproteins have been cited as Se extracellular carriers in plasma, namely selenoprotein P and GPx-3. However, both of these selenoproteins contain Se as Se-Cys making neither of them the probable carriers of Se. Nevertheless, the low molecular weight forms of Se have been identified as the possible Se carriers in plasma.[124,127]

The total amount of Se in the human body varies from 10 to 20 mg. 50% of the body Se is located in the skeletal muscles although organs like the kidneys, testes, and liver have the highest relative concentrations of Se. On the other hand, the cells that reveal a higher Se consumption are those of the immune system, erythrocytes, and platelets. As afore-mentioned, the dietary Se is absorbed in the intestine and transferred into the liver. The body Se content is regulated by the hepatic production of methylated Se compounds and its urinary excretion, not by the intestinal absorption of Se.[128,129]

Liver is the key organ for Se metabolism, in which most of the Se-containing proteins are synthesized.[49] Though our understanding of the assimilation process of the dietary Se into proteins is incomplete, hydrogen selenide (H2Se) is known to act as a precursor for the Se-containing protein synthesis of both organic and inorganic Se compounds.[6,49] Hydrogen selenide is formed from sodium selenite (Na2SeO3) via selenodiglutathione (GS-Se-SG) and through reduction by thiols and NADPH-dependent reductases. It can be also formed through the demethylation of

methylselenol (CH3SeH) via methyltransferases or released from Sec through the trans-selenation pathway analogous to the trans-sulfuration pathway.[130,131] Thus, it seems to be the common point for regulating Se metabolism. Although the main pathway in animals is methylation, demethylation back to the inorganic Se can also occur. Hydrogen selenide provides Se for the synthesis of selenoproteins through a previous activation to selenophosphate. After the catabolism of Se-containing proteins and subsequently, component amino acids, the Se of the Se-Met is finally available for its specific use. In this sense, Se is entered into the upregulated metabolism and could be incorporated into macromolecules to be transported to other organs or be even excreted.[132]

Hydrogen selenide is also involved as a key metabolite in Se excretion when methylation by thiol S-methyltransferases generates different methylated metabolic forms of Se. Although the mechanism that regulates the production of excretory metabolites has not yet been discovered, urine excretion has been reported to be the body's mechanism for maintaining Se homeostasis. Therefore, under physiological conditions, Se homeostasis is not regulated by absorption, but rather by urinary excretion.[133] Despite this, the transporters, receptors, and enzymes involved in the absorption or movement of Se across the membranes of intestinal cells are generally unknown. Se intestinal excretion is a secondary path of elimination. Also, it has been observed that when the body Se status is low, Se urinary excretion is diminished to keep the element homeostasis within a narrow range as reported in the patients with cardiovascular diseases.[134] However, when large amounts are to be excreted, respiration can also contain volatile Se compounds usually in the form of dimethyl selenide. Various selenocompounds are claimed to be present as urinary Se metabolites, such as selenite, selenate, mehylselenite, methylselenol, trimethylselenonium ion, Se-Met, Se-Cis, Se-Cys, selenodiglutathione, selenoethionine, methylselenomethionine, selenocistamine, selenoadenosyl-Met, and selenosgars 1, 2, and 3. Among all these Se compounds, only trimethylselenonium ion has been found in human urine. It has been reported that new Se-containing selenosugars are the major urinary metabolites in humans, thus trimethylselenonium ion being less significant. Specifically, the metabolite methyl-2-acetamido-2-deoxy-1-seleno-β-d-galactopyranoside (called selenosugar 2) has been identified.[135,136]

Se volatilization into breath is observed only at high Se intakes. The volatile compound dimethylselenide has been identified as one of the methylated forms of Se that account for most Se excretion in the urine and breath.[137] Fecal Se excretion is regulated by the dietary Se intake at the deficient to moderately high Se intakes. Fecal Se excretion has plateaued at moderately high Se intake. Characterization of fecal Se excretion has been relatively minimal.[138]

Clinical Impacts of Se

The trace mineral Se is an essential nutrient of fundamental importance to human physiology. This has become increasingly obvious as new research has revealed a hitherto unsuspected role for this element in the areas important to human health. The major functions of Se in the body are as follows: Se constitutes an integral part of selenoproteins and some antioxidant enzymes that protect cells from the damaging effects of the free radicals produced during oxidative stress,[139] while they are responsible for the control of a proper development, growth, and cell metabolism.[87]

However, some reviews and studies report no disease prevention, protection, or treatment benefits from antioxidant supplements, including Se or Se alone.[140-146] Contrarily, most recent studies have reported that Se intakes higher than recommended and normal plasma Se concentrations (alone or with other antioxidant vitamins and minerals) may provide a protection against the pathologies associated with inflammatory processes and oxidative stress like cardiovascular diseases, hepatopathies, arthritis, and cancer or provide

other additional health benefits.[147,148]

The anticancer mechanism of Se is mainly related to its anti-free radical activity as commonly known. Yet, Se significant impact on the cytotoxic activities of Natural Killer (NK) cells can be highlighted.[83] Clinical studies have shown that Se may provide a protection against the occurrence of prostate, lung, and colorectal cancers.[48] The most efficient anticarcinogenic effect is achieved when Se is administered as a preventive agent prior to the onset of a disease or at its early stage of development.[88,149]

In a review study, it has been found that the dietary Se supplements may provide a safe and convenient method for increasing the antioxidant protection in the aged individuals, particularly those at the risk of an ischemic heart disease or undergoing clinical procedures involving transient periods of myocardial hypoxia.[150] Other authors have documented that when patients with critical illnesses are supplemented with widely varying doses of Se (between 200 and 1000 μg) alone or in combination with other antioxidants, the length of hospital stay, rate of infection, and need to heamodialysis are reduced. Nevertheless, no trial has been reported with a statistically significant improvement in mortality despite a recent meta-analysis suggesting a trend towards a reduced mortality due to Se supplementation.[151]

Se has been found to additionally improve the immune system's ability to respond to infections and inhibit prostaglandins that cause inflammation. At this condition, Se stimulates the immune system to increase the production of antibodies (IgG, IgM) and cause the increased activities of T cells and macrophages.[152] Furthermore, the synergistic effect of Se and vitamin E contributes to a slowdown of the aging process and an enhancement in the speed of cell regeneration.

Moreover, this element exhibits antibacterial and antiviral properties and alleviates the courses of disease in patients infected with hepatitis A and hepatitis E. It also exhibits protective properties against hepatitis B and C. It is noteworthy to say that Se can inhibit the progression of HIV infection into full-blown AIDS. In addition, Se supplementation has considerably lowered hospital admissions. Besides, Se deficiency has been observed to be associated with a higher mortality rate among the patients infected with HIV.[153-155]

In addition, the element has been shown to be important for the transmission of nerve impulses in the central nervous system, while Se abnormal levels have been found in the plasmas of patients with impaired cognitive functions and neurological disorders.[156] A study reported that the elderly women in the highest third of functional capacity indices in New Zealand had significantly higher biochemical Se values than those in the lowest third. Therefore, the suboptimal levels of trace elements may be more common among those with poor physical functions and thus promoting the consumption of high Se foods or supplements to improve Se levels in elderly women in New Zealand may be beneficial.[157] Se has been also shown to play an important role in male and female fertilities and a low Se level of plasma during the early stage of pregnancy has been proved to be a reliable predictor of the low birth weight of a newborn infant.[158] Moreover, Se protects against the toxic effects of metals, such as lead, mercury, cadmium, arsenic, and organic compounds as exemplified by the paraquat herbicide.[87] It has been found that in type 2 diabetic patients, activation of NF-κβ measured in the peripheral blood monocytes can be reduced by Se supplementation, thus confirming its importance in the prevention of cardiovascular diseases.[159]

In recent years, genomic and proteomic sciences have been growing rapidly. Because of the need to define the capacities of nutrients like Se, these sciences have concerned with the study of nutrients like Se to facilitate the up- or down-regulation of specific genes and thus enhance or diminish protein synthesis.

Conclusion and Future Prospects

Se as a trace element and its compounds are potent anti-proliferative agents with modest effects on normal

tissues that have been discovered to be clinically well-tolerated. As a word of warning, however, it must be remembered that Se is a toxic mineral with a fairly small therapeutic window, while there is a very narrow quantitative range of doses between the deficiency, physiological, and toxic statuses. Despite the fact that Se field has been dramatically expanding and numerous mechanisms have been proposed over the last few decades as a result of new findings in the disease-related functional genomics and proteomics, the exact mechanism by which the potential anticancer properties of Se are mediated remains unclear. As a matter of fact, Se is distinct depending on its bioavailability and system examined. Also, the functions of most molecules containing Se and selenoproteins are still unknown. Therefore, continued studies on the biochemical properties of Se will hopefully lead to new discoveries in this field to improve human health. Moreover, there may be a need to the development of rational combination therapies that can be predicted to have synergistic or additive effects. To this end, understanding of the underlying mechanisms of specific Se compounds in basic science research and clinical trials are an essential requirement. Furthermore, further research is required to optimize the benefits and reduce potential risks associated with Se supplementation in the context of cancers and hence clarify the optimal nutrition level of Se to be introduced as a daily supplement.

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Competing interests

The authors declare that they have no competing interests.

Abbreviations

Selenium: Se;

selenocysteine: Se-Cys;

selenomethionine: Se-Met;

Se-Binding Proteins: SBPs;

methionine-R-sulfoxide reductase: MsrB;

cysteine: Cys;.

methionine: Met;

thyroxine: T4;

triiodothyronine: T3;

Recommended Dietary Allowance: RDA;

glutathioneperoxidase: GPx;

National Research Council: NRC;

Growth Hormone: GH;

Insulin-like Growth Factor: IGF-I;

Selenodiglutathione: GS-Se-SG;

World Health Organization: WHO

Authors' contributions

SZ and SMH were responsible for study concept and design. SZ wrote the first draft. SMH contributed to the writing of the second and third draft. SZ and SMH provided comments on initial drafts and coordinated the final draft. All authors read and approved the final manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

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