Natural Minerals and Cancer

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ABSTRACT

Various minerals have been reported which are directly linked to our health and cancer development in body. The immune system (immunoglobulin’s, cell mediated immunity, phagocytosis complement, lysosomes, interferon, metabolic function, hormones, metabolic and respiratory alkalosis) is the natural mechanism which defends against cancer. Minerals like zinc, selenium, magnesium, vanadium, and germanium augment this natural mechanism. In this review various aspects of these mineral are discussed and their relation with cancer.

Keywords: Mineral, anticancer, chemoprotective, tumour.

INTRODUCTION

Most doctors are amazed when a patient spontaneously (without medical interference) recovers from cancer. Simple mechanical cures are possible for some outgrowing cancers (Braverman and Pfeiffer, 1982) and also bioorganometallic chemistry has emerged in the last decade as an important new field of medicinal chemistry (Gomez-Ruiz et al., 2008). Both of above phrases reflecting use of a common thing, which are minerals or essential trace elements. Minerals are essential for all living organisms and should be in optimum level (Campbell, 2011). According to Commission on New Minerals and Mineral Names (CNMMN), a mineral is defined as an element or chemical compound that is normally crystalline and that has been formed as a result of geological processes (Nickel, 1995). The presence of certain elements in diet is as important as the choice of diet for reducing the incidence of cancer and even in the management of the cancer patient. For example, selenium deficiency has been associated with increased cancer incidence. Other elements with some anticancer activity include molybdenum, zinc, magnesium, and germanium (Sartori, 1984). While intensive efforts have been made for the treatment of cancer, this disease is still the second leading cause of death in many countries (Balaz and Sedlak, 2010). Cancer mortality is second only to cardiovascular disease as the most common cause of death in the USA and in most European countries (Sartori, 1984). Colon cancer is one of the most common malignancies in many regions of the world (Kanna et al., 2003), while Prostate cancer is the most commonly diagnosed and second leading cause of cancer death in men in the United States (Zhong and Oberley, 2001). Metastatic breast cancer, late-stage colon cancer, malignant melanoma, and other forms of cancer are still essentially incurable in most cases (Balaz and Sedlak, 2010). Cancer grows rapidly in young people, i.e. ovarian, breast, seminoma, but these cancers in older people may progress slowly over a ten year period (Braverman and Pfeiffer, 1982).
ANTICANCER MINERALS

From the plethora of essential and non-essential minerals few of them show their potential as anticancer candidates.

Selenium

Selenium (Se), an essential trace element and a mineral for animals including humans, has been shown to affect the functions of several specific intracellular selenoproteins by being a component of their essential constituent selenocysteine (SeCys) (Zeng and Combs, 2008). It was demonstrated that trace amounts of Se protected against liver necrosis in vitamin E deficient rats and hence established its nutritional essentiality (Zeng, 2008). The form of selenium in all selenoproteins is an amino acid, L-selenocysteine. Both inorganic (e.g., selenite and selenate) and organic (seleno amino acids) forms of selenium have shown impressive cancer chemopreventive effects in humans and in animal models (Woo et al.). In the research field of trace metals and carcinogenesis selenium has gained a disproportionate amount of attention. Various studies emphasize selenium’s antioxidant properties, inhibition of tumor growth and inverse epidemiological correlations with cancer. The inhibitory effect of selenium on growth of tumors has a gain been documented and it has been reported to inhibit the development of a variety of experimental tumors, including tumors of the gastro-intestinal tract (Braverman et al., 1982 & Bogden et al., 1986).

Lee et al. reported the inhibition of LNCaP human prostate cancer xenograft by monomethylated selenium (MSC). The mice were first co-inoculating with LNCaP cells with matrigel and the mice having tumours were treated with MSC for 2 weeks. The MSC treated mice were compared with controls and found out that serum PSA levels were significantly lower in the MSC-treated group than in the controls. This proves that selenium (MSC) inhibited LNCaP tumor growth in nude mice model accompanied by a reduction of AR and AR-regulated gene PSA expression in vivo which was reported by Dong Y and Lee et al.

Philchenkov et al., reported apoptosis induction by selenium compounds in human lymphoblastic leukemia MT-4 cells to understand the mechanism of apoptosis by various selenium compounds. MT-4 cells were exposed to various concentrations of sodium selenite or sodium selenate for 24-72 hr and their viability was assessed by flow cytometry after a treatment over a period of 24 h. Selenite, but not selenate, treatment was shown to result in increasing DNA single-strand breaks in cells under study as detected by COMET assay (Single Cell Gel Electrophoresis assay). They concluded that selenite-induced apoptosis of MT-4 cells involves DNA damage. This study revealed the evidence and method of selenium anticancer action.

Many studies were done on rats to check viability of selenium in preventing intestinal tumours. Rats were fed a cancer-causing agent known to cause colon cancer. The rats whose diets were supplemented with selenium had a tumor incidence of only 3 percent, whereas the rats that received no selenium supplementation had a 29 percent tumor incidence. Other animal studies have shown that selenium supplementation reduces the incidence of intestinal tumors by 50 percent compared with rats given the cancer-causing agent without selenium supplementation (Soullier et al., 1981 & Jacobs, 1983 & Fiala et al., 1991 & Reddy et al., 1985). Table 1 shows different Selenoproteins of particular relevance to cancer and Fig.1 demonstrates the proposed pathway for metabolism of selenomolecules.

Selenium is naturally available from many natural sources like Brazil nuts but selenium content in foods can vary. Selected food sources of selenium are provided in Table 2 with daily value. So we can conclude that selenium is an important mineral which is found in food at nutritional doses, Se is an essential component of SeCys in selenoproteins, and it promotes cell cycle progression and prevents cell death. But at higher doses that are greater than the nutritional requirement but not toxic, Se induces cell cycle arrest and apoptosis (Zeng, 2009). So we can say that selenium can be used in therapies for prevention and curing of various types of cancers.
Zinc

Zinc is an essential mineral that acts as a co-factor for more than seventy enzymes. The role of zinc in cancer has received increasing attention, with a link between zinc deficiency and cancer having been established in human, animal and cell culture studies. Many researchers have reported that zinc inhibits the development of cancer and that low serum zinc is associated with several forms of cancer. In 1959, Addink and Frank reported that blood and serum from cancer patients generally show subnormal zinc levels, supplementation of the same was associated with a favorable prognosis. High levels of zinc, 300 ppm, decrease tumor incidence and increase the latent period of PYB6 induced neoplasms in mice (Mulhern, 1980). Cancer inhibition is a general effect of deficiency of any nutrient which is involved in protein synthesis, irrespective of cell type, cell growth rate, species or site of growth. In view of the fact that zinc is required for cell division and protein synthesis, it is not surprising to observe a decrease in tumor growth as a result of a short term zinc deficiency. Long term effects of a deficiency result in immune defects which cancel this benefit and promote tumor growth. Zinc may prevent cancer via the metabolism of high density lipoprotein (HDL), vitamin A and DNA synthesis. In a 24 year study of business and professional men, 32 men who died from cancer had the highest mean HDL, a significant difference from survivors. High levels of zinc supplementation in normal subjects, 440 mg of zinc sulfate per day for five weeks, result in a 25 percent decrease below baseline levels of HDL. Zinc may exert a prophylactic anti-cancer effect by preventing elevation of HDL (Eric, 1982). In another study, Golub et al. reported zinc deficiency caused oxidative DNA damage and chromosome breaks in animals fed with a zinc-deficient diet. Where as in rats, dietary zinc deficiency led to an increased susceptibility to tumor development.
when exposed to carcinogenic compounds (Fong and Magee, 1999). Much of the interest in zinc as an agent for cancer treatment and prevention is due to studies that have shown a marked reduction in prostate tissue zinc levels in prostate cancer cells versus normal prostate cells. In normal prostate tissue, zinc acts as an inhibitor of an enzyme (macoinitase), which is part of the Krebs cycle. With the inhibition removed by the low levels of zinc, the malignant cells are now able to complete the Krebs cycle and go from energy-inefficient secretory epithelial cells to energy efficient cells (Costello et al., 1998 & Costello et al., 2004).

In another study done by Philips et al they reported aqueous zinc acetate injected intraperitoneally prevented tumor growth in 50 to 70 percent of male mice previously inoculated with L1210 leukemia cells. Subcutaneous injections in a different strain did not prevent tumor growth but significantly increased mean survival (Philips et al., 1976). Sliwinski et al. reported a study to understand interaction between zinc and DNA. They studied cyto- and genotoxicity of zinc sulfate (ZnSO4) in normal human lymphocytes and human myelogenous leukemia K562 cancer cells in the presence of zinc and hydrogen peroxide (H2O2). The results indicated zinc showed a protective action against H2O2 to prevent normal cell damage and also zinc inhibited the repair of DNA damage induced by H2O2 in cancer cells. The zinc may protect normal cells against DNA-damaging action and increase this action in cancer cells, which indicates the dual action of this element in dependency of target cells and can be useful in cancer therapy.

Recently studies are being done to synthesize water-soluble zinc ionophores which increase the intracellular concentrations of free zinc and to help in producing an antiproliferative activity on cancer cultures. Magda et al. reported synthesis of water-solubilized versions of the zinc ionophore1-hydroxyypyridine-2-thione (ZnHPT) like PCI-5001, PCI-5002, and PCI-5003 which produce an antiproliferative activity in exponential phase A549 human lung cancer cultures. They proposed that these water solubilized zinc ionophores represent a potential new class of anticancer agents.

From all the above studies it was concluded that zinc is an essential mineral involved in cancer development and it can used in prevention and treatment of various types of cancers and can be included in various anticancer therapies.

**Vanadium**

Vanadium is considered to be a micronutrient and is included in the list of 40 essential micronutrients that are required in small amounts for normal metabolism. Vanadium has a role in the DNA maintenance reaction and may protect the genomic instability that may lead to cancer (Elberg et al., 1998).

Vanadium has shown documentary roles in chemoprevention in mouse tumor models, hepatic cancer, rat mammary cancer models, leiomyosarcomas in Wister rats and in many human cancer cell lines. Several other reports on vanadium and vanado compounds have indicated that low doses of vanadium are beneficial compared with toxic higher doses. Recent studies indicate the role of the micronutrient vanadium in chemoprevention in many animal models, human cancer cell lines, and also in xenografted human carcinomas of the lung, breast, and gastrointestinal tract.

Ray et al. reported the antineoplastic potential of vanadium in a defined model of mammary carcinogenesis. Female Sprague-Dawley rats, at 50 days of age, were treated with 7, 12-dimethylbenz (α) anthracene (DMBA) by a tail vein injection in oil emulsion. Vanadium (ammonium metavanadate) at a concentration of 0.5 ppm was supplemented in drinking water and given ad libitum to the experimental group after the carcinogen treatment, and it continued until the termination of the study. In vivo studies of DNA chain breaks demonstrated that vanadium offered significant protection against generation of single-strand breaks when compared with the DMBA control group. Supplementation of vanadium normalizes the level of zinc, iron, and copper as revealed by proton-induced X-ray emission analysis to a substantial extent. In vitro study of chromosomal aberrations (CAs) revealed that vanadium triggered a protective effect on induction of CAs, which was maximum on structural aberrations followed by numerical and physiological types. Histopathological and morphological analyses were done as end-point biomarkers. They concluded that vanadium has the potential to reduce genomic instability in mammary carcinoma in rats. Various other studies were done in which administration of vanadium compounds in humans and animals revealed that vanadium may exert various toxic effects. Studies on animals (mainly rats and mice) showed that the toxic effects of vanadium compounds are related to the species, the dose, the route and the duration of administration as well as to the nature of the compound. Studies dealing with the administration of vanadium salts in humans, suffering from either diabetes mellitus or coronary artery disease indicated that with short-term treatment (maximum for 4 weeks) the most common side effect was mild gastrointestinal disturbance (Cohen et al., 1995 & Goldfine et al., 1995 & Boden et al., 1996).

Studies on animals indicated a variety of toxic effects induced by vanadium compounds. Functional disturbances and histopathological alterations of liver and kidneys are the most common toxic effects. Oral administration of NaVO3 (between 5 and 10 µM, in the drinking water) for 3 months, induced mild and dose dependent histopathological lesions in kidneys and spleen accompanied by increased plasma concentrations of urea and uric acid at the highest exposed groups (Domingo et al., 1985).

**Mode of action**

Vanadium compounds exert preventive effects against chemical carcinogenesis on animals, leads to inhibition of carcinogen-derived active metabolites when various xenobiotic enzymes undergoes modification. Studies on various cell lines revealed that vanadium exerts its antitumor effects through inhibition of cellular tyrosine phosphatases and/or activation of tyrosine phosphorylases. Both effects activate signal transduction pathways leading either to apoptosis and/or to activation of tumor suppressor genes. Vanadium compounds may induce cell-cycle
arrest and/or cytotoxic effects through DNA cleavage, fragmentation and plasma membrane lipoperoxidation. Reactive oxygen species generated by Fenton-like reactions and/or during the intracellular reduction of V (V) to V (IV) by, mainly, NADPH, participate to the majority of the vanadium-induced intracellular events as shown in Fig. 2. Vanadium may also exert inhibitory effects on cancer cell metastatic potential through modulation of cellular adhesive molecules and reverse antineoplastic drug resistance. Table 3 shows dietary reference intake (DRI) - Recommended dietary allowance of vanadium. The anti-carcinogenic effects of vanadium, in combination to its low toxicity, established also, by its administration in humans, suggest vanadium as a candidate antineoplastic agent against human cancer (Evangelou, 2002).

**Table. 3:** Dietary Reference Intake (DRI) of Vanadium - Recommended Dietary Allowance / Intake (RDA / RDI) for Adults, Children. (Dietary reference Intake 2001).

<table>
<thead>
<tr>
<th>DRI (RDA)</th>
<th>Suggested Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-10 years</td>
<td>10 mcg - 50 mcg</td>
</tr>
<tr>
<td>11-18 years males</td>
<td>50 mcg - 100 mcg</td>
</tr>
<tr>
<td>19 + years males</td>
<td>50 mcg - 100 mcg</td>
</tr>
<tr>
<td>11-18 years females</td>
<td>50 mcg - 100 mcg</td>
</tr>
<tr>
<td>19 + years females</td>
<td>50 mcg - 100 mcg</td>
</tr>
<tr>
<td>UL*</td>
<td>1,800 mcg</td>
</tr>
<tr>
<td>Therapeutic Range</td>
<td>10mg - 125mg</td>
</tr>
</tbody>
</table>

**Magnesium**

Magnesium is the fourth most abundant mineral in the body and is essential for good health. Approximately 50% of total body magnesium is found in bones. The other half is found predominantly inside cells of body tissues and organs. Only 1% of magnesium is found in blood, but the body works very hard to keep blood levels of magnesium constant (Rude, 1998). Magnesium (Mg) is essential for the function of important enzymes, including those related to the transfer of phosphate groups, all reactions that require ATP, and every step related to the replication and transcription of DNA and the translation of mRNA. This cation is also required for cellular energy metabolism and has an important role in membrane stabilization, nerve conduction, ion transport and calcium channel activity. Magnesium deficiency may thus result in a variety of metabolic abnormalities and clinical consequences even cancer development (Weisinger and Bellorin, 1998). **Aleksandrowicz et al.** in Poland concluded that an inadequacy of Magnesium (Mg) and other antioxidants are important risk factors in the predisposition to various forms of leukemia. Other researchers found out that 46% of patients admitted to an ICU in a tertiary cancer center presented low (Mg) levels. They concluded that the incidence of hypomagnesaemia in critically ill-cancer patients is high. This shows magnesium link with cancer (Deheinzelin et al., 2000).
Ma *et al.* reported high dietary intake of magnesium may decrease risk of colorectal cancer in Japanese men. They studied and examined the association between dietary intake of magnesium and CRC risk in Japanese men and women aged 45–74 y and they concluded that higher dietary intake of magnesium may decrease the risk of colorectal cancer (CRC) in Japanese men.

Over 300 enzymes and ion transportation requires magnesium for its role in fatty acid and phospholipids metabolism which affects permeability and the stability of membranes. We can see that Magnesium deficiency would lead to a functional imbalance in cells, ultimately setting the stage for cancer. Anything that weakens cell physiology will lead to the infections that surround and penetrate tumor tissues. These infections are proving to be an integral part of cancer. Magnesium deficiency poses a direct threat to the health of our cells. Without sufficient amounts our cells calcify and lead to death.

A study of rats surviving magnesium deficiency sufficient to cause death and convulsions during early infancy in some, and heart/kidney lesions weeks later in others, disclosed that some of survivors had thymic nodules or lymphosarcoma which also shows a link between magnesium and cancer (Bois, 1964). It is known that carcinogenesis induces magnesium distribution disturbances, which cause its mobilization through blood cells and depletion in non-neoplastic tissues. Magnesium deficiency seems to be carcinogenic, and in the case of solid tumors, a high level of supplemented magnesium inhibits carcinogenesis (Durlach *et al.*, 1986).

Both carcinogenesis and magnesium deficiency increase the plasma membrane permeability and fluidity. Scientists found out that there is much less Mg**⁺** binding to membrane phospholipids of cancer cells, than to normal cell membranes (Anghileri, 1979). It has been suggested that magnesium deficiency may trigger carcinogenesis by increasing membrane permeability (Blondell, 1980). Anghileri *et al.* proposed that modifications of cell membranes were principal triggering factors in cell transformation leading to cancer. Using cells from induced cancers, they found that there is much less magnesium binding to membrane phospholipids of cancer cells, than to normal cell membranes (Anghileri, 1979 & Anghileri *et al.*, 1981 & Anghileri *et al.*, 1977).

Several other studies have shown an increased cancer rate in regions with low magnesium levels in soil and drinking water, and the same for selenium. In Egypt, the cancer rate was only about 10% of that in Europe and America. In the rural Fellah, it was practically non-existent. The main difference was an extremely high magnesium intake of 2.5 to 3g in these cancer free populations, ten times more than in most western countries (Schrumpf-Pierre, 1931). The risk of most cancers increases with aging, and with length of exposure to agents with oncogenic potential. Epidemiologic and experimental data suggested that adequate magnesium might protect against initiation of precancerous cellular changes. Despite provocative findings suggested that magnesium deficiency might be implicated in aspects of pathogenesis and treatment of neoplasms, there are many unknowns. Investigation of these questions might lead to means to prevent lympholeukemias. Table 4 and Table 5 shows recommended dietary allowances for magnesium for children, adults and infants.

**Table 4: Recommended Dietary Allowances for Magnesium for children and adults** (Institute of Medicine. Food and Nutrition Board, Dietary Reference Intake, 1999).

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Males (mg/day)</th>
<th>Females (mg/day)</th>
<th>Pregnancy (mg/day)</th>
<th>Lactation (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>80</td>
<td>80</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>4-8</td>
<td>130</td>
<td>130</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>9-13</td>
<td>240</td>
<td>240</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>14-18</td>
<td>410</td>
<td>360</td>
<td>400</td>
<td>360</td>
</tr>
<tr>
<td>19-30</td>
<td>400</td>
<td>310</td>
<td>350</td>
<td>310</td>
</tr>
<tr>
<td>31+</td>
<td>420</td>
<td>320</td>
<td>360</td>
<td>320</td>
</tr>
</tbody>
</table>

There is insufficient information on magnesium to establish a RDA for infants. For infants 0 to 12 months, the DRI is in the form of an Adequate Intake (AI), which is the mean intake of magnesium in healthy, breastfed infants. Table 5 lists the AIs for infants in milligrams (mg).

**Table 5: Recommended Adequate Intake for magnesium for infants** (Institute of Medicine. Food and Nutrition Board Dietary Reference Intake, 1999).

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Males and Females (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 6</td>
<td>30</td>
</tr>
<tr>
<td>7 to 12</td>
<td>75</td>
</tr>
</tbody>
</table>

**Germanium**

Germanium is an element which is found in small quantities in some plant-based foods. Both organic and inorganic germanium has been sold as dietary supplements, though the organic forms are more commonly used today. Inorganic germanium is mined and widely used as a semiconductor in electronics industry. Germanium is a constituent of many medicinal plants such as ginseng root, ginger, garlic and it is considered to play an important role in the pharmacological effects of the plants (Lu, 1998).

Germanium is a powerful antioxidant which has been shown to protect against cancer. Researchers found that germanium reduces the spread of cancer by slowing down the process that causes cancer cells to multiply. At the same time, the researchers observed that germanium has no interference with normal healthy cells, which were left alone to grow and carry out their functions as nature intended. It is also reported that many organogermainium compounds can inhibit tumor and metastatic growth and modify immune response by inducing interferon-γ (IFN-γ), enhancing NK cell activity, and increasing peritoneal macrophage activity (Aso *et al.*, 1985 & Suzuki, 1985 & Kuwabara *et al.*, 2002 & Kaplan *et al.*, 2004). Two organogermainium compounds were studied extensively: spiogermainium and germanium sesquioxide. While both were effective against some cancers, their mechanisms of action were completely different. Spiogermainium was found to be effective in killing cancer cells, even when the cells were cultured outside (*in vitro*) the body (Slavik *et al.* & Jeyaraman and Sellappa, 2011). Japanese researchers have found excellent results using germanium sesquioxide to treat cancer (Sato and Iwaguchi, 1979 & Kumano et
Organic germanium compounds is indeed the "new nutrition kid on the block," a landmark in development of nutritional medicine for cancer therapy and treatment.

CONCLUSION

The role of minerals in fighting cancer is a constantly-evolving field of research, with promising data that the nutrients you eat can help fight the development or progression of cancer. However mineral supplements cannot replace surgery, chemotherapy or other cancer treatments. These mineral are necessary for the formation of a healthy immune system. In summary, selenium, zinc, molybdenum, vanadium and germanium are needed by the cancer patient in order to prevent and to increase the chances for natural immunological remission of cancer. If these minerals are taken in proper amounts these can be helpful in cancer therapy. In addition, taking mineral supplements along with anti-cancer medications can prove harmful, since minerals may decrease the efficacy of some pharmaceuticals. If you're interested in mineral supplements to fight cancer, consult a medical professional to determine the safety and potential benefits of mineral supplements for treating cancer condition.

REFERENCES


