

A REVIEW ON SELENIUM COMPOUNDS ROLE IN CHEMOTHERAPY

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ABSTRACT

The use of selenium compounds as a cancer treatment predates most conventional treatments currently in use. In spite of this, comparatively little is known regarding the use of selenium as cancer therapy in living systems. Selenium normally acts in concert with a class of enzymes and transporters called Selenoproteins (proteins with selenium in them), many of which are intrinsic anti-oxidant enzymes. In these selenoproteins, selenium acts as a prosthetic group or active site. Distinctly, Selenoprotein S is involved in protection against endoplasmic reticulum stress and regulation of proinflammatory cytokine release. In epidemiological studies of populations exposed to high levels of selenium in food and water, discoloration of the skin, pathological deformation and loss of nails, loss of hair, excessive tooth decay and discoloration, garlic odor in breath and urine, lack of mental alertness, and listlessness were reported. Taking antioxidants, including selenium, along with these drugs may reduce their effectiveness. Theoretically, selenium may also reduce the effectiveness of other statins, including atorvastatin, fluvastatin, lovastatin and pravastatin.

KEYWORDS: Selenoproteins, Recommended Dietary allowance (RDA), Blind staggers, Alkali disease.

INTRODUCTION

- Selenium was discovered by the Swedish chemist Jons Jacob Berzelius in 1817 and has been recognized as an essential trace element for many life forms including human being since 1957 when the element was found to be the active principle in liver that could replace vitamin E in the diets of rats and chicks for the prevention of vascular, muscular and/or hepatic lesions.^[1,2]
- Try Brazil nuts, whole meal bread, sunflower and pumpkin seeds, free-range eggs, skinless chicken breast, tuna fish, onions, wheat germ, tomatoes and broccoli. It is important to consume a spectrum of selenium-containing foods.^[3]
- Se exerts many cellular physiological functions mediated by its incorporation into selenoproteins, mainly in the form of selenocysteine (Sec), the 21st amino acid. The human genome harbors 25 selenoprotein genes.
- Some of these proteins are essential enzymes that do not only integrate Se in the form of Sec, but also requires Sec in their active site for an intact enzymatic activity. The antioxidant function of Se is conferred by some of these selenoproteins that directly protects against oxidative stress.
- However, at elevated doses, Se typically turns into a pro-oxidant with well-established growth inhibiting properties and with high cytotoxic activities.

- Large-scale epidemiologic studies have repeatedly demonstrated that populations with low selenium levels are at significantly increased risk for developing many different types of cancer.^[4,5,6]

Biological Significance

- It normally acts in concert with a class of enzymes and transporters called Selenoproteins (proteins with selenium in them), many of which are intrinsic anti-oxidant enzymes. In these selenoproteins, selenium acts as a prosthetic group or active site.^[7]
- Distinctly, Selenoprotein S is involved in protection against endoplasmic reticulum stress and regulation of proinflammatory cytokine release.^[8]
- Selenium is essential for the functioning of the iodothyronine deiodinases which catalyze the deiodination of thyroid hormones, converting T4 to T3 and rT3, with implications for growth and thermogenesis.
- In thioredoxin reductases it plays a role in redox reactions that control transcription factors, cell proliferation and apoptosis.^[8,9] Thioredoxin reductases can also reduce dehydroascorbic acid, an oxidized form of ascorbic acid.^[10]

Recommended Intake

- RDA is based on the amount of selenium required to maximize the activity of glutathione peroxidase (GPx) in serum. Due to inadequate evidence in

infants, an adequate intake (AI) is set based on the average intake, primarily from breast milk.

- This is 15ug/day from 0-6 months of age and 20ug from 7-12 months.
- The RDAs are 20ug/day from age 1-3, 30ug from 4-8, 40ug from 9-13, and 55ug for 14 and older, with no differences between males and females. The RDAs for pregnant and breastfeeding women are 60ug and 70ug, respectively.^[11]

Acute Side Effects

- Acute exposure of humans via inhalation to selenium compounds (selenium dioxide, hydrogen selenide) results primarily in respiratory effects. Acute inhalation exposure to elemental selenium dust results in irritation of the mucous membranes in the nose and throat, producing coughing, nosebleeds, dyspnea, bronchial spasms, bronchitis, and chemical pneumonia.^[12]
- Gastrointestinal effects including vomiting and nausea; cardiovascular effects; neurological effects such as headaches and malaise; and irritation of the eyes were reported in humans acutely exposed to selenium compounds via inhalation.^[12]
- Acute human exposure to selenium compounds via the oral route has resulted in pulmonary edema and lesions of the lung; cardiovascular effects such as tachycardia; gastrointestinal effects including nausea, vomiting, diarrhea, and abdominal pain; effects on the liver; and neurological effects such as aches, irritability, chills, and tremors.^[12,13]
- "Blind staggers" disease is a disease in livestock that results from acute consumption of plants high in selenium. It is characterized by impaired vision, aimless wandering behavior, reduced consumption of food and water, and paralysis.^[12,13,15]
- Acute animal tests in rats, mice, and guinea pigs, have shown hydrogen selenide to have extreme toxicity from inhalation exposure, sodium selenite to have extreme toxicity from oral exposure, and elemental selenium to have low toxicity from oral exposure.^[12,14]

Chronic Side Effects (Noncancer)

- No information is available on the chronic effects of selenium in humans from inhalation exposure.
- In epidemiological studies of populations exposed to high levels of selenium in food and water, discoloration of the skin, pathological deformation and loss of nails, loss of hair, excessive tooth decay and discoloration, garlic odor in breath and urine, lack of mental alertness, and listlessness were reported.^[12,13]
- "Alkali disease" is a disease in livestock resulting from chronic consumption of high levels of selenium; it is characterized by hair loss, deformation and sloughing of the hooves, erosion of the joints of the bones, anemia, and effects on the heart, kidney, and liver.^[12,13]

- The California Environmental Protection Agency (CalEPA) has calculated a chronic reference exposure level of 0.02 milligrams per cubic meter (mg/m) for selenium and selenium compounds based on clinical selenosis in humans, and a chronic reference exposure level of 0.00008 mg/m^[14] for hydrogen selenide based on respiratory effects in guinea pigs. The CalEPA reference exposure level is a concentration at or below which adverse health effects are not likely to occur.^[16]
- Selenium is an essential element in human nutrition, with recommended daily allowances of 0.070 mg/d for men, 0.055 mg/d for women, and 8.7 × 10 mg/kg/d for infants.
- Two diseases, "Keshan disease" and "Kashin-Beck disease" have been reported in humans in selenium deficient populations in China. Keshan disease is characterized by heart failure, cardiac enlargement, abnormalities of EKG, and cardiogenic shock. Kashin-Beck disease, which occurs primarily in children
- Some epidemiological studies have suggested that selenium deficiency may contribute to cardiovascular disease in humans. However, these studies are inconclusive due to confounding factors.

Reproductive/Developmental Effects

- No information is available on the developmental or reproductive effects of selenium in humans.^[12]
- The consumption of high levels of selenium in the diet by pigs, sheep, and cattle has been shown to interfere with normal fetal development and to produce fetal malformations.^[12,13]
- Sodium selenate, administered in the drinking water to mice, did not result in birth defects, but did result in an increased incidence of fetal deaths and a high proportion of runts, while chronic exposure of mice to selenium in the diet has been shown to affect their fertility and to reduce the viability of the offspring of pairs that are able to breed.^[12,13]

Selenium in Cancer

- The use of selenium compounds as a cancer treatment predates most conventional treatments currently in use.^[17] In spite of this, comparatively little is known regarding the use of selenium as cancer therapy in living systems.
- Selenium is available as two forms. Organic and Inorganic forms.
- The three forms of selenium most important in cancer prevention are sodium selenite, L-selenomethionine, and selenium-methyl Lselenocysteine.

The organic selenium compound L-selenomethionine.

Selenium-methyl Lselenocysteine

The inorganic selenium compound is Sodium selenite.

Sodium Selenite in Cancer

- Inorganic sodium selenite destroys cancer cells from a variety of cancers through a variety of mechanisms.^[23-30] One of its most intriguing anti-cancer mechanisms is the selective generation of toxic reactive oxygen species and targeted destruction of mitochondria that exist in tumor cells but not in healthy tissue.^[24-26]
- Paradoxically, sodium selenite has been shown to increase the activity of the antioxidant enzyme glutathione peroxidase in healthy tissue, thereby conferring double protection.^[22,27]
- Sodium selenite enhances the repair of damaged DNA segments, reducing the risk of new cancer development.^[28] And, by enhancing immune system responsiveness, sodium selenite increases the likelihood that abnormal cancer cells will be destroyed.^[22,29,30]
- A vital mechanism of sodium selenite's action is to decrease a protein called *Bcl-2* that is abnormally elevated in cancer cells, preventing their natural death by apoptosis.^[31,32] As a result, sodium selenite increases cancer cell death by apoptosis.^[24,33,34]
- Numerous human studies with sodium selenite support the use of this form of selenium as a possible adjunct therapy for cancer patients and for preventing new or recurring cases of cancer.
- In a randomized controlled clinical trial of sodium selenite using 200 mcg per day versus placebo in patients with aggressive head and neck cancers, the supplemented patients showed an increased ability to destroy tumor cells, which is the result of enhanced immune responses.^[29] Remarkably, the enhanced immunity achieved by those supplemented continued even after the conclusion of therapy.
- Another study demonstrated that temporary use by individuals diagnosed with oral tumors of 1,000 mcg of sodium selenite effectively reduced potentially deadly swelling in these patients after surgery.^[35]
- In terms of prevention, sodium selenite supplementation reduced the occurrence of new cases of liver cancer by 50% in a large group of Chinese people living in a high-risk area for that cancer. This study provided patients with 500 mcg per day for 3 years.^[27] And a reduction in new breast cancer cases was demonstrated in a group of women with the high-risk BRCA1 gene mutation, during double-blind supplementation trial.^[28]

L-Selenomethionine

- L-selenomethionine is an organic complex of selenium with the natural amino acid L-methionine.^[36] It is the form of selenium found in most preparations of selenium-enriched yeast, which has been used in many clinical trials.
- To some extent, L-selenomethionine can be credited with the recent upsurge in interest in selenium as a cancer-preventing supplement.
- In a now-famous 1996 study, Dr. Larry C. Clark of the University of Arizona was attempting to prevent

skin cancers with a 200 mcg supplement of L-selenomethionine. While the supplement proved ineffective at preventing either of the two major forms of skin cancer^[37,38] the supplemented patients were significantly protected from death by *all* cancers (a 50% reduction compared with controls), from developing any cancer (a 37% reduction), and specifically from developing lung, colorectal, and prostate cancers.^[37] These unexpected results were so compelling that the blinded phase of the study was stopped early to allow all subjects to achieve maximum protection.

- Subsequent reports from Dr. Clark and collaborators have demonstrated a 63% reduction in occurrence of prostate cancer among men with a history of prior cancers; that protection rate rose to 74% when including only patients with initially normal levels of the cancer marker prostate specific antigen (PSA).^[39]
- Lab studies show that L-selenomethionine inhibits growth of cancer cells at rates more than a thousand times greater than it does healthy normal tissue.^[40] This finding is one reason that L-selenomethionine is considered to have an excellent safety profile.^[41]
- Selenium acts by multiple, complementary pathways to prevent cancers from developing. This phenomenon, known to scientists as pleiotropy, allows selenium to attack cancer on many different fronts, at many different stages. Pleiotropy is a vital characteristic in any cancer preventive strategy, because cancers all have multiple causes and mechanisms of their own, readily overcoming single-targeted therapies.
- Detailed studies now reveal the following 12 distinct mechanisms by which selenium prevents potentially cancerous cells from attaining full-blown tumor status:
 - ✓ Regulation of lipoygenases, enzymes that produce inflammatory molecules that promote cancer growth;
 - ✓ Direct reduction of oxidative stress that causes free radical damage;
 - ✓ Protection of the antioxidant-recycling seleno-proteins;
 - ✓ Detoxification of cancer-inducing metals;
 - ✓ Induction of protective "phase II" liver enzymes that neutralize organic carcinogenic toxin
 - ✓ Inhibition of DNA alterations, precursors to initiation of cancerous changes
 - ✓ Inactivation of molecular transcription factors required by cancer cells to support their growth and development;
 - ✓ Shutting down of the essential cell replication cycle needed by cancer cells to produce their explosive growth;
 - ✓ Induction of apoptosis, the programmed cell death, a natural feature of all normal body cells that is missing in cancerous cells, allowing them to continue to reproduce indefinitely;

- ✓ Enhanced immune system activity to detect and destroy incipient cancer cells;
- ✓ Downregulation of sex hormone receptors used by certain cancers to sustain their growth
- ✓ Limiting effects on tumor invasion and metastasis.
- These 12 mechanisms act together to maximize cancer protection, and new mechanisms are still being discovered.^[20,21] But unlike most nutrients, not every form of selenium produces all of the same beneficial effects.

Selenium-Methyl L-Selenocysteine

- Selenium-methyl L-selenocysteine is an organic complex of selenium with a sulfur-containing amino acid, in this case, L-cysteine. This compound is the most recent form of selenium to attract scientific interest. Found in plants in the allium family (garlic and onions) grown in selenium-enriched soil, it is one of the most potent forms of selenium known.^[42]
- Laboratory studies reveal several mechanisms of action unique to this form of selenium. Perhaps most intriguingly, selenium-methyl L-selenocysteine supplements restore proteins associated with normal circadian rhythms.^[43]
- Disruptions in circadian rhythms are associated with development of several cancer types, most notably breast cancers. Restoring those important regulatory proteins with selenium-methyl L-selenocysteine normalizes levels of melatonin and estrogen receptors related to the aggressiveness of breast cancers.
- Another action of selenium-methyl L-selenocysteine in tumors is its ability to inhibit new blood vessel formation, or angiogenesis.^[44,45] This effect dramatically reduces tumor growth and enhances the delivery of cancer chemotherapy drugs to tumors.^[46] Selenium-methyl L-selenocysteine has shown promising synergistic effects with various chemotherapy drugs, including those used in prostate and breast cancers.^[46-48]
- Selenium-methyl L-selenocysteine downregulates expression of a protein known as Bcl-2 that slows beneficial apoptosis of cancer cells.^[49] What this means is that this form of selenium rapidly induces appropriate destruction of cancer cells. Selenium-methyl L-selenocysteine shuts down the inflammatory response prompted by the master inflammation-inducing regulator called NF-kappaB.^[50]
- In combination with the breast cancer drug tamoxifen, selenium-methyl L-selenocysteine enhances that drug's ability to inhibit growth of breast cancers implanted into mice.^[45] Such studies have been sufficiently encouraging that selenium-methyl L-selenocysteine is now being specifically developed for breast cancer chemoprevention. Additionally, the compound is showing a favorable profile in preventing colon, prostate, and head and neck cancers.^[47,51-53]

Selenium with Radiation

- Little is known about the interaction between selenium supplementation and radiotherapy. In the one human trial available, patients with advanced rectal cancer were given daily supplementation with 400 mcg of selenium after treatment.
- The selenium was well-tolerated, but the researchers presented no data regarding interaction between the two treatments.^[54] An animal study suggests that selenium depletion reduces the lethal dose of radiation.^[55]
- Until more is known regarding the effect of selenium on radiotherapy, pharmacological doses (above 400 mcg/day) cannot be advised.

Selenium with Chemotherapy

- Interactions between selenium and platinum-containing chemotherapy agents have been extensively studied. In a mouse study, selenium decreased nephrotoxicity of cisplatin, while simultaneously increasing its anti-tumor activity.
- Other animal studies confirmed these findings.^[56] A randomized crossover trial in humans looked at the effect of selenium (4000 mcg/day from four days before until four days post-chemotherapy) on the toxicity of cisplatin.
- Selenium consumption was associated with a higher WBC count, even with less consumption of granulocyte stimulating factor. Nephrotoxicity, measured by urine enzymes, was also significantly less in patients taking selenium. No mention is made in this study of any effect of selenium intake on the therapeutic activity of cisplatin.^[57] One in vitro study suggests a selenium containing antioxidant compound called Ebselen (2-phenyl-1, 3-benzisoxaselenazol- 3(2H) one) has a mild inhibitory effect on the anti-tumor effect of bleomycin.
- The authors did not speculate on whether dietary selenium would have an adverse effect on therapeutic use of bleomycin.^[58] Perhaps until these results are followed up, it would be best to avoid this combination.

Selenium's Additional Benefits

- In addition to protecting against various cancers, a host of clinical studies^[59] show that selenium plays a role in the prevention and treatment of a remarkable array of pathologies, including:
 - Cardiovascular disease
 - Osteoarthritis
 - Rheumatoid arthritis
 - Hypothyroidism
 - Stroke
 - Atherosclerosis
 - HIV
 - AIDS
 - Alzheimer's disease
 - Amyotrophic lateral sclerosis
 - Pancreatitis

- Depression

Interactions

- If you are being treated with any of the following medications, you should not use selenium supplements without first talking to your health care provider.^[60]

Drugs that affect selenium levels in the body

These drugs may lower levels of selenium:

- ✓ Cisplatin, a chemotherapy drug
- ✓ Clozapine
- ✓ Corticosteroids, such as prednisone
- ✓ Valproic acid

Anticoagulants and antiplatelet drugs (blood thinners)

When combined with these drugs, selenium may increase the risk of bleeding:

- ✓ Clopidogrel
- ✓ Warfarin
- ✓ Heparin
- ✓ Aspirin

Barbiturates

In animal tests, selenium seems to make the sedative effects of these drugs last longer:

- ✓ Butobarbital
- ✓ Metharbital
- ✓ Phenobarbital
- ✓ Secobarbital

Chemotherapy

- Although selenium may help reduce side effects from drugs such as cisplatin, doxorubicin, and bleomycin, it may also interfere with their cancer-fighting ability.
- If you are undergoing chemotherapy, talk to your oncologist before taking selenium or any other supplement.

Cholesterol-lowering medications

- Simvastatin and niacin have been shown to lower LDL ("bad") cholesterol and raise HDL ("good") cholesterol in people with heart disease.
- Taking antioxidants, including selenium, along with these drugs may reduce their effectiveness. Theoretically, selenium may also reduce the effectiveness of other statins, including atorvastatin, fluvastatin, lovastatin and pravastatin.

CONCLUSION

- Selenium is unique among the antioxidants and a great body of evidence clearly show the potential of this element in large-scale general prevention of human cancers.
- Prevention is exerted through several different complex mechanisms and in all stages of the carcinogenic process.

- Selenium compounds are generally cheap and in the correct dose harmless why selenium supplementation is an attractive and achievable way to reach decreased cancer incidences for the benefit of large groups of people worldwide.
- If only a fraction of the results indicated in the positive correctly performed trials could be reached in a large scale this would have a great impact to reduce healthcare expenses and human suffering.

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