

# Selenium

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## Abstract

Selenium biomedical research is presently both very exciting and very frustrating. It is exciting because there is a chance that many people obtain their good health by enhancing their selenium consumption. This interest is under the influence of the present and recent past existence of journal's entirely dedicated to selenium research. This chapter deals with overview of function, overview of metabolism, nutritional status assessment, bioavailability from foods and supplements, current research on supplement use such as cancer, cardio vascular disease, arthritis, pancreatitis, mood, immune function, asthma, ketogenic diet in epilepsy patient, normal antioxidant effects and finally toxicity.

## Introduction

Selenium plays a major role in certain enzymes, but the incorporation of selenium into these enzymes is quite distinct from the processes for the minerals. Selenium has drawn the attention for its roles in antioxidant defense, thyroid hormone production and for possible applications in cancer obstruction. Some other application of selenium supplements also have some data to encourage usefulness.

## Methodology

### Overview of Function:

Selenium is a component of number of Proteins. Selenium persists as an anion at biological pH, which makes it able to both give and accept electrons. The best physiological actions of selenium are 2 enzyme functions. One of these functions is performed as part of family of proteins termed as glutathione peroxidase. (One is seen inside of cell, another is outside the cells in places like plasma). Glutathione peroxidase is part of the body's antioxidant defense network by removing peroxidase Including hydrogen peroxide, which can be both precursor and products of free radicals. Selenium plays a role as an enzyme that is part of thyroid hormone synthesis. A more recently observed selenium enzyme is termed as thioredoxin reductase, which seems to have a number of regulatory roles within cells and seems to affect antioxidant defence by showing an impact on electron flow in some reactions. One interesting point about this enzyme is that in rats, the enzyme activities can be enhanced by Increasing selenium intake above these normally normally treated adequate. Seleno proteins show non enzymatic functions. Sperm

capsule Seleno protein is a structural protein observed in the middle piece of the sperm tail. In selenium deficiency, morphological anomalies in this region give rise to spermatozoa with abnormal motility. There are also several other selenoproteins in the male gonads that are linked to the male reproductive function. In addition, selenium is required for normal testosterone metabolism and testicular morphology. A protein known as selenoprotein P has been studied from a regulatory perspective, but the functional significance of this protein is not completely understood. There are other proteins in the body that have been found to have selenium, but their function is not yet known. Selenium may also show some enzyme- independent functions related to cancer prevention. Selenium deficiency can also influence immune function, though the mechanisms are not fully clear. Both the antioxidant and thyroid modulating actions of selenium are involved, even though there may be other mechanisms as well. One usual interaction between selenium status and immune function shows an influence on viral virulence. This is discussed further in human immunodeficiency virus (HIV) subsection. Selenium interactions with viral virulence also spread to other virus classes. For example, in mice, selenium deficiency enhances the pathology of an influenza virus Infection.

### **Overview of Metabolism**

The absorption of selenium from foods occurs with the help of mechanisms that overlap amino acid absorption. Selenium absorption is not regulated by homeostatic mechanisms such as those that prevail for minerals namely calcium and iron. Most minerals that prevail in metalloproteins are incorporated into the protein by binding with selected amino acids or in case of some iron proteins, by insertion into a heme or cytochrome structure, which can be incorporated into a protein. Selenium is different in that that is substituted for a sulphur amino acids, especially cysteine. This selenocysteine amino acid becomes a part of certain proteins during protein synthesis. Selenocysteine consists of its own codon and specific biosynthetic and insertion machinery. In the presence of a downstream stop- loop structure, the UGA codon in mRNA instead of behaving as a stop codon, indicates the insertion of a seleno-cysteine an expanding peptide chain.

### **Nutritional Status Assessment**

Unlike the case for a lot of minerals, selenium shows some-well established methods for status assessment. Plasma selenium is proportional to selenium consumption at both high and low levels. Whole blood or red blood cell selenium can also be essential for acting long -term selenium status. Plasma glutathione peroxidase activities are proportional to selenium consumption, but do plateau at certain intakes. Erythrocyte glutathione peroxidase activity is also sometimes helpful to estimate selenium status, even though the values may be influenced to a small degree by some influences excluding selenium status. The combination of glutathione peroxidase activities and plasma selenium yield information on the response to selenium supplementation in subjects who are already deficient or in adequate status, particularly before treatment. For example, if the supplementation enhances plasma selenium but not glutathione peroxidase, the subjects are likely in sufficient status but the selenium supplement added to body selenium. This type of analysis plays a major role in cancer prevention studies, where the aim is

not always just to rectify deficiency, but to yield an above-adequate consumption. A number of large-scale studies use toenail selenium, particularly for status assessment. There is a data demonstrating higher values with long-term selenium supplementation and a little degree of association with dietary selenium consumption. Values may enhance very slowly with enhanced selenium consumption, which means the major utility of this parameter would be for long-term assessments.

**Bioavailability from Foods and Supplements**

Selenium in diet is normally part of selenocysteine and selenomethionine. Due to the absorption of these compounds are similar to the common amino acids, the percent absorptions for selenium are very high against especially other trace minerals. One exception, at least based on a rat study, is the selenium in Tuna. The bio availability is not as high as most other types of foods or even other seafoods. One another food with low selenium bioavailability, established on a study is In Finnish women is mushrooms. There are 4 main selenium supplements such as sodium selenate, sodium selenite, L-selenomethionine and high selenium yeast which consists of protein-bound L-selenomethionine, which is released during digestion. The absorption of selenium supplements happens relatively well. Examples of these studies where L-Selenomethionine exhibits an advantage are shown in table 1.

**Table 1**

**Examples of better activity of L-selenomethionine (free or in yeast) vs selenite**

| <b>Subject type</b>             | <b>Key finding</b>  |
|---------------------------------|---|
| Humans, low Se areas of china   | Better enhancement in plasma and erythrocyte Se           |
| Young adult women in newzealand | Higher blood Se   |
| Dairy cows                      | Higher blood and milk Se and blood glutathione peroxidase |

Whatever it may be, for certain circumstances in some of the studies L selenomethionine is not better at even the parameters listed. Originally, for some measures in some circumstances, sodium selenite or sodium selenate performs better. For example, in an experimental work, the yeast works better for blood selenium, but selenate exhibits a higher effect on glutathione peroxidase activities in the platelets. To make matters more intricate, in rats given a chemical that causes colon cancer, supplemental selenite or selenate but not L-selenomethionine, decreases values for precancer indicators. The protective effect of selenite and selenate is not due to better enhancement of tissue selenium contents or glutathione peroxidase activity. Originally,

selenomethionine yields better results in these regards. The mechanisms responsible for the safety effects on the inorganic selenium or not clear. It is more important that in most publicised study of human cancer obstruction by selenium, selenomethionine in Yeast is utilised. Selenate and Selenite exhibit both similarities and differences regarding bioactivity. For example, when relatively low doses administered to human subjects, selenate absorption and urinary elimination are faster than that of selenite, even though retention is about the same. One negative result is seen in a study in selenium replete humans.

### **Current Research on Supplement Use:**

#### **Cancer**

Selenium consumption and cancer could not be connected is old only. The first impetus for this connection uses a series of epidemiological observations as well as rodent carcinogenesis experimental works. The rodent experiments exhibit discrepancies between high and low selenium consumption related to resistance to chemically induced carcinogenesis. The major problem with various early studies is that the more selenium consumption levels are too high to have practical human applications. To little extent the emphasis on research elucidating the link of selenium to cancer has to focused on deficiency, severe or marginal. Generally, lack of selenium could compromise immune action, which could also influence cancer risk. Besides, lack of selenium leads to the occurrence of low glutathione peroxidase activities, which could produce high oxidant stress, which is a factor in cancer onset. In spite of this rationale, a lot of the research work on selenium and cancer has accepted. Selenium supplementation for purposes other than rectifying a deficiency. The supplementation levels (normally 200 grams per day) are normally more compared to RDA. At those consumptions, glutathione peroxidase functions would not be expected to enhance beyond those produced by RDA level consumptions. Possible anti- cancer mechanisms for the high selenium consumption include Immune activation, which selenium could conceivably do even when consumption is enhanced from RDA levels to above -adequate levels. Another chance is that thioreredoxin reductase activity is also involved. More dietary selenium may be required to saturate this enzyme functionality compared to glutathione peroxidase. Other expected mechanisms are linked to moderately high concentration of selenium compound metabolites namely methyl selenol and lead to the occurrence of apoptosis of cancer cells (programmed cell death) and consisting of other controllable effects. It may be related to these latter mechanisms that oral selenium supplementation enhances prostate selenium levels, especially in non- selenium deficient men. This author also creates another possible anti- cancer mechanisms for a moderately high selenium consumption. This mechanism is also linked to glutathione peroxidase. Even though, erythrocyte glutathione peroxidase activities generally plateau at RDA consumption levels. This enzyme activity may not plateau as easily at some potential cancer sites, specifically if pre cancer processes influence selenium distribution. So, high level selenium consumption may be required to maximize glutathione functions at a very few particular sites in certain circumstances. More proof has been utilized to show a link between selenium and cancer. Examples are given in Table 2. Remember that an important aspect is where some type of reading is noted. (Eg. serum selenium) for samples obtained earlier testing for an outcome, (in this case, a cancer- related measure). For example, serum selenium readings are taken for cancer- free subjects who are then monitored for cancer

onset. It is an important that the perspective studies given in Table 2 are just few examples of various studies. These studies have surveyed literally tens of thousands of people. For example, in a study of Taiwanese men with chronic- hepatitis virus infection, a noted risk factor liver cancer, over 7000 men are examined. In this experiment, an inverse link is observed between selenium levels in stored plasma and later development of hepatocellular carcinoma. Table 7.2.

### **Examples of Evidences Linking Selenium to Cancer Risk**

1. Chinese hepatitis carriers: Liver cancer cases, Selenium supplements Versus placebo.
2. Long- term selenium supplementation in U.S in subjects along with a history of non-melanoma, skin cancer, lesser cancer mortality and lesser cancer incidence, lower prostate, lung and colorectal cancer incidence.
3. Prostate specific antigen levels, which are linked to prostate cancer risk.
4. Prospective studies serum or toenail Selenium cases, selenium supplement versus placebo.
5. Selenium in salt in China, 35% decrement in liver cancer incidence versus control towns.
6. Selenium supplements (3 and 9 months) yields a small but significant decrement in PSA.

Many opinions can be made regarding supportive as well as non supportive studies for selenium consumption and cancer obstruction.

### **Examples of Negative Results for Studies on Selenium as well as Cancer Risk.**

1. Association is not seen for selenium, selenium and later lung cancer in Chinese tin minerals.
2. Lack of union of toenail, selenium and some cancers.
3. Serum selenium exhibits no predictive values for later colon cancer incidence.

**Cardiovascular Disease.** More selenium deficiency, specifically, if combined with viral infection, leads to the occurrence of cardiovascular problems along with cardiomyopathy. Whatever it may be, much of the current focus In selenium and cardiovascular health centres Around 2 different questions. One can marginal Selenium deficiency enhance the risk of common cardiovascular disease. Two, Can above a adequate selenium consumption decrease the risk of common cardio Vascular disease? One theory explains that selenium may assist in preventing common cardiovascular disease. One opinion is that selenium consists of Antioxidant roles land oxidant stress assists in causing cardiovascular disease, whatever it may be Other possible mechanisms, namely stoppage of platelet aggregation, which is an action of selenium. Older epidemiological studies gave some proof for a possible role of selenium Consumption in cardiovascular disease. On the other hand, studies on serum patterns within populations are clashing. Some exhibit a relationship, others do not. The review also explains that even if low serum selenium is linked to some cases of cardiovascular disease. It may just be a regulatory reaction to inflammation. More studies of nutrient supplements and cardiovascular disease utilise markers of risk, namely cholesterol or LDL oxidation. Whatever it may be, in the case of selenium, the main mechanisms of protection against cardiovascular disease may not influence these measurements. This is why studies on selenium supplementation must utilise original cardiovascular disease events as endpoints. In spite of this type in the popular Press and on the

Internet About selenium supplements and cardiovascular disease, there are no straight. Demonstrations on this Concept under an incident proof is not perfect.

**Arthritis**

According to previous information, serum selenium values decline in humans along with inflammation, namely arthritis. One discussion for marginal selenium deficiency linked to arthritis risk Is large case control study in Finland. This study serutizes serum selenium in people who do not exhibit arthritis earlier.

**Pancreatitis**

A recent experimental work includes that there is proof that patients with chronic pancreatitis exhibit high level of free radical production and antioxidant deficiencies, particularly for selenium. The review states that limited published research implies that dietary antioxidant supplementation may improve the Pain regarding chronic pancreatitis, reduce the frequency of acute worsening as well as reduce the requirement for pancreatic surgery, the best known study of selenium And chronic pancreatitis is from the Manchester Royal Infirmary, Manchester, UK. In fact, the connection between chronic pancreatitis and antioxidant therapy is sometimes termed as Manchester oxidant stress hypothesis. The treatment of the combination of selenium 600 milligram per day plus other antioxidants in patients with chronic and recurrent pancreatitis significantly decreases pain and number of days spent in hospital. In animal models for severe acute pancreatitis, selino compound which has A glutathione peroxidase like activity shows protective action. Finally, there are indications that chronic pancreatitis can be helped by supplementation with selenium plus other antioxidants, even though a large scale demonstration is required for confirmation.

**Human immunodeficiency virus (HIV)**

There is a pattern for tying selenium status to a development of a viral disease. As mentioned earlier, the classic selenium deficiency termed as keshan disease involves improved virulence of virus. During the progression of acquired Immune deficiency Syndrome (AIDS). Selenium deficiency can be stantial, Even though A degree of malnutrition can exist for a number of nutrients. Whatever it may be, the reduction in selenium status exhibit predictive value for the rate of AIDS progression and mortality. Even though this may be coincidental to macronutrient depletion. In a mouse model for AIDS selenium supplementation is higher glutathione peroxidase activities and lower peroxidase values and indication of reduced oxidation stress. Some immunological effects are also observed. There have been a few experimental works of selenium supplementation in HIV positive people, even though none has demonstrated a major large scale physiological effect. One experimental work reports inconsistent results. An additional study of selenium supplementation has been performed in 186 HIV positive men and women.

**Male Infertility**

There is a form of glutathione peroxidase that seems to be especially participated in providing protection to the fertility of spermatozoa. In one study of fertile men, the sperm protein activity

of this enzyme, infertile men is just half that of fertile men. Another theory for selenium infertility connection is that in animals taking selenium deficient diets, structural abnormalities in the sperm mid piece happen that are related to poor motility and frequent tail breakage. That is why, selenium nutritional status plays a role in human male infertility. One theory for selenium human infertility connection is that seminal fluid, selenium concentrations correlate positively with sperm count and with total sperm count, particularly in a group of sub fertile Norwegian men. It should be considered that in an experimental work, selenium concentration in 211 Semen samples from normozoospermic, Oligozoospermic, Asthmemozoospermic And azoospermic men observes no correlation with Sperm count or motility. In an experimental study, supplementation of sub fertile men with 100 gram selenium per day for 3 months significantly enhances the sperm motility. This study is conducted with subjects from the UK, where mean Selenium consumption has become marginal in recent years. It is also noteworthy that in a study of sub fertile Polish Men, administration of 200 gram selenium per day shows no benefit for sperm motility. Finally, there is only one week. Or inconsistent proof that selenium supplementation could assist many men with infertility.

### **Pregnancy Miscarriage**

One line of reasoning is that selenium supplementation has a very few times been utilised to stop miscarriages in veterinary practice. Moreover, the proof for Marginal selenium deficiency Linked to miscarriage is not very strong because number of studies is low. Most of the studies focus on just serum selenium and the studies give mixed results. Some studies discover depressed serum selenium in women with recurring miscarriage, which others don't. Prominent Absent from most studies on selenium and miscarriage is measurement of glutathione peroxidase. In one exception, red blood cell and plasma Glutathione peroxidase activities of women also had a miscarriage of significantly lower than in normal pregnancies. In spite of the existing data, it is still possible that selenium status plays a major role in substantial number of miscarriages.

### **Mood**

Particularly during selenium deficiency, the brain retains this mineral better than other tissues. Some selenium plays a role in the brain are of high priority. One possible function is mood maintenance. The mechanisms that could be involved are not known, even though speculations include the involvement of thyroid hormone. Many studies have demonstrated that low selenium consumption is linked to poorer mood. One example is a study where healthy men are provided diets to deplete then replete selenium.

### **Immune Function**

Along with effects on viral virulence (See the HIV Subsection), Selenium can show other effects on immune function. This can be seen in selenium- deficient animals even though as noted earlier, the mechanisms are not completely clear. Some experimental works provide multiple nutrients, not just selenium. In another experimental work, although just selenium is tested and an improvement is demonstrated for some of the parameters, the subject size is very small. In some other experimental works, the beginning selenium status of the subjects is not well characterized or only high selenium doses are tested. In some of the high- dose

experimental works, a very few laboratory parameters of immune function, namely natural killer cell activity, do enhance. In one of these experimental works, the subjects are declared to be selenium replete, which enhances the possibility of an activating effect on immune function of above -adequate selenium consumptions. Whatever it may be, this concept would need preferably more verification before it would be accepted.

### **Asthma**

A very few Internet sites and alternative medicine writings are declaring that selenium stops and treats asthma. There may be truth in this claim, but at this point the claim is still hypothetical. Many experimental works demonstrate that values for some selenium status assessment tools are low in asthmatics vs controls and low for atopic vs non atopic subjects. A very few small selenium supplementation studies have been tried, particularly with asthmatic subjects. In one ,anti- inflammatory regulatory actions are observed if cells challenged outside the body. This experimental work quite interesting, but it requires follow -up in other study designs. A different study which examines cortico dependent asthmatics in Slovakia, reports that selenium brings about decreased consumption of Inhaled corticosteroids. Whatever it may be, the study is small plus, it is not placebo controlled inspite of involving a -controlled endpoint. In an additional experimental work, a significant improvement is reported especially for assembled clinical evaluating in 12 selenium-supplemented Swedish asthmatics compared to a placebo group. Finally, there is some data in connecting selenium status with asthma prevention or treatment, but the case is not completely yet.

### **Ketogenic Diet in Epilepsy Patients**

A very recent study claims a patient particularly on this diet, who had no detectable whole blood selenium plus cardiomyopathy, the classic symptom of keshan disease. In further work in this study 10 of 39 children express low blood selenium values which improves upon especially selenium supplementation. This study is very essential for children particularly on the ketogenic diet. Follow- up experimental works should add other measures of selenium status, (example., glutathione peroxidase) and more parameters indicative of potential health consequences of selenium deficiency. The so- called ketogenic diet is frequently applied to intractable epilepsy, although diet is deficient in a number of nutrients.

### **Normal Antioxidant Effects**

In this authors plan, there is a requirement for a general characterization of different markers of an antioxidant action and oxidant stress in people with differing beginning selenium status and health states. Particularly in some of the studies, selenium is administered only as part of an antioxidant mixture. At present, we do not know to maximum extent about how much variations in selenium status originally affect antioxidant capacities and in whom. Unfortunately, a comprehensive version of such a study did not get funds by U.S. government grant agencies because it would be labeled as a loser descriptive study.

### **Toxicity**

The biggest known case of selenium toxicity from foods or supplements happened in certain areas of China, the same country that has shown the biggest population group for selenium

deficiency. The toxicity cause was consuming food grown in high- selenium soil, the exact opposite of the case for keshan disease in another part of China. The adult upper level is dependent on the consumption from food plus supplements that should stay below the total intake that cause an early toxic reaction seen in China. This reaction is manifested by hair loss and nail Sloughing.

### **Conclusion**

For parts of the world with low soil selenium or low availability of soil selenium, it seems helpful to enhance either selenium supplementation, selenium food fortification, high -selenium fertilizers for food plant growing, or the importing of grain foods, particularly from high-selenium soil regions. Selenium supplementation for the obstruction of cancers, as part of the treatment of chronic pancreatitis and as a support on nutritional basis for epileptic children on the ketogenic diet, all may show some merit in spite of non- confirmation of these applications. The use of selenium supplements to cure or stop other health problems demonstrate various degrees of support, but all still remain fairly theoretical. Toxicity risks from selenium supplement doses are short.

### **References:**

1. . Sunde, R.A., Selenium, in Handbook of Nutritionally Essential Mineral Elements, OiDell, B.L., and Sunde, R.A., Eds., Marcel Dekker, New York, 1997, chap. 18.
2. Kehrer, J.P., Free radicals as mediators of tissue injury and disease, Crit Rev. Toxicol., 23, 21, 1993.
3. Brown, K.M. and Arthur, J.R., Selenium, selenoproteins and human health: a review, Public Health Nutr., 4, 593, 2001.
4. Schallreuter, K.U. and Wood, J.M., Thioredoxin reductase ó its role in epidermal redox status, J. Photochem. Photobiol., B, 64, 179, 2001.
5. Berggren, M.M., Mangin, J.F., Gasdaka, J.R., and Powis, G., Effect of selenium on rat thioredoxin reductase activity: increase by supranutritional selenium and decrease by selenium deficiency, Biochem. Pharmacol., 57, 187, 1999.
6. Hansen, J.C. and Deguchi, Y., Selenium and fertility in animals and man ó a review, Acta Vet. Scand., 37, 19, 1996.
- 7 . Behne, D., Duk, M., and Elger, W., Selenium content and glutathione peroxidase activity in the testis of the maturing rat, J. Nutr., 116, 1442, 1986.
8. Arthur, J.R., McKenzie, R.C., and Beckett, G.J., Selenium in the immune system, J. Nutr., 133, 1457S, 2003.
9. Beck, M.A., Levander, O.A., and Handy, J., Selenium deficiency and viral infection, J. Nutr., 133, 1463S, 2003.
10. Sunde, R.A., Selenium, in Present Knowledge in Nutrition, 8th ed., Bowman, B.A., and Russell, R.M., Eds., ILSI Press, Washington, 2001, chap. 33.
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11. Hambidge, M., Biomarkers of trace mineral intake and status, J. Nutr., 133 Suppl. 3, 948S, 2003.

12. Liábbe, M.R., Collins, M.W., Trick, K.D., and Laffey, P.J., Glutathione peroxidase activity in a healthy Canadian population. Effects of age, smoking and drinking habits, exercise and oral contraceptive use, *Trace Elem. Med.*, 9, 45, 1992.
13. van den Brandt, P.A., Goldbohm, R.A., van't Veer, P., Bode, P., Hermus, R.J., and Sturmans, F., Predictors of toenail selenium levels in men and women, *Cancer Epidemiol. Biomarkers Prev.*, 2, 107, 1993.
14. Hunter, D.J., Morris, J.S., Chute, C.G., Kushner, E., Colditz, G.A., Stampfer, M.J., Speizer, F.E., and Willett, W.C., Predictors of selenium concentration in human toenails, *Am. J. Epidemiol.*, 132, 114, 1990.
15. Longnecker, M.P., Stampfer, M.J., Morris, J.S., Spate, V., Baskett, C., Mason, M., and Willett, W.C., A 1-y trial of the effect of high-selenium bread on selenium concentrations in blood and toenails, *Am. J. Clin. Nutr.*, 57, 408, 1993.
16. Alexander, A.R., Whanger, P.D., and Miller, L.T., Bioavailability to rats of selenium in various tuna and wheat products, *J. Nutr.*, 113, 196, 1983.
17. Mutanen, M., Bioavailability of selenium in mushrooms, *Boletus edulis*, to young women, *Int. J. Vitam. Nutr. Res.*, 56, 297, 1986.
18. Yoshida, M., Sugihara, S., Suenaga, T., Naito, C., Fukunaga, K., and Tsuchita, H., Digestibility and chemical species of selenium contained in high-selenium yeast, *J. Nutr. Sci. Vitaminol. (Tokyo)*, 48, 401, 2002.
19. Barceloux, D.G., Selenium, *J. Toxicol. Clin. Toxicol.*, 37, 145, 1999.
20. Thomson, C.D., Robinson, M.F., Butler, J.A., and Whanger, P.D., Long-term supplementation with selenate and selenomethionine: selenium and glutathione peroxidase (EC 1.11.1.9) in blood components of New Zealand women, *Br. J. Nutr.*, 69, 577, 1993.
21. Duffield-Lillico, A.J., Reid, M.E., Turnbull, B.W., Combs, G.F., Jr., Slate, E.H., Fischbach, L.A., Marshall, J.R., and Clark, L.C., Baseline characteristics and the effect of selenium supplementation on cancer incidence in a randomized clinical trial: a summary report of the Nutritional Prevention of Cancer Trial, *Cancer Epidemiol. Biomarkers Prev.*, 11, 630, 2002.
22. Gianduzzo, T.R., Holmes, e.g., Tinggi, U., Shahin, M., Mactaggart, P., and Nicol, D., Prostatic and peripheral blood selenium levels after oral supplementation, *J. Urol.*, 170, 870, 2003.
23. Yu, M.W., Horng, I.S., Hsu, K.H., Chiang, Y.C., Liaw, Y.F., and Chen, C.J., Plasma selenium levels and risk of hepatocellular carcinoma among men with chronic hepatitis virus infection, *Am. J. Epidemiol.*, 150, 367, 1999.
24. Yu, S.Y., Zhu, Y.J., and Li, W.G., Protective role of selenium against hepatitis B virus and primary liver cancer in Qidong, *Biol. Trace Elem. Res.*, 56, 117, 1997.
25. Neve, J., Selenium as a risk factor for cardiovascular diseases, *J. Cardiovasc. Risk*, 3, 42, 1996.
26. Rayman, M.P. and Rayman, M.P., The argument for increasing selenium intake, *Proc. Nutr. Soc.*, 61, 203, 2002.
27. Zachara, B.A., Dobrzynski, W., Trafifikowska, U., and Szymanski, W., Blood selenium and glutathione peroxidases in miscarriage, *BJOG*, 108, 244, 2001.
28. Kiremidjian-Schumacher, L., Roy, M., Wishe, H.I., Cohen, M.W., and Stotzky, G., Supplementation with selenium and human immune cell functions. II. Effect on cytotoxic lymphocytes and natural killer cells, *Biol. Trace Elem. Res.*, 41, 115, 1994.

29. Pearson, D.J., Suarez-Mendez, V.J., Day, J.P., and Miller, P.F., Selenium status in relation to reduced glutathione peroxidase activity in aspirin-sensitive asthma, *Clin. Exp. Allergy*, 21, 203, 1991.