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THERAPEUTIC APPLICATION OF SELENIUM COMPOUNDS AS POTENTIAL CHEMOTHERAPEUTIC AGENTS

M. A. Lavanya[1]*, Sowparnika Treasa Sabu[2] and Prof. Dr. Shaiju S. Dharan[3]

[1]Student, 5th Year PharmD, Ezhuthachan College of Pharmaceutical Sciences.

[2]Assistant Professor, Department of Pharmacy Practice, Ezhuthachan College of Pharmaceutical Sciences.

[3]Principal, Ezhuthachan College of Pharmaceutical Sciences.

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***Corresponding Author**
M. A. Lavanya
Student, 5th Year PharmD,
Ezhuthachan College of
Pharmaceutical Sciences.

ABSTRACT

Background: Cancer is one of the most devastating disorders of the 21st century. It is a disease caused by an uncontrolled division of abnormal cells in the body. Selenium (Se) metal was discovered by Jons Jacob Berzelius in 1817. It was discovered as a by-product of sulphuric acid synthesis. Selenium is well documented to inhibit cancer at higher doses. Selenium is generally known as an antioxidant due to its presence in selenoproteins as selenocysteine, but it is also toxic. The toxic effects of selenium are, however, strictly depends on concentration and chemical species. In this review, relevant forms of Se species especially focus on selenium nanoparticles and overview their potential functions and applications in oncology is organized. **Methods**: Previously published articles regarding the therapeutic application of selenium compounds as chemotherapeutic agent for improved cancer treatment have been collected and reviewed. **Observations**: The number of incidences related to cancer is expected to rise due to the changes in the lifestyle. Selenium deficiency is one of the risk factor. Experimental data suggest that catalytic oxidation of cellular glutathione and reduction of molecular oxygen are part of the mechanism of the antitumor activity of selenium. This provides provocative possibilities for the inclusion of selenium into cancer therapy regimens. Most of the studies failed to examine and establish correlation with the dynamics of selenoproteins. To make better use of Se compounds in cancer prevention and therapy and to understand the underlying mechanisms of the Se compounds further studies are thus warranted.

KEYWORDS: Selenium, Chemotherapeutics, Nanoparticle, Reactive Oxygen Species(ROS).

INTRODUCTION

Cancer is the second leading cause of death in both developing and developed countries. Globally, about 1 in 6 deaths is due to cancer. It mainly occurs due to 5 leading behavioural and dietary risk including high BMI, low fruit and vegetable intake, lack of physical activity, tobacco use, alcohol use. Also, economic impact of cancer is significantly increasing.

Selenium (Se) is an important trace element and it's average nutritional intake is 50–350 g/day.[1] Dietary selenium is predominantly in the form of organic compounds, primarily selenomethionine and selenocysteine, is usually ingested in the form of grains, meat, yeast, and vegetables. It plays a crucial role in human health and regulates many important cellular functions.

Se supplementation directly or indirectly exerts anti-oxidant functions and thereby increasing the cellular defense against oxidative stress. Chemical derivatives of Se include inorganic compounds like selenite and organic compounds like selenomethylselenocysteine and selenomethione.

There are 25 selenoprotein genes in human genome. Se is incorporated as selenocysteine (SEC) in various antioxidant enzymes like glutathione peroxidase (GPX), thioredoxin reductase (TXNRD) and selenoprotein P (SELENOP). Se acts as the redox centre of all these enzymes and is essential for their biochemical activity. Some of the other important Se containing compounds are sodium selenite, selenomethionine and monomethylated Se which can act as anticancer agents (mainly chemopreventive) by different mechanisms. Se or Se-containing compounds can be grouped into three main categories: inorganic, organic (also known as the organo-selenium compounds), and Se-containing nanoparticles(SeNPs).

Selenite is reported to trigger caspase-mediated apoptosis in association with DNA fragmentation, phosphorylation of JNK1/2 and p38 MAPK/SAPK2 along with mitochondrial superoxide generation in PC-3 cells. It is also reported to cause the G2/M cell cycle arrest and induction of apoptosis in HCT116 and SW620 colorectal carcinoma cells through Bax-dependent mitochondrial pathway.

Se has a narrow therapeutic window and the toxicity margins are very delicate whereas the nanoparticles of Se (SeNPs) possess remarkably reduced toxicity. The cytotoxic effects of all selenium compounds with effects against tumor cells are dependent on the appearance and regeneration of free selenols and selenolates, either chemically by the oxidation of any accessible thiols, protein bound or free (e.g., glutathione), or enzymatically generated by reductases as exemplified by the thioredoxin and glutaredoxin systems.

This work is aimed at systematically organizing the relevant forms of Se species with slightly more emphasize on SeNPs, and reviewing their recent developments and potential in cancer prevention and therapy.

SELENIUM NANOPARTICLES

Among different NPs, inorganic NPs of metals like Ag, Au, Ce, Fe, Se, Ti and Zn possess a significant place owing to their unique bioactivities in nanoforms. In case of Se, the major hurdle is the small therapeutic window with low margin of dosage error and the use of Se in the form of nanoparticles has overcome the toxicological concerns associated with Se. The major drawback of SeNPs is poor cellular uptake and can be overcome by conjugation of targeting ligands[2] on the exterior surface of nanoparticles. This provides a beneficial platform for anticancer therapy.

Internalized nanoparticles triggered ROS overproduction and induced apoptosis by activating p53 and MAPKs pathways. The nanomaterials overcame the multidrug resistance in R-HepG2 cells through inhibition of ABC family proteins expression[3] in cancerous cell. Effect of SeNPs on normal and cancerous cell is shown in ***fig.1***. Biogenic SeNPs represents more cytotoxicity on cancer cells compared to normal cells. *Bacillus licheniformis* derived biogenic SeNPs are very effective in inducing prostate cancer cell death at a minimum concentration of 2 µg Se/ml through a *TNF/IRF1* mediated necroptosis pathway and by *AR* down-regulation. The use of *Bacillus licheniformis* derived biogenic SeNPs for cancer chemoprevention is more successful and safest therapy.[4]

Based on the Auger- electron effect and Compton effect of Se atoms, cancer-targeted SeNPs in combination with ^{125}I seeds achieve synergetic effects to inhibit cancer-cell growth and colony formation through the induction of cell apoptosis and cell cycle arrest.[5] Bacillus licheniformis JS2 strain was used for the biosynthesis[6] of spherical SeNPs of an approximate size of 110 nm under aerobic condition in 1.8 mM sodium selenite stress.

X-ray responsive selenium nanoparticles were fabricated by using PEG as surface decorator and template. This nanosysytem (PEG-SeNPs) demonstrated X-ray responsive property that was attributed to its amorphous characteristics. Co-treatment of cancer cells with PEG-SeNPs[7] and X-ray enhance the cell growth inhibition through induction of cell apoptosis through DNA fragmentation and activation of caspase-3.

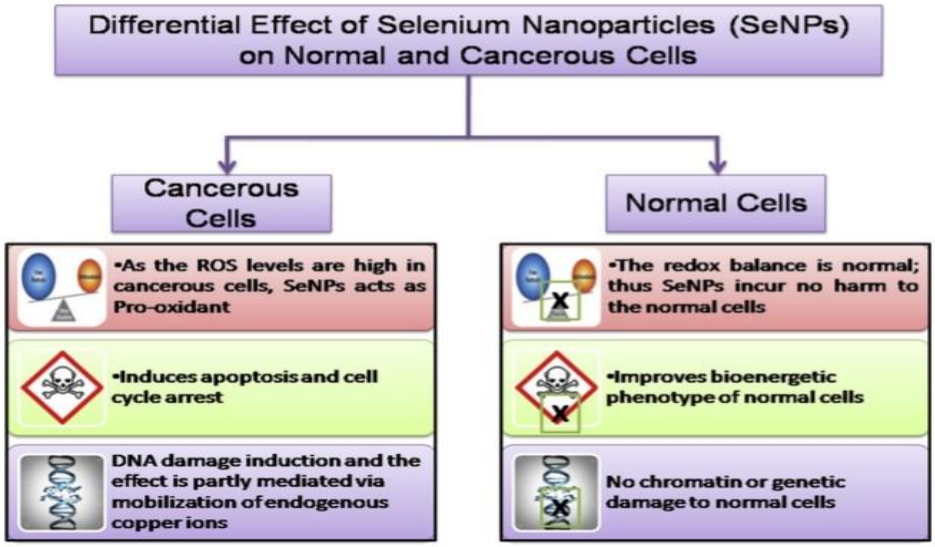

Fig 1: representing effect of SeNPs on cancerous and normal cells.

MECHANISM OF ACTION

The result from in vitro studies shows different mechanism of action among variable selenium compound. Four different pathways relating to cell proliferation and apoptosis are activated depending on the specific chemical form of selenium. First, selenium in the reductive pathway to selenide (seleno-digluatathione and hydrogen selenide) induce irreversible apoptosis with DNA strand breaks. Second, methylated forms of selenium appear to induce cell cycle arrest and/or apoptosis independent of DNA strand breaks. Third, selenite and methyl-selenic acid may induce changes in the microgen activated cell signalling pathways. Fourth, some forms of selenium such as the synthetic organo-selenium compounds benzylselenocyanate(BSC) and 1,4-pheynylenebis (methylene) selenocyanate(p-XSC) may be directly cytotoxic.[8]

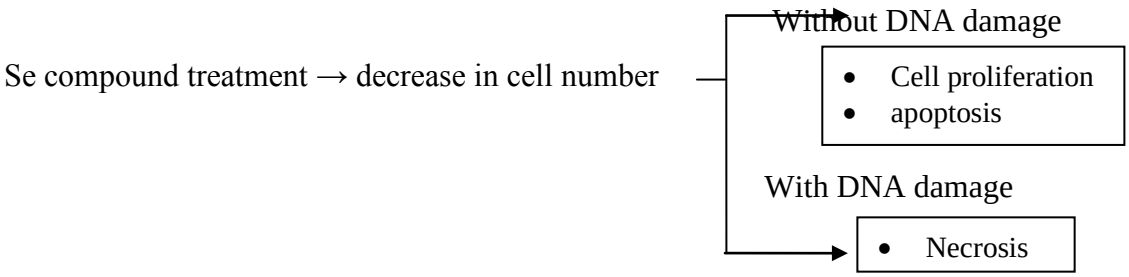

Fig.1: Figure representing mechanism of selenium compounds.

Methylselenic acid (MSA) induces Endoplasmic Reticulum (ER) stress[9] in normal and malignant cells but modultates apoptosis in a different manner. Capsase-8 was down regulated by MSA in a concentration dependent manner in normal PBMCs and was upregulated in malignant THP1 cells at the same concentration.

Dietary Se compounds are metabolized by several distinct pathways producing various Se metabolites, which, in turn, determine their specific biological activity. Amongst the metabolites produced, hydrogen selenide (HSe-) and methyl selenol (CH3Se-) act as pro-oxidants and. play a central role in redox cycling with glutathione (GSH) or the Trx/ Grx systems, producing superoxides and hydrogen peroxide, further resulting in ROS generation. The increased nucleophilic nature of these redox active Se metabolites confers high reactivity and therefore an efficient anti-cancer agent.

SELENIUM COMPOUNDS

Table 1: Cytotoxicity of selenium compounds against hl-60 human leukemia cells.

DRUG	IC $_{50}$ (µM)
Sodium selenite	29
Sodium selenate	>100
Selemocystine	10.5
selenomethionine	>100

Inorganic Se compounds

Sodium selenite exhibit good anticancerous effect and highly effective against peritoneal carcinomatosis by producing ROS and causes apoptotic response.[10] Selenosufate($SeSO_3^-$) have greater cytotoxic effects on cancer cells than selenite. The cytotoxic activity depends on the sensitivity of cells and also supplements like amino acids[11] and reductive state of extracellular environment. Hydrogen selenide(H_2Se) is an intermediate of se metabolism also trigger apoptosis of cancer cells.

Organic Se compounds

Organic Se compounds exhibiting anticancerous activity includes- selenides, selenocyanates, selenoaminoacid derivatives, methylselenic acid, Se-heterocyclic compounds. All these compounds exhibit action through various mechanism including reduction of oxidative stress, induction of apoptotic events, enhancement of chemotherapeutic drug activity. Organo-selenides down regulate the expression of Bcl-2 and up-regulate the expression levels of IL-2, IL-6 and CD40 especially in hepatocellular carcinoma.[12]

SCOPE OF REVIEW

This review aims in summarizing and providing the recent developments of our understanding of mechanism that underlie the potential anti-cancer effects of selenium compound and thereby they can be used as chemotherapeutic agent in a better way.

CONCLUSION

Selenium deficiency leads to cancer and thus selenium compounds can be used for the treatment of cancer. Se at higher doses readily can turn into a prooxidant and thereby exert its potential anticancer properties through multiple mechansim. They are not only used for the treatment of cancer but also have been proven to be useful in diagnosis, imaging, and non-cancer-related fields.

SeNPs possess all the properties required for clinical translation except their detailed safety owing to the small therapeutic window. Thus extensive preclinical safety studies are thus needed. In the present review, the importance of Se compounds (including organic, inorganic) over their elemental counterpart are highlighted. To conclude, in order to determine the potential of Se compounds as chemotherapeutic agent, further studies are required.

CONFLICT OF INTEREST

The author(s) declared no conflict of interest with respect to the authorship, research or publication of the article.

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