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The Pharmacology and Biochemistry of Selenium in Cancer

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1. Introduction

Cancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries (WHO)¹. It is extraordinarily complex with novel mutations and phenotypes that are often unique to an individual. It is a disease of the chromosomes and the problem is, in almost all cancers, it isn't just one mutation but may be much more. Cancer may be regarded as a complex metabolic deficiency disease [9, 10, 11, 12, 13, 14]

Cancer diet is also used as a complementary approach to cancer that involves the use of special nutritional supplements. Selenium (Se) and cancer is a term that can be referred to the approach or associations between cancer and nutrition that is to lower an individual's risk of cancer. Selenium was first recognized as having some nutritional importance almost six decades ago [15]. Selenium is found in food as selenoamino acids or selenoproteins, and as selenide, selenite, or selenate [16]. Selenium is a critical cofactor in the activity of glutathione peroxidase and is also important in the management of peroxynitrite. The selenium content of food depends upon soil content and varies regionally and nationally, with soil levels relatively low in most European countries [17, 18, 19]. Soil conditions have been associated with clinical selenium toxicity in animals (selenosis) in some areas with very high selenium content, and with selenium deficiency syndromes in animals and humans in areas of low soil selenium [17].

Selenium is essential nutrient that act as cofactor in enzyme oxidation–reduction reactions (e.g. iodothyronine deiodinase and glutathione peroxidases) [20]. It maintains the specific configuration of proteins, is incorporated into the structure of hormones, and plays a structural and catalytic role in gene expression and transcriptional regulation. The trace element selenium is contained in soil and drinking water varies from area to area, which determines the variation in intake seen in different communities and the amount and chemistry of dietary constituents

eaten with the this element affect the absorption efficiency of the selenium is said be 'the only trace element to be specified in the genetic code' [21].

Selenocysteine is a vital component of 35 or more selenoproteins, some of which are important enzymes [22]. Selenium functions as a redox centre, an example of which is the reduction of hydrogen peroxide and lipid and phospholipid hydroperoxides to nondamaging water and alcohols by the glutathione peroxidases [23]. Functions of this kind help maintain membrane integrity, and protect prostacyclin production. Prevention of the oxidative chain reactions in this way prevents further damage to lipids, lipoproteins, and DNA; hence its antioxidant function helps prevent atheroma and cancer, among other things [24, 25, 26].

2. Clinical applications

Selenium deficiency results in impaired immunity [27], and supplementation is immune stimulant. Deficiency increases the virulence of some viruses such as in Keshan disease [28, 29] by altering their genome to a more virulent one. Deficiency may also be associated with low mood [30], increased cognitive decline in older people, and susceptibility to epilepsy [31], exacerbates hypothyroidism in iodine deficiency [32], protective against cardiovascular disease and cancer [33, 34], beneficial in a variety of inflammatory conditions by reducing oxidative stress, and in male fertility [35] through testosterone synthesis and spermatozoa function.

The conventional cancer therapies currently available are surgery, radiotherapy, and chemotherapy. Chemotherapy is typically the main regimen for most cancers. However, many tumours develop resistance to these harsh drugs, known as chemo resistance, which can lead to other complications [36]. A number of natural products and compounds have been shown to act as effective chemo sensitizers. However, taking antioxidants during cancer treatment could interfere with the way chemotherapy work and diminish their benefits to the patient [37]. It was conclude that the use of supplemental antioxidants during chemotherapy and radiation therapy should be discouraged because of the possibility of tumour protection and reduced survival [37]. This is because radiation and some chemotherapy agents work by generating free radicals, which then kill rapidly dividing cancer cells. Since antioxidants scavenge free radicals, they might interfere with the therapeutic effects of these treatments. However, oxidation supports the proliferation of malignant cells and may itself interfere with treatment [38]. People who hold this view maintain that antioxidants may counter the harmful effects of oxidation in the malignant process and thereby increase the effects of drugs or radiation therapy to the benefit of the patient. Moreover, they note that some evidence suggests that antioxidant supplements offer patients protection from the toxic effects of therapy [39].

The balance between oxidants and antioxidants can be a key issue in the development of cancer [40] and reactive oxygen species (ROS) are involved in aging, chronic illness, and cancer. Oxidants also cause free radical damage, thus the body generates large amounts of antioxidants to prevent harm and maintain health. However, Watson [41] reported that antioxidants can promote cancer growth of late stage metastatic cancers. The process is explained in terms

of redox signalling, redox being a term used for reduction and oxidation. Healthy cells and also malignant ones benefit from intact Keap1/Nrf2 signalling, making a dysregulated hydroperoxide signaling a plausible explanation for the increased cancer risk in selenium deficiency [42]. Therefore, a research agenda to investigate the synergistic operation of such substances in cancer treatment is required.

3. Cancer and oxidation

Cancer is a generic term for a large group of diseases that can affect any part of the body and it can exist in many different forms and types, some of which are brought on by the destructive choices people make while others are less predictable and are not the result of destructive decisions. It can be broadly grouped into different types (Carcinomas, Sarcomas, Lymphomas and Leukaemia's), depending on which tissues they come from [43, 44]. Cancer develops when cells multiply in the presence of oxidation and other damage. According to micro-evolutionary models, cells become damaged and change their behaviour, growing uncontrollably, and act like the single-celled organisms from which they originally evolved. The cancer cells' individualism overwhelms the cooperative control processes that are essential to a complex multicellular organism [45, 46]. As cancers become malignant, they exhibit incredible genetic diversity. Whereas a benign tumour is like a colony of similar abnormal cells, a malignant tumour is a whole ecosystem. At this late stage, some (but not all) antioxidants can indeed promote cancer cell growth. Thousands of different cell types coexist: cooperating, competing, and struggling to survive. A consequence of the anaerobic conditions that prevail during the early development of a malignancy is that cancer cells differ from healthy cells, in that they have been selected for the way they generate energy (i.e. anaerobically, using glucose) [47, 48].

The sulfhydryl group is the most sensitive to the oxidizing effects of ROS among the amino acid side chains in protein; it is often involved in the intracellular transduction machinery of redox signals in response to physiological and oxidative stimuli. In fact, a variety of biological functions, not directly related to peroxidase activity, have also been reported for the Prx family [49]. Oxidative damage in DNA can cause cancer. Several antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, glutathione S-transferase etc. protect DNA from oxidative stress. It has been proposed that polymorphisms in these enzymes are associated with DNA damage and subsequently the individual's risk of cancer susceptibility [50].

Nutrition and physical activity and major lifestyle changes can reduce the risk of cancer [51, 52]. Antioxidants are becoming an increasingly common choice as a hopeful cancer prevention agent. Importantly, antioxidants limit oxidative damage and thus inhibit early benign cancer growth, preventing cancer from developing. Selenium has received publicity over the past decades based on some confusing and contradictory research about whether low-selenium diets are implicated in cancer risk. To date, this is still a question without a clear answer. However, selenium is required for the proper activity of a group of enzymes collectively called glutathione peroxidase. Each of these enzymes helps to turn toxic hydrogen peroxide into

harmless water. Of the eight known glutathione peroxidase enzymes, five of them require selenium. It is a necessary component for appropriate function of the immune system, muscle function, successful reproduction, and peak brain function. Also, selenium produces valuable antioxidant enzymes. Deficiencies in selenium have been linked to decreased thyroid function, cardiovascular disease, and cancers [24]. Research shows selenium, especially when used in conjunction with vitamin C, vitamin E and beta-carotene, works to block chemical reactions that create free radicals in the body (which can damage DNA and cause degenerative change in cells, leading to cancer). Also research has demonstrated that selenium is also linked to reduction in risk to some carcinomas [6, 7].

4. Pathophysiology of cancer and causes

Cancer is a disease of regulation of tissue growth. In this disease, the cells of the body display uncontrolled growth, invasion that intrudes and destroys adjacent tissues and spreads to other body locations. In order for a normal cell to transform into a cancer cell, genes which regulate cell growth and differentiation must be altered and DNA repair genes are altered and turned off [53, 54]. The pathophysiology of cancer is a complicated issue. Genes that are influenced in the pathogenesis of cancer are proteins that are involved in a variety of processes including cell growth and differentiation, cell cycle processes, and angiogenesis, which is the formation of new blood vessels [55]. These proteins also play a role in tumour progression, immune regulation, and apoptosis. Since the cells involved are complex and have such a broad range of functions, the pathophysiology of cancer has been hard to determine precisely.

Understanding what causes cancer is a complex process. Cancer has been linked to many factors, such as environmental exposures, lifestyle practices, medical interventions, genetic traits, viruses, familial susceptibility, and aging. Cancer is most probably the result of interactions between repeated carcinogenic exposures and an individual's susceptibility status [56]. Environmental exposures and lifestyle practices have been determined to be the major risk factors in the development of cancer [57, 58]. The major lifestyle factors that contribute to cancer include smoking, alcohol, diet, medical practices, and ultraviolet exposures.

Genes that are influenced in the pathogenesis of lung cancer are proteins that are involved in a variety of processes including cell growth and differentiation, cell cycle processes, and angiogenesis, which is the formation of new blood vessels. The proteins also play a role in tumour progression, immune regulation, and apoptosis [59, 60]. Since the cells involved are complex and have such a broad range of functions, the pathophysiology of lung cancer has been hard to determine precisely. A healthy cell becomes a cancer cell by undergoing the following processes in which proto-oncogenes are changed to oncogenes. Proto-oncogenes are genes that are coded to maintain normal cell growth. In cases of a developing cancer, oncogene takes its place. Oncogene is a gene that makes cells grow and divide rapidly [61]. Pharmaceutical companies are continuing to develop approaches for targeting oncogene activity in the ongoing war on cancer [61]. Pathology of cancers and other complex disorders have undergone a big change after development of

technologies like immunohistochemistry, flow cytometry, and molecular biologic approaches to cancer diagnosis. Cancer is not a singular, specific disease but a group of variable tissue responses that result in uncontrolled cell growth [56].

5. Selenium mechanism

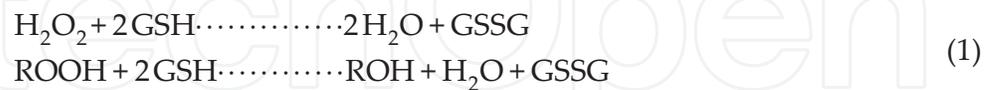
The biochemistry of selenium differs from other dietary minerals and trace elements. Selenium is not a structural component nor a metal coordination complex and the biosynthesis of selenocysteine is regulated by four genes and begins with the aminoacylation of the amino acid serine by the enzyme serine synthetase to produce Ser-tRNA^{Sec} [62, 63]. However, selenocysteine is the active site in which, at physiological pH, selenium is fully ionized and is a very efficient redox catalyst [64]. Selenium exists in elemental, organic, and inorganic forms, with four important oxidation states: selenide (Se²⁻), elemental (Se⁰) selenite (Se⁺⁴), and selenate (Se⁺⁶) [62, 65]. Selenium compounds inhibit signaling enzymes such as protein kinase C (PKC) [66] that play crucial roles in tumor promotion. The selenium-containing nutrient, selenomethionine has been shown to regulate the tumor suppressor p53 by the redox factor refl-dependent redox mechanism. Studies continue to support evidence that one important pathway is that many selenium-containing nutrients can be converted in the body to methylselenol. Methylselenol has been shown to block expansion of pre-malignant cells forming into fully developed cancers [67]. Several pathways have been proposed that could explain how selenium-containing compounds could block mutated cells from progressing to cancer. Methylseleninic acid has been shown to inhibit NF-kappa B and regulate I kappa B in prostate cancer cells [68]. Selenium compounds inhibit signaling enzymes such as protein kinase C (PKC) [66] that play crucial roles in tumor promotion. A representative of the hydrogen selenide metabolic pool has been found to protect liver cells against damage to DNA. The cellular redox-milieu involves several metabolic, antioxidative and regulatory aspects that are maintained and regulated largely by two enzyme-based systems: the glutathione and thioredoxin systems [69]. The thioredoxin and glutathione systems constitute a balanced redox network. The thioredoxin system may influence virtually all phases of tumorigenesis via its involvement in transcription and translation [69].

There are several possible mechanisms for the protective effect of selenium. Selenium activates an enzyme in the body called glutathione peroxidase that protects against the formation of free radicals—those loose molecular cannons that can damage DNA. There appear to be at least two distinct families of selenium-containing enzymes [70, 71]. The first includes glutathione peroxidases Bermano et al [72] and thioredoxin reductase [73], which are involved in controlling tissue concentrations of highly reactive oxygen-containing metabolites. These metabolites are essential at low concentrations for maintaining cell-mediated immunity against infections but highly toxic if produced in excess.

The role of selenium in the cytosolic enzyme glutathione peroxidase (GPx) was first illustrated [74, 75]. During stress, infection, or tissue injury, selenoenzymes may protect against the damaging effects of hydrogen peroxide or oxygen-rich free radicals. This family of enzymes

catalyses the destruction of hydrogen peroxide or lipid hydroperoxides according to the following general reactions:

Selenium-containing glutathione peroxidases (GPx) constitute a family of anti-oxidative enzymes that are capable of reducing organic and inorganic hydroperoxides to the corresponding hydroxy compounds utilizing glutathione or other hydrogen donors as reducing equivalents



Where GSH is glutathione and GSSG is its oxidized form. At least four forms of GPx exist; they differ both in their tissue distribution and in their sensitivity to selenium depletion [72]. The GPx enzymes of liver and blood plasma fall in activity rapidly at early stages of selenium deficiency. In contrast, a form of GPx associated specifically with phospholipid-rich tissue membranes is preserved against selenium deficiency and is believed to have broader metabolic roles (e.g., in prostaglandin synthesis) [76]. In concert with vitamin E, selenium is also involved in the protection of cell membranes against oxidative damage. The selenoenzyme thioredoxin reductase is involved in disposal of the products of oxidative metabolism [77]. It contains two selenocysteine groups per molecule and is a major component of a redox system with a multiplicity of functions, among which is the capacity to degrade locally excessive and potentially toxic concentrations of peroxide and hydroperoxides likely to induce cell death and tissue atrophy [76].

There is strong evidence that oxidative free radicals have a role in the development of degenerative diseases including CHD [78]. Oxidative free radicals increase the peroxidation of low density lipoprotein thereby increasing its uptake by macrophages with increased foam cell formation and atherosclerosis [79], though other mechanisms may exist. Anti-oxidants in the diet include vitamin A (carotenoids, which are metabolised to retinol), vitamin C (ascorbate), vitamin E (tocopherol), and selenium, which is an integral part of the antioxidant enzyme glutathione peroxidase:

6. Selenium function

Despite an evident progress in cancer diagnosis and treatment, there is a constant need of a drug which could arrest the premalignant process, thus reducing the risk of cancer. However, the role of selenium (Se) as an antioxidant and anticancer agent is well documented [80]. In addition, it has been proven that an adequate concentration of selenium can restore the sensitivity to chemotherapeutic agents of cytostatic-resistant malignant cells [81]. Selenium can exist with oxidation state -2, +2, +4, +6, and Se (II) is the dominant form in organoselenium chemistry [82]. The highest activity as a free radical scavenger and anticancer agent is assigned to selenium compounds containing selenium at the +4 oxidation level [83]. Other essential role of selenium in human and animal nutrition is well established. In humans, it has been

demonstrated that an endemic cardiomyopathy (Keshan disease) prevalent in certain areas of China is correlated with selenium deficiency [84, 85]. Selenium is often thought to be a dietary antioxidant, but the antioxidant effects of selenium are most likely due to the antioxidant activity of proteins that have this element as an essential component (i.e., selenium-containing proteins), and not to selenium itself [86]. The damage to cells caused by free radicals, especially the damage to DNA, may play a role in the development of cancer and other health conditions [40]. Many observational studies, including case-control studies and cohort studies, have been conducted to investigate whether the use of dietary antioxidant supplements is associated with reduced risks of cancer in humans. Overall, these studies have yielded mixed results [87]. Healthy Chinese men and women at increased risk of developing esophageal cancer and gastric cancer were randomly assigned to take a combination of 15 milligrams (mg) beta-carotene, 30 mg α -tocopherol, and 50 micrograms (μ g) selenium daily for 5 years or to take no antioxidant supplements. The initial results of the trial showed that people who took antioxidant supplements had a lower risk of death from gastric cancer but not from oesophageal cancer. However, their risks of developing gastric cancer and/or esophageal cancer were not affected by antioxidant supplementation [88].

As an essential trace element in humans [89], its only established function is its presence in the enzyme glutathione peroxidase [90]. Using GSH2 as the reducing equivalent, this enzyme plays a significant role in detoxification of peroxides induced by oxygen radicals. As such it may be important in the toxicity of anticancer treatments that generate such reactive molecules [91]. In addition, epidemiological and experimental data suggest an anti-carcinogenic activity by selenium [92]. Considerable epidemiological data suggests that cancer mortality is inversely correlated with selenium consumption. Chemoprotective effect of diphenylmethyl selenocyanate against cyclophosphamide (CP) induced cellular toxicity and antitumor efficacy was evaluated in mice bearing Ehrlich ascites carcinoma [93], their results indicate that diphenylmethyl selenocyanate has the potential to reduce the cellular toxicity of CP at the same time improving its antitumor efficacy. Supplementation of a torula yeast-based diet with 2.5 or 5.0 ppm Selenium as Na_2SeO_3 also significantly increased the survival time of EAT-bearing mice [94]. Their data show that the form and mode of administration of selenium influence the antitumorigenic properties of this trace element. In addition, they suggested that some intermediate in the normal pathway for selenium detoxification is probably responsible for this trace element's antitumorigenic properties [94]. The ability of selenium to inhibit or prevent the growth of Ehrlich as cites tumour cells was highly dependent upon the form and quantity of selenium administered [95]. The only significant alteration that has been observed in mice treated with quantities of selenium at dosages of $4\mu\text{g}$ 3 times weekly was a slight reduction in intestinal weights. The reduction in intestinal weights was not attributable to a reduction in the intestinal macro constituents, suggesting that selenium may have altered rapidly dividing cells [95]. In fact selenocystine was used in the treatment of human leukaemia in 1956 with some short term success [96, 97]. The mechanism of its effect was thought to be competitive deprivation of cystine, but this was not proven. Others have shown that selenium compounds can cause chromosome breaks and inhibit critical DNA synthetic enzymes [98]. Specific incorporation of selenium into RNA molecules has been observed in several bacterial species. Since in a number of instances modified bases in RNAs have been shown to be involved in regulatory functions of the RNAs, the selenium-modified bases may have similar roles.

Furthermore, some RNA viruses, as well as leader mRNAs contain RNA-like segments that may interact with specific enzymes and, thus, play regulatory roles [99]. Hence, it is reasonable to assume that detailed information concerning selenium-modified RNAs may contribute to the understanding of the biological roles of selenium [100]. Near toxic levels of selenium have been reported to produce tumours in rats but other studies indicated that these concentrations of selenium created chronic toxic hepatitis that resembled hyperplasia.

In mammals glutathione peroxidase is the only selenium-dependent enzyme so far identified, but it seems unlikely that the complicated biological effects of selenium in man and animals are attributable solely to variations in the level of this enzyme. In fact, at least two other seleno proteins of unknown catalytic activity have been detected in animals. Investigations in a variety of animal systems have suggested that there is a significant interaction of selenium with glutathione independent of the enzyme glutathione peroxidase [101]. White muscle disease (WMD), a degenerative muscle disease, found in domestic animals [102, 103]. It is caused by a deficiency of selenium and/or vitamin E. Selenium and vitamin E deficiencies can produce symptoms of ill thrift and reproductive losses: lower conception rates, fetal reabsorption, dystocia, retained placenta, reduced milk production, and reduced semen quality, poor rate of growth or ill thrift in young lambs, low wool yields and have increased incidence of periodontal disease [102, 103]. Selenium appears to be a key nutrient in counteracting the development of virulence and inhibition of HIV progression to AIDS. It is required for sperm motility and may reduce the risk of miscarriage. Selenium deficiency has been linked to adverse mood states and some findings suggest that selenium deficiency may be a risk factor in cardiovascular diseases [104]. Studies continue to confirm that people with higher levels of selenium in their blood have lower rates of prostate and lung cancers [105].

Selenium is synergistic with vitamin E; they serve related metabolic functions and share in common the role of endogenous antioxidants [106]. Vitamin E has a free radical Scavenger, and Se as a component of the peroxide reducing enzyme, glutathione peroxidase. Vitamin E restricts the formation of peroxides by neutralizing free radicals, an integral component of glutathione peroxidase, an enzyme responsible for the removal of hydrogen peroxide and organic hydroperoxides [107].

Selenium and vitamin C; CH_3SeH is thought to be a critical metabolite in Se chemoprevention [108, 109]. The family of selenoenzymes called thioredoxin reductases catalyze the NADPH-dependent reduction of oxidized thioredoxin, hyperoxides, dehydroascorbate, ubiquinol and other substrates [110]. The action of thioredoxin reductases in recycling dehydroascorbate to ascorbate (vitamin C) now explain the synergistic action of selenium and vitamin C [111]. The thioredoxin system is also capable of regenerating proteins inactivated by ROS. Daily supplementation with vitamin C (120 mg), vitamin E (30 mg), beta-carotene (6 mg), and the minerals selenium (100 μg) and zinc (20 mg) for a median of 7.5 years had no effect on the incidence of cancer or cardiovascular disease or on all-cause mortality [112]. Antioxidant and mineral supplementation was associated with lower total cancer incidence and all-cause mortality among men but not among women, and with an increase in skin cancer incidence, including melanoma, among women but not among men [113].

Selenium and Silver; Selenium serves as a major protective factor in precipitating the silver in a highly insoluble and hence inert form of silver selenide. Although some of this may be taken

up in lysosomes in macrophages, the deposits are essentially long lived or permanent [114]. A lack of positive effect of Se supplementation on the prostate cancer incidence was observed in this study.

7. Conclusion

Selenium as non-metals is an essential nutrient that acts as cofactor in enzyme oxidation–reduction reactions. It maintains the specific configurations of proteins, is incorporated into the structure of hormones, and plays a structural and catalytic role in gene expression and transcriptional regulation. In the physiological dosage range, Se appears to function as an antimutagenic agent, preventing the malignant transformation of normal cells and the activation of oncogenes. These protective effects of Se seem to be primarily associated with its presence in the glutathione peroxidases, which are known to protect DNA and other cellular components from damage by oxygen radicals. Selenoenzymes are also known to play roles in carcinogen metabolism, in the control of cell division, oxygen metabolism, detoxification processes, apoptosis induction and the functioning of the immune system. Other modes of action, either direct or indirect, may also be operative, such as the partial retransformation of tumor cells and the inactivation of oncogenes.

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