Organoselenium Compounds in Cancer Chemoprevention

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Abstract: Selenium is an important trace element involved in different physiological functions of human body. Knowledge of selenium in biology of cancer has increased at rapid rate especially during last two decades. Basic research and clinical studies involving animal models and more recently studies in human strongly support the protective role of selenium against various types of cancer. Selenium's role as an essential nutrient is as a result of its unique chemistry enabled by the presence of selenium in selenoproteins. Epidemiological findings have linked inadequate status of selenium to increased risk of cancer. The protective action of selenium is a combination of various mechanisms. Amongst all the diverse mechanism that have been proposed some important ones are (a) Protective role of selenoproteins / selenoenzymes (b) induction of apoptosis (c) immune system effects (d) detoxification of antagonistic metals (e) inactivation of nuclear transcription factor (f) regulation of lipoxygenases (g) effect on advanced cancer condition (h) reduction of oxidative stress (i) induction of Phase II enzymes (j) androgen receptor down regulation (k) inhibition of DNA adduct formation (l) cell cycle arrest. The purpose of this review is to focus the recent development in the field of cancer prevention utilizing selenium. The metabolism of selenium compounds , carcinogenesis studies, epidemiological data, and various proposed chemopreventive mechanisms of selenium compounds along with results of human intervention trials have been discussed.

Key Words: Selenium, cancer chemoprevention, apoptosis, immunomodulation, selenoenzyme, selenomethionine.

INTRODUCTION

Cancer is becoming an increasing significant disease all around the globe and is responsible for more than 7 million deaths worldwide [1]. As per the estimate of the American Institute of Cancer and World Research Fund, 40% of the all cancer of the world can be prevented by the combination of appropriate diet and physical activity [1]. Cancer chemoprevention is a relatively new approach in the management of cancer. Cancer chemoprevention coined by Sporn [2, 3] and coworkers in 1976 has been defined as a strategy for reducing cancer mortality and involves the prevention, delay and reversal of cancer by ingestion of dietary or pharmaceutical agents capable of modulating the process of carcinogenesis [4]. The nutrition related research of selenium (a metalloid classified in group VI A existing both in amorphous and crystalline state) is concerned it, started over seven decades ago. It was found that the plant-eating animals in South Dakota and Nebraska suffered from liver and nervous system injury because of selenium toxicity [5]. Countrywide selenium maps were constructed for United States of America on basis of the selenium contents in soil [6]. It was about five decades back that selenium was recognized as one of the essential nutrients in the nutrition of human. Schwarz *et al.* in 1957 recognized selenium as an essential nutrient in nutrition of animals and humans [7]. A large number of findings later have indicated that supplementation of selenium in the diet is inversely related to incidence of cancer. Majority of studies in numerous animal models have shown that intake of selenium above the dietary requirement can prevent cancer.

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Amongst all the micronutrients that have been studied so far selenium has emerged as a most successful factor with consistency in the protective nature against cancer. Most recently the knowledge of selenium in cancer chemoprevention has increased manifold with incoming of new and highly sophisticated biological tools. There have been numerous epidemiological and specific studies relating to potential clinical and molecular role of selenium in prevention of cancer. Significant inverse relationship between intake of dietary selenium and over all cancer risk has been reported. A substantial amount of basic carcinogenesis research on different animal models, clinical research, epidemiological data strongly support the protective role of selenium in cancer chemoprevention.

In this review an attempt has been made to summarize recent developments in the field of selenium related cancer chemoprevention. A number of studies and reviews are available, summarizing cancer chemopreventive potential of selenium but they are too specific [8-13]. We felt a need for a comprehensive review covering various aspects of selenium's cancer protective ability along with proposed action mechanism and major phase trials. Various epidemiological studies, metabolic pathway, experimental carcinogenesis to show cancer chemopreventive nature of selenium have been discussed in the present review. The article also highlights some of the existing gaps in understanding cancer chemopreventive role of selenium.

Role of Selenium Metabolites in Cancer Chemoprevention

There are many lines of evidence suggesting that metabolism is necessary for the anticarcinogenic activity of selenium compounds. Although there appears to be a lot of similarity between chemistry of selenium and sulfur however the interchangeability is not always possible in biological sys-

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tems. With better understanding of metabolism of selenium compounds with reference to their assimilation and detoxification, the significant role of critical selenium metabolites has been established. The metabolism of selenium is dynamic resulting in formation of a large number of products. Human and animals both synthesize many different intermediary metabolites in the course of converting inorganic selenium to organic forms. Methylation is a major pathway and as is evident from experimental studies that monomethylated forms of selenium have emerged as a significant metabolite against cancer. Selenium enters human body as selenomethionine or selenite. The metabolism of selenite and selenomethionine has been shown in the Fig. **1** [14]. Hydrogen selenide is a key metabolite, formed from inorganic sodium selenite as shown in Figure. It is reasonable to believe that intermediary metabolism of the administered selenium compound ultimately produces critical metabolites responsible for cancer protection. Since the forms of selenium that are readily converted to dimethyl selenide and trimethyl selenonium are to be avoided as they are excreted making it poor choice for anticarcinogenesis. Demethylation of dimethyl selenide and trimethyl selenonium has been accepted as important concept in selenium metabolism [15-17].

It has been suggested that selenium compounds that are able to supply a steady stream of methylated metabolites particularly the monomethylated ones are good chemopreventive agent. The reason is that these compounds have an escape mechanism *via* random incorporation into proteins, or rapid conversion to dimethyl selenide and trimethyl selenium. It was first shown by Ganther that selenium is metabolized by animals resulting in the formation of dimethyl selenide. As far as the release of monomethylated selenium species a ß-lyase-mediated reaction is needed to free the species from Se-methylselenocysteine or its selenoxide form.

$$CH_3SeCH_2CHNH_2COOH \longrightarrow CH_3SeH + pyruvate + NH_3$$

$$CH_3SeOCH_2CHNH_2COOH \longrightarrow CH_3SeOH + pyruvate + NH_3$$

A large number of researchers have shown the importance of small molecular weight metabolites of selenium in cancer chemo prevention. Nakamuro *et al.* evaluated the methylated selenium metabolites after oral administration of various selenium compounds and concluded that CH_3SeH can be directly formed from selenomethionine by action of γ-lyase [18]. Stored form of the selenium *i.e.* γ glutamyl selenomethyl (Se Me)-Se-cysteine present in *Brassica* and *Allium* families gets metabolized to SeMe-SeCys which is acted upon by β-lyase to give CH_3SeH directly. Precursor of CH_3SeH typically methyl selenic acids in experimental *in vitro* systems have been shown to induce apoptosis as discussed later in the text.

Chemical species specific metabolic pathway for selenium was explained by the metabolic regulation through selenide as common intermediate for inorganic and organic selenium sources [19]. Selenium in form of selenodiglutathione is enzymatically reduced by glutathione reductase and NADPH to yield H_2Se. The reduction proceeds *via* two steps, the first of which results in the production of selenopersulfide, GSSeH, followed further by a NADPH linked reduction to yields H_2Se. Chemopreventive activity of selenobetaine and Se-methylselenocysteine has been evaluated and dose dependent inhibitory response to both these compounds has been reported [20]. Studies have shown that intake of selenomethionine rich diet by animals causes a greater tissue accumulation of selenium than other forms of selenium [21].

Selenobetaine methyl ester has been found to be highly efficient in inhibiting carcinogenesis. Foster *et al.* have studied dimethylselenoxide and selenobetaine methyl ester supplementation in diet [22]. These two compounds have been reported to preferentially enter the metabolic pathway at the dimethylselenide step. Dimethylselenoxide has been found to be less active in chemoprevention of cancer, which can be explained on its facile reduction to volatile dimethylselenide thus leading to excretory pathway [23]. Selenobetaine and Se-methylselenocysteine is converted to methylselenol. Trimethylselenonium as shown in the Fig. **1** is an end product of selenium metabolism excreted in the urine. Ip *et al.* have shown that the supplementation of trimethylselenonium is totally ineffective in cancer chemoprevention [24]. In a significant study Foster *et al.* have shown demethylation of trimethylselenonium resulting in the formation of dimethylselenide. Arsenic induced demethylation can be the reason for increased efficacy of dimethylselenide [25].

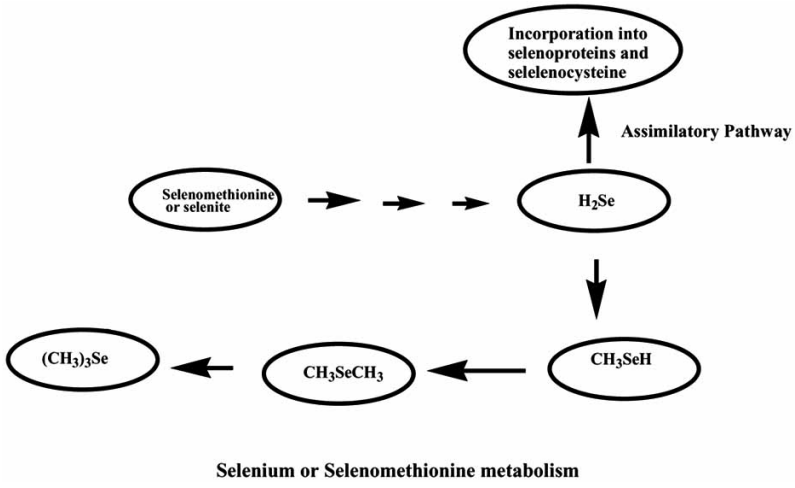

Fig. (1). Selenium or Selenomethionine metabolism.

EPIDEMIOLOGICAL STUDIES

There have been numerous epidemiological studies, which strongly support protective action of selenium against prostate, lung, colorectal, stomach and other cancers. Majority of epidemiological studies strongly suggest protective role of selenium against various types of cancer. The epidemiological findings have come as a much encouragement in the possible use of selenium compounds as potential cancer chemopreventive agents. In one of the pioneering studies, Shamberger and Frost compared the human mortality rates in various regions having different selenium concentration in locally grown forage crops [26]. Lesser deaths were reported from areas with high concentration of selenium as compared to regions having low concentration of selenium. Significant findings by Shamberger *et al.* suggested that inverse relationship existed between death rates in humans and concentration of selenium in the forage crops in California [27,28]. The parts of the human body that would come into direct contact with dietary selenium, such as pharynx, esophagus, stomach, bladder and intestine, showed a substantially lower rate ratio of cancer incidence in the cities having high selenium concentration plants as compared to the one having low concentration. There have been scores of other ecological studies, which have correlated cancer related deaths to the deficiency of selenium in different geographical areas all around the globe. A Dutch study carried by van den Brandt *et al.* showed that individuals with lowest quartile of toe-nail selenium were 2.5 times more likely to develop lung cancer than those in higher quartile, however no relationship was found for cancers of stomach, colon and rectum [29,30]. In an investigation dealing 27 county comparisons it was found that the per capita Se intake was inversely related to the total cancer mortality [31]. Yu and colleagues showed that cancer mortality incidence due to various cancers was inversely related to the selenium level in China [32].

The fact that dietary selenium intake in Finland is much less than in United States but still the mortality rates for breast, cancer and large bowel cancer is much higher in United States. This suggests that incidence of cancer is influenced by various other food constituents, selenium being one of the factor [33]. Perspective studies from Finland suggested an inverse relationship between selenium status and risk of cancer [34]. A prospective study in the US also concluded an inverse relationship between cancer risk and selenium status [35]. In subgroup analyses based on the average selenium level in the study population it has been suggested that selenium may have some protective effect against lung cancer in populations where average selenium levels are low [36]. A nested case–control study was conducted to examine the associations of α-tocopherol, γ-tocopherol, and selenium with incidence of prostate cancer. Statistically significant protective associations for high levels of selenium and α-

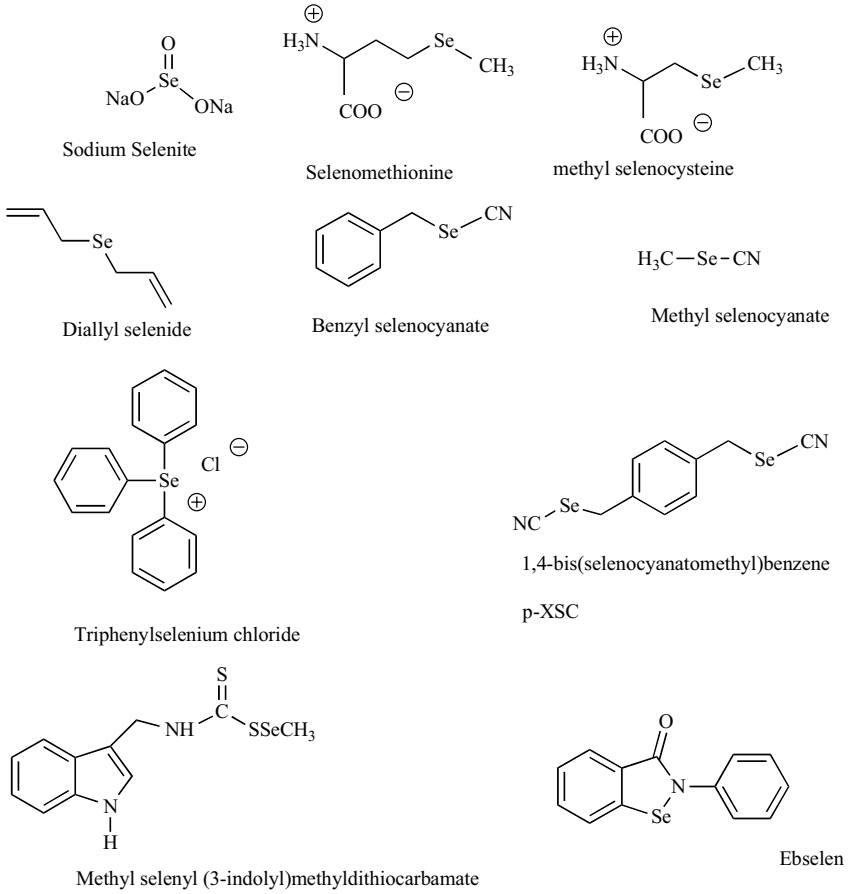

Fig. (2). Structures of selenium compounds tested for cancer chemopreventive activities.

tocopherol were observed [37]. Majority of geographic and epidemiological studies of cancer incidence in groups have shown a trend for individuals with lower selenium levels (blood and nails) to have a higher incidence of several different types of cancer. In a major study amongst Taiwanese men, decreased plasma selenium concentration was associated with increased risk of liver cancer [38]. Case control studies conducted in men with prediagnostic plasma selenium level in the lowest quartile were four to five times more likely to develop prostate cancer [39]. Within a perspective study of more than 9000 Japanese American men; a case control study concluded that the risk of developing prostate cancer was 50% less in men with selenium level in the highest quartile compared to those in lower quartile [40]. Case control study within a perspective study of 50,000 male health professionals in US found a significant inverse relation ship between toe nail selenium content and risk of prostate cancer [41]. The hypothesis that low selenium may be a risk factor for cancer of lungs was evaluated by Knekt *et al.* in case control study. The findings suggested that low selenium status may be a risk factor in lung cancer [42a]. The association of serum selenium with the subsequent risk of death from cancer was investigated in a case-control study that was nested in a prospective nine-year follow-up study in the Netherlands. A medical survey was conducted with an enrollment of 10,500 subjects in Zoetermeer. The data generated from this study showed an increased cancer risk associated with low selenium level however amongst women no substantial effect was visible [42b].

Although majority of studies show protective effect of selenium against different cancer there are a couple of studies, which have shown that there is no substantial relation between concentration of selenium and the incidence of cancer. In a perspective study of more than 60,000 female nurses in United States no relation was found between toe nail selenium level and total cancer incidence [43]. Coates *et al.* conducted a nested case-control study to study the correlation between serum levels of selenium and retinol and the incidence of cancer [44]. It was found that serum levels of selenium or retinol do not have any appreciable effect on cancer incidence. Investigations were carried by Allen *et al.* to study the association between the selenium level in fingernails and prostate cancer risk in a case-control study among 656 British subjects [45]. The finding suggested no strong association between selenium with prostate cancer risk in British men. Good man *et al.* has analyzed the Se serum concentration in 356 Carotene and Retinol Efficacy Trial (CARET) participants [46]. It was found that there was no substantial relationship between selenium concentration and cancer incidence. A case control study involving 164 subjects was conducted to study relationship of plasma selenium and activity of glutathione peroxidase. It was concluded that there was no substantial relationship between level of selenium and glutathione peroxidase activity [47]. In a similar study no association was noticed between toe- nail selenium cancer of breast and prostate however statistically significant inverse association between toe-nail selenium level and the risk of colon cancer for both genders combined was observed [48]. In a study conducted dealing with breast cancer patients it was found that protective role of selenium was much less as compared to vitamin C and E. There was an 84% and 77% lower risk of breast cancer if the levels of vitamin C and vitamin E were increased by 1 unit, respectively. Similarly, there was a 7% lower risk of breast cancer if the level of selenium was increased by 1 unit [49]. A case control study to examine concentration of selenium and zinc in nail tissue concluded that toe- nail selenium was not in anyway connected to the risk of oral cancer [50].

Carcinogenesis Studies

Protective role of selenium in the prevention of cancer has been well established by numerous *in vitro, in vivo,* studies in different models. The experimental data generated on various animal model and cell lines demonstrates significant beneficial effect of selenium in cancer chemoprevention.

In one of the pioneering studies, Ip *et al.* evaluated cancer-protecting effect of selenium in the initiation and promotion phase of 7,12-dimethylbenz[a]anthracene induced mammary carcinogenesis in rats [51]. It was suggested that selenium is not only capable of inhibiting initiation and promotion phase of carcinogenesis but also effective as an adjuvant chemotherapeutic agent.

The synergistic effect of Vitamin E and selenium in chemoprevention of mammary carcinogenesis was investigated in rats and it was found that vitamin E, although ineffective by itself, was able to potentiate the ability of selenium to inhibit the development of mammary tumors induced by DMBA in rats [52]. It has been shown that sodium selenite inhibits the binding of DMBA to DNA in the tertiary cultures of fetal mouse, however the action is selective and inhibits the induction process [53]. In a detailed study conducted to explore the synergistic mechanism of selenium and vitamin E; the chemopreventive efficacies of selenite and selenomethionine were examined in rats during carcinogenesis induced by mammary tumor model and it was found that vitamin A enhanced the protective effect of selenite [54]. The effect of retinoid and selenium supplemented diets in pancreatic and liver carcinogenesis was examined in rats induced by aza serine. It was found that although retinoid inhibited the pancreatic carcinogenesis, it was more effective when used in combination with selenium [55]. However in liver, it was noticed that retinoid alone inhibited carcinogenesis but when combined with selenium it was ineffective. Selenium alone was found to be ineffective when used alone in both the cancers. An inverse relation between the incidence of liver cancer and selenium content in the blood was observed in Jaingsu province of China [56]. The authors on basis of their experimentation on animal models, exposed to aflatoxin B1 suggested a protective effect of selenium supplementation on the cellular DNA damage.

In a detailed investigation of the chemopreventive action of sodium selenite, magnesium chloride, ascorbic acid and retinyl acetate given singly or in combination on mammary carcinogenesis induced by 30 mg of DMBA in female adult rats, Ramesha *et al.* found that each modulator was able to reduce the tumor incidence by itself however with the concurrent use of all four modulators the tumor incidence was reduced to 12% [57]. Hussain *et al.* studied the impact of selenium supplementation on precancerous and cancerous lesions in the cervical epithelium induced by methyl cholan-

threne [58]. The effect of selenium administration through drinking water was visible as the incidence of cervical was 37% as compared to 72% in the control mice. In a study to see the effect of excess selenomethionine on selenium status Hawkes *et al.* treated forty pregnant macaques with L-selenomethionine and analyzed plasma selenium and glutathione peroxidase specific activities. It was found that the activity was directly related to the selenomthionine intake [59]. Ip *et al.* evaluated the nutritional bioavailability of selenium from the selenium enriched garlic by using two liver selenoenzyme as biomarkers: glutathione peroxidase and type I 5′ iodinase [60]. The studies found that selenium enriched garlic was just as effective as selenite as far as the restoration of activity of both these enzymes is concerned. Vadhanavikit *et al.* studied the effect of sodium selenite and methylated selenium compound administered at cancer chemoprevention levels in the rat [61]. It was found that animal body has remarkable capabilities for inter converting selenium and a significant amount of it was retained in the tissues of body. It was concluded that the high protective activity of cancer is due to excessive excretion of methylated selenium.

In a study to evaluate the activity of 1,4-phenylenebis(methylene)selenocyanate (*p*-XSC), cell lines of mouse mammary carcinoma cell lines were used. Treatment with *p*-XSC caused a 3-to 6-fold greater accumulation of selenium within cells than did treatment with equivalent amounts of selenite.In addition cells were able to better tolerate higher cellular levels of selenium derived from *p*-XSC [62]. In another study by Lu *et al.* to evaluate the effect of synthetic triphenylselenonium chloride in mammary cell culture model it was also inferred that triphenylselenonium represented a new type of selenium compound that had a distinct mechanism from those induced by selenium. It was further found that the *p*-XSC caused greater accumulation of selenium within cells [63]. In a study by El Bayoumy *et al.* it was demonstrated that that *p*-XSC inhibited mammary tumor development induced by DMBA during the initiation and post-initiation phases of carcinogenesis in female rats. Inhibition of cell growth and apoptosis was also noticed in mammary carcinoma cells. *p*-XSC was found more effective than selenite and sulfur analog [64]. Short *et al.* synthesized two new classes of selenazolidine carboxylic acids as latent forms of selenocysteine [65] (Fig. **3**).

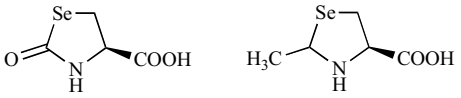

Fig. (3). Selenazolidine carboxylic acids.

Results indicate that the *p*-X SeSG administered during the post initiation phase significantly inhibited the incidence and multiplicity of AOM induced colon adenocarcinoma. In an effort to study the to see the effect of triphenylselenonium chloride supplementation on glutathione peroxidase or thioredoxin activities it was found that although it could lead to suppression of mammary tumorigenesis by 50% there was no effect on the enzyme activity. The authors evaluated the effect of sodium selenite (Na_2SeO_3) or L selenomethionine and observed differential dose-dependant growth inhibition and apoptosis within cancer prostate cancer cells. L selenomethionine caused an increase in arrest in the G2-M phase of the cell cycle [66].

Ip *et al.* found that triphenylselenonium chloride suppressed mammary tomorigenesis by approximately 50% irrespective of the selenium status and it was also suggested that chemopreventive mechanism for triphenylselenonium chloride is not related to selenoprotein synthesis [67,68]. During the *in vitro* testing in mouse mammary epithelial cells both Se-allylselenocysteine and Se-propylselenocysteine have been shown to be very active. ASC was found to increase the rate of apoptosis and oxidation of pyrimidines. On basis of *in vitro* experiments it was found that methylselenic acid was more potent than methyl selenocysteine in inhibiting cell accumulation and inducing apoptosis in mouse mammary epithelial cells [69]. Cytocidal response of the sodium selenite in MCF-7 human breast adenocarcinoma cells was examined. Selenium resulted in inhibition of DNA synthesis as observed by cell cycle analysis. Fragmentation of DNA was also noticed with relatively higher concentration [70].

Experimental studies designed to evaluate the efficacy of combined regimen of oxidants namely alpha-tocopherol, ascorbic acid and selenium, have revealed significant lower development of neoplasm in-group of animals receiving alpha-tocopherol and selenium supplementation [71]. Sohn *et al.* examined the cancer chemopreventive activity of *p*-XSC and its analogs on xenobiotic metabolizing enzymes. The level of glutathione S-transferases in liver kidney lungs was found to increase. Increased level of glutathione peroxidase was also noticed in colon and mammary glands [72].

The organoselenium compounds benzylselenocyanate (BSC) and *p*-XSC as well as sodium selenite have been found to be effective against tumors in animal models at both initiation and post initiation stages as evident by the inhibition of excess DNA(cytosine-5)-methyl transferase [73]. Seleno methionine treatment inhibited tumor growth, induced apoptosis and resulted in decrease of polyamine concentration in A549 and HT 29 cancer cell lines [74]. The effect of selenium compounds was examined on the expression levels of growth arrest and DNA damage-inducible (gadd) genes. Experiments revealed time-dependant and selenium species-specific induction pattern for gadd genes [75]. Experimental studies have suggested that dietary supplementation with selenium compounds can inhibit development of colon cancer (namely *p*-methoxynenzylselenocyanate, and 1,4 phenylenebis(methylene)selenocyanate (*p*-XSC). Both these agents were tested with low and high fat diets. It was found that both of these agents are effective in inhibiting colon cancer [76].

The chemopreventive effect of dietary selenium (as sodium selenite or as Se-rich egg) on mouse skin tumor induced by the topical application of 2-(4-nitrophenoxy) oxirane, as tumor initiator and 12-O-tetradecanoylphorbol-13-acetate (TPA) as promoter was evaluated. The studies concluded that selenium proved to be effective chemopreventive agent at the promotional stage [77]. As a part of program directed towards developing lesser toxic selenium compounds benzyl selenocyanate, and its *o-m, p* nitro isomers, dibenzyldiselenide, *ortho, meta* and *para* isomers of XSC,

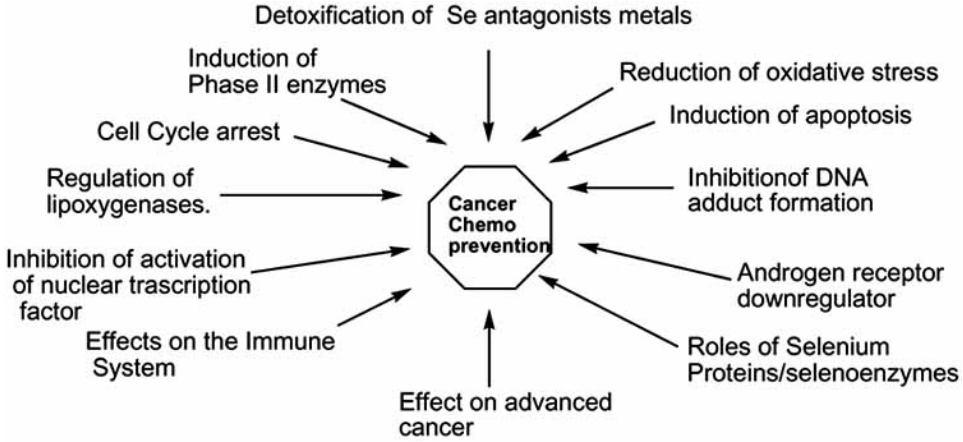

Fig. (4). Possible Mechanism of Cancer Chemoprevention by Selenium.

were synthesized and evaluated and it was found that these compounds were inhibiting crypt multiplicity during the initiation phase and during post initiation phase [76]. Cytogenetic *in vitro* testing of organoselenium compounds and its sulfur analogs has been carried in rat bone marrow culture cells and it was found that the data reflected higher activity of the selenium compounds as compared to its sulfur analog. [78].

In an effort to compare the effect of organic and inorganic selenocyanate derivatives against DMBA induced mammary carcinogenesis it was found that XSC is not efficiently incorporated into glutathione peroxidase as the selenium from selenite [79]. Cao *et al.* have carried out detailed studies on athymic nude mice having human squamous cell carcinoma of the head and neck and colon carcinoma xenografts to evaluate the potential role of selenium-containing compounds as selective modulators of the toxicity and antitumor activity The protective role of selenium thus established in this model [80]. In a study dealing with the metabolism of various methylated selenium compounds it was concluded that high anticarcinogenic effect is associated with extensive excretion of methylated selenium metabolite [81]. Karunasinghe *et al.* have studied the relation between the stability of DNA and the serum selenium level in a high-risk group for prostate cancer [82]. The dietary effect of benzylselenocyanate and its sulfur analogs were investigated [83] and it was noticed that the inhibition by BSC was 68% as compared to 35% by BTC. Synergistic effects of various chemopreventive agents $Na_2Se_2O_3$, 1% BHT and 0.5 β-carotene was noticed in DMBA induced carcinogenesis in rodents [84]. Positive effect of dietary methoxybenzeneselenol, a new organoselenium compound was evaluated on AOM induced female F-344 rats [85].

In an excellent review, El-Bayoumy and colleagues have discussed molecular mechanism for cancer chemoprevention using microarray analysis. It was proposed that dose and form of selenium are important determining factor in cancer chemoprevention. Regulation of Phase II detoxification enzymes, cell cycle arrest in G1 phase along with inhibition of CYCLIN A, CYCLIN D1, CDC25 A, CDK4, PCNA, and E2F gene expression may contribute to the cancer protecting effects of selenium [86]. Shah *et al.* have shown that the MSA inhibited the estrogen receptor signaling in ER positive MCF-7 breast cancer cells as evidenced by decreased estradiol dependant cell growth [87]. Organic compound MSA was found to potentiate growth inhibition by 4-hydroxytamoxifen in different cell lines. Thirunavakkarasu *et al.* studied activity of sodiumselenite in lymphocytes obtained from the hepatoma bearing rats on DNA damage in correlation with oxidative stress [88]. The study explained the association between anti-peroxidative effect of selenium and cancer chemopreventive property. Gasparain *et al.* have forwarded that targetting of Nf-κB activation pathway by selenium as one of the mechanism to explain the cancer protecting nature of selenium compounds. It has been shown that sodium selenite and methyl selenic acid (MeSeA) induced apoptosis and inhibited Nf-κB DNA binding in prostate cells [89]. The data generated in the lab of Antonio *et al.* suggested that induced cell growth inhibition might be, in part, mediated by COX-2 dependent mechanisms. Se-Met suppressed COX-2 RNA level in HCA-7 cells [90]. It was shown that SeMet could activate p53 by a redox mechanism independent of DNA damage. At the selenium concentrations used, within the physiological range of clinical studies p53-dependent DNA repair was activated [91]. In order to critically address the issue of p53 requirement for the apoptosis Jiang *et al.* have investigated the human prostate cancer cells cancer cells containing a wild type p53. It was found that p53 Sort 15 P was involved in activating the apoptosis involving both the caspase-8 and caspase-9 pathways in the cells [92]. Selenium was found to be effective in individuals with high risk of malignant mesotheliomas (MMs) [93]. Wycherly *et al.* suggested that high dietary intake of inorganic selenium may promote *in vivo* DNA oxidation instead of inhibiting oxidative DNA damage [94]. Role of selenium as cancer chemopreventive agent may be in part due to its role in regulating GPX1 [95]. Studies have shown that site specific phosphorylation of AKT declined and levels of gadd 445, a DNA damage response, increased significantly as a consequence of elevated GPx –1 expression.

Detailed investigations were conducted by Thompson *et al.* to determine the effect of dietary level of selenium on the induction of tracheal cancer by 1-methyl –1-nitrosourea (MNU). It was found that there was no significant difference among groups in the incidence of either benign lesions or carcinomas and distribution of the tumor type was not in any

way related to selenium treatment [96]. Although majority of experimental research studies have established protective effect of selenium against cancer; there have been some studies, which have reported absolute, no relationship between carcinogenesis incidence and selenium intake.

Pence and Buddingh, showed that dietary selenium deficiency in diet had no effect on the incidence and size of 1,2-dimethylhydrazine-induced colon tumors in rats [97]. Similarly, Beams demonstrated that dietary level of selenium had absolutely no influence on the tumor response in the respiratory tract and other organs of hamster after the intratracheal instillation of the indirect-acting carcinogen benzo(a)pyrene [98]. In other study by Bergman *et al.* the increased intake of selenium had no effect on the incidence of stomach tumor [99]. Similarly Aquino *et al.* found that 2μg of selenium per gram of diet had no inhibitory effect in rat model of hepatocarcinogenesis induced with diethylnitrosamine [100].

MAJOR HUMAN INTERVENTION TRIALS

Deficiency of selenium has been associated with an increased cancer risk, and several clinical and animal trials have suggested that improved selenium nutrition may reduce the incidence of several kinds of cancers. Encouraging results from the selenium cancer chemoprevention studies has resulted in several large-scale human intervention trials all around the globe. Majority of these trials have been supportive of the chemopreventive action of selenium. One of major trial was conducted in Quidong county China, which is one of the regions in the world having very high rates of primary liver cancer (PLC). The intervention trial was conducted by Yu *et al.* among the general population involving about 130,000 subjects and the population was observed for the protective effect of selenium against liver cancer [101]. The evaluation consisted of an 8-yr follow-up study showing reduction in PLC incidence by 35.1% in selenized table salt supplemented *vs.* the no supplemented population. Increase in the incidence rate of cancer was noticed on withdrawal of selenium supplementation. The study also suggested that a continuous intake of Se was important to sustain the chemopreventive effect.

A double blind, randomized, placebo-controlled cancer prevention trial was conducted by Clarke *et al.* to determine the cancer chemopreventive effect of selenium supplementation in the diet. Around 1300 individuals were enrolled in the studies [102]. The studies concluded that selenium treatment had no protective role against development of basal or squamous cell carcinomas of the skin. Secondary end-point analyses did support that selenium may reduce the incidence of carcinomas of various sites. A very large scale major human intervention trial sponsored by the National Cancer Institute, the protecting effect of selenium (200 m g L-selenomethionine) and Vitamin E (400 mg DL-a -tocopherol) alone or in combination in prevention of prostate cancer is currently being studied. The Selenium and Vitamin E Cancer Prevention Trial (SELECT), is a phase III randomized double-blind placebo-controlled trial designed to test efficacy of selenium. Involving more than 32,000 male volunteers, the final results of this trial are expected in 2013 [103].

In a trial in western Indian state of Maharashtra, it was concluded that increased selenium level is associated with decreased cancer incidence and decreased cancer mortality. The study was aimed at finding the relationship of selenium level with site, extent of disease, recurrence of disease, histopathological diagnosis, anemia and serum protein level of cancer patients. One hundred patients were selected and plasma selenium level were studied in and mean selenium level of 75.35 ng/ml in cancer patients was significantly less than control values (116.99 ng/ml) in normal healthy individuals ($P < 0.003$). The strongest association of plasma selenium level and cancer was found in cancer breast (70.50 ng/ml) and gastrointestinal tract (73.05 ng/ml) cancer [104].

A nutrition intervention trial was conducted in Linxian, China to study the effect of supplementation with specific vitamin/mineral combinations on cancer incidence and disease related mortality. The population of Linxian County, China, has one of the world's highest rates of esophageal/gastric cancer and a persistently low intake of several micronutrients. [105]. One of the combinations of the nutrient was beta-carotene, vitamin E, and selenium. Doses ranged from one to two times U.S. recommended daily allowances. Significantly lower total mortality occurred among those receiving supplementation with beta-carotene, vitamin E, and selenium. The reduction was mainly due to lower cancer rates especially stomach cancer. The reduced risk was noticed to arise about 1–2 years after the start of supplementation with these vitamins and minerals. Another prostate cancer prevention trial (APPOSE) involving selenium is underway in Australia [106]. It would test the hypothesis that daily dietary supplementation with selenium reduces prostate cancer incidence in a population of male subjects who are at increased risk.

The Wheat Bran Fiber Trial (Martinez 1998), Polyp Prevention Trial (Alberts *et al.* 2000), the phoenix, colon cancer prevention physician network program (Schatzkin *et al.* 2000) and the Polyp Prevention Study (Greenberg *et al.* 1994) were 3–4-year interventions in subjects that had recently undergone adenoma removal, 1763 of whom had baseline serum or plasma Se levels measured. Analysis of pooled data showed that the subjects with baseline serum or plasma Se in the highest quartile when compared with those in the lowest quartile had a significantly lower risk of adenoma. These results support previous findings that are suggestive of a beneficial effect of higher Se status on colorectal cancer risk [107-110].

Mechanisms of Cancer Chemoprevention by Selenium

From the late 1960s and early 1970s selenium intake was related to decline in the cancer mortality. Cancer protective effect of selenium was evident initially mainly on basis of ecological and correlation studies. The chemopreventive protective action of selenium occurs at systemic, cellular and molecular level. The anticarcinogenic effect of selenium depends on its chemical form, and dosage. The element is supposed to exert its anticancer action on molecular level in different ways. Studies have indicated that protecting action of any chemopreventive agents may not be attributed to a single mechanism, similarly the chemoprevention activity of organoselenium compounds may be explained on the basis of various mechanisms. Some of the major mechanisms proposed for chemopreventive activity shown in the Fig. (**3**).

Literature survey reveals a number of mechanisms that have been proposed to explain anticancer effect of selenium; amongst them the important ones are (a**)** Protective role of selenoproteins and selenoenzymes (b) induction of apoptosis (c) immune system effects (d) detoxification of antagonistic metals (e) inactivation of nuclear transcription factor (f) regulation of lipoxygenases (g) effect on advanced cancer condition (h) reduction of oxidative stress (i) induction of Phase II enzymes (j) androgen receptor down regulation (k) inhibition of DNA adduct formation (l) cell cycle arrest.

(a) Roles of Selenium Proteins

There are about twenty-five human selenoproteins believed to be involved in antioxidant and anabolic processes. Selenium is an essential part of enzyme glutathione peroxidase (GPx1, GPx2, GPx3, and GPx4). The glutathione peroxidase is a antioxidant enzyme involved in removal of hydroperoxides and lipid hydroperoxides which is critical in the enzymatic chemopreventive action of selenium [111]. Another selenoprotein P is antioxidant and acts as a scavenger for peroxynitrite particularly at the endothelium [112]. Besides thioredoxin reductase (1, 2 and 3) is another important class involved in regeneration of anti-oxidant systems, maintenance of intracellular redox state, reduction of nucleotides in cell synthesis. It has been also found to be critical for cellular viability and proliferation [113]. Behne *et al.* have shown chemopreventive nature of another selenoprotein 15 kDa against development of carcinoma in human prostate cells [114].

(b) Detoxification of Se Antagonists' Metals

A number of metals (Cd, As, Zn, Hg, Pb) occurring in the environment contaminate food, drinking water and environment. These metals compete with Se intake thus reducing or completely abolishing the cancer protecting property of selenium under normal physiological conditions. Sugaware *et al.* have reported protection against cadmium induced peroxidative damage [115]. Nelson *et al.* have shown that the supplementation by selenite decreases the expression of MAZ, the c-myc-activating zinc finger protein that is involved with activation of the oncogene c-myc, in HT29 human colon adenocarcinoma cells [116].

In one of the interesting findings amongst tannery workers, who during their working shift were exposed to an atmosphere containing chromium compounds, concentration of Se in blood and blood plasma was lower than in people who are not occupationally exposed to chromium compounds. The fact that diet of the people living in that area could be considered identical as far as selenium concentration was concerned it could be inferred that exposure of chromium was responsible for low selenium concentration [117a]. The differential effects of arsenic compounds and the effect of selenium on arsenic-induced changes in cytotoxicity, viability, and cell cycle of porcine aorta endothelial cells (PAECs) were investigated. An increased G2/M phase was observed in $NaAsO_2$-treated PAECs, however there was increase in secondary necrosis (late apoptosis) in As_2O_3-treated PAECs [117b]. In a key study to evaluate the supplemental selenium in areas having higher arsenic levels and low selenium level it was found that the 300 μg of selenium increased plasma glutathione peroxidase (GSH-Px) activity and reduced the concentration of lipid hydroperoxides. Thus the detoxification of Se antagonistic metals through the formation of metal selenides and protein complexes is an important mechanism. One of the key conclusions is that the selenium protecting effects of selenium are not absolute, it depends to a large scale on the Se antagonistic elements in the system. Schrauzer *et al.* found out that addition of arsenic to the drinking completely removed the anticarcinogenic effect of selenium [118].

(c) Inhibition of Activation of Nuclear Transcription Factor

One other important mechanism by which selenium can act as anticarcinogenic agent is by activation/inactivation of nuclear transcription factor [119]. Flohe *et al.* found that selenium is involved in the inhibition of nuclear transcription factor resulting in the cancer protecting property [120]. Inhibition of activation of NFκB is further associated to the sensitization of tumor necrosis factor (TNF)-α which in turn is known to have cytotoxicity against variety of tumor cells. In another study conducted by Otsuka and his colleagues it was found that inhibition of activation of nuclear transcription factor $nF_{\dot{K}}B$ activation confers sensivity to tumor necrosis factor α by impairment of cell cycle progression in human glioma cells [121].

(d) Effect on Immunity

Both the innate and acquired immune systems are influenced by selenium [122]. The supplementation of selenium enhances lymphocytes response ability to mitogen and facilitates neutrophil chemotaxis [123]. One of the most investigated effects of selenium on the immune system is its effect on neutrophil function. It's been found that neutrophils from selenium deficient rats and cattle have low ability to kill pathogens than the neutrophils from selenium sufficient animals. The defective function may be attributed to the decreased cystolic GPx (GPx1) activity of neutrophils. Selenium deficiency can favor formation of pro-inflammatory compounds that would predispose towards disease such as heart disease and cancer [124].

(e) Effect of Selenium on Advanced Cancer Condition

There are a number of studies, which support the inhibitory effect of selenium on advanced cancers (cancer progression and metastasis). In a study dealing with serum selenium level and risk of prostate cancer Nomura *et al.* [125] have suggested that effect of selenium was more pronounced during advanced stage than the primary stage. Another perspective study by Li *et al.* has confirmed enhanced protective effect of selenium on the tumor spread [126].

In a series of findings by Jiang *et al.* vascular endothelial growth factors (required for the progression and metastasis) are significantly lowered as a result of selenium supplementation [127-129]. They also found that significant lower level of vascular endothelial growth factor expression was observed in sizable portion of selenium treated carcinomas as compared to untreated control and thus it was shown that inhibition of angiogenesis might be the one of the contributing mechanism.

(f) Induction of Apoptosis

Selenodiglutathione (SDG), the initial metabolite of selenite, is shown to be a more powerful inhibitor of cell growth *in vitro* than selenite itself [130a]. Unni *et al.* have found that selenium methyl selenocysteine a naturally occuring selnium compound induced apoptosis after a cell growth arrest in S-phase [130b]. Wang *et al.* have shown that methylselenol was responsible for caspase-mediated apoptosis [131]. In order to provide insight to the mechanistic aspect of apoptosis induction by selenium Ghosh and colleagues have investigated the signal transduction pathways affected by selenium compounds in biopsies of normal human oral mucosa cells and human oral squamous carcinoma cells using a primary culture system [132]. Medina *et al.* who suggested that the chemopreventive activity of se-methyl selenocysteine could partly be explained by its capacity to induce apoptosis reported a similar finding. Exposure of DU 145 cells to methylselenic acid resulted in profound G1 arrest, DNA fragmentation and caspase mediated cleavage of poly (ADP-ribose)polymerase resulting in apoptosis [133].

(g) Reduction of Oxidative Stress

Oxidative stress can be described as a condition when the generation of reactive oxygen species (ROS) in a system exceeds the ability of the subject to neutralize and eliminate them [134, 135]. One of the main reason for this imbalance is the lack of antioxidant capacity which in turn may be caused by disturbance in production, distribution, or by an over abundance of ROS from various sources. If not regulated properly, excess ROS can damage cellular lipids, proteins or DNA, thus inhibiting signal transduction pathways, and, in general, normal cellular function. There is emerging attention on micronutrient elements such as selenium (Se) and zinc which are important as integral constituents of protective enzymes *via* special amino acids (e.g. selenocysteine, selenomethionine) or structural components (e.g. Zn fingers, Zn-metallothionein) Overall, these low-molecular-mass antioxidant molecules add to the enzymatic defense system provided by superoxide dismutases, catalase etc [135]. Sies *et al.* have demonstrated a novel function of selenoproteins containing selenocysteine or selenomethionine, in the maintenance of a defense line against peroxynitrite-mediated oxidations [136]. In a different investigation dealing with selenium serum level and subsequent risk of cancer amongst Finnish men and women it was found that lowest level of dietary antioxidants is related to strongest effect of selenium [137]. Evaluating the effect of selenium (Se)-induced oxidative stress on the oxidation reduction system, Bansal *et al.* found that the glutathione reductase and superoxide dismutase activities were decreased in the Se-deficient group, whereas the enzyme levels were significantly increased in the Se-excess group [138].

(h) Phase II Enzymes Induction

In order to evaluate phase II enzyme induction by selenium compounds Xiao *et al.* tested twenty-seven selenium compounds for quinone reductase (QR) and glutathione-S-transferase (GST) inducing activity in murine hepatoma (Hepa 1c1c7) cells. Sixteen selenium compounds were able to double QR activity, and seven of them also doubled GST activity [139]. Modulation of phases I and phase II xenobiotic-metabolizing enzymes by selenium-enriched garlic in rats has also been reported [140]. Sohn *et al.* evaluated different isomers of *p*-XSC on Phase I and Phase II enzymes and it was found that the activity varied with different isomers [141].

(i) Inhibition of DNA Adduct formation

In multiple organ systems in rodents, including the lungs, several forms of selenium have inhibited carcinogen-induced covalent DNA adduct formation along with retarded oxidative damage to DNA and decreased Mtase (methyl transferase) activity [142]. It was noticed that *p*-XSC inhibited DMBA-DNA adduct formation in the mammary glands. In collaboration with several other groups, Bayoumy *et al.* demonstrated that *p*-XSC inhibited thymidine kinase in mammary tumor cell lines derived from both humans and rats. Dietary *p*-XSC inhibited the formation of DNA adducts, as well as lung tumor development by the tobacco-specific nitrosamine [143].

(j) Cell Cycle Arrest

Cell cycle arrest is one of the major mechanisms proposed to explain cancer-protecting mechanism of selenium. Studies have revealed that selenium caused G1 arrest of LNCaP with no effect on PC3. Treatment of LNCaP and PC3 cells with selenium induced growth arrest of LNCaP as early as 24 h after treatment as revealed by flow cytometric studies. Selenium treatment resulted in the 58.1% reduction in the S phase [144]. It was concluded that MSeA exposure led to a profound G_1 arrest, irrespective of apoptosis induction; in contrast, selenite exposure led to cell cycle arrest, in S phase These patterns were in agreement with data obtained in mammary cancer cell lines [145].

(k) Androgen Receptor Down Regulation

Zhao *et al.* suggested that chemopreventive effect of methyl selenic acid against prostate cancer may be by modulating the expression of AR and AR-regulated genes [146]. These studies provide an important molecular mechanism of selenium chemoprevention and potential therapy for prostate cancer. In this study, the mechanisms of selenium-mediated AR signaling down-regulation were examined. Selenium decreased AR mRNA stability, accelerated AR protein degradation, and blocked AR nuclear translocation. In addition, selenium inhibited the recruitment of co activators and maintained co repressors bound to the promoters of AR target genes [147]. A study by Dong *et al.* concluded that selenium was able to significantly down-regulate the expression of prostate-specific antigen (PSA) transcript and protein within hours in the androgen-responsive LNCaP cells [148]. PSA is a accepted prognostic indicator of prostate cancer, thus can be safely implied that selenium intervention strategy to down regulate androgen signaling could be helpful in controlling morbidity of this disease.

(l) Regulation of Lipoxygenases

PHGPx is an enzyme recognized for its involvement in the removal of esterified lipid hydroperoxides. Additionally, PHGPx may be involved with the silencing of several lipoxygenases, including 5-, 12-, and 15-lipoxygenase. Since, the

selenoprotein PHGPx can silence lipoxygenases, this may partially explain the observed anticancerous effects of this trace element [149-151].The importance of this regulation stems from the recognition that lipoxygenases generates metabolites that mediate signals for increasing cell growth and proliferation [152] and inhibiting apoptosis [153].

CONCLUSION

There are many chemical compounds that are being evaluated for their protective action against various forms of cancer. Considering all the human cancer intervention studies selenium compounds have emerged as one of the most studied class of chemopreventive agents with highly encouraging results. Extensive evidence in the literature strongly supports that selenium supplementation at level above the dietary requirement is anticarcinogenic. Results described in this review strongly suggest modulation of molecular targets by organoselenium compounds thus indicating their role as chemopreventive agent. In this case scenario developing novel molecular targets for selenium is of utmost importance so that dietary strategy to enhance selenium intakes for cancer prevention could be evolved.

Similar to other cancer chemopreventive agents there are many gaps in the understanding of chemical forms of selenium and its relation to anticarcinogenecity. Since various chemical forms are the main determining factors for its biological activities there is need for developing sophisticated analytical tools to directly analyze selenoaminoacids and selenoproteins in the living system. It is evident that selenium has an impact on gene multi-step carcinogenesis process. Studies with emphasis on *in vitro* studies using genomic approach should examine in parallel the effect of selenium compounds. Another issue that needs to be addressed is the dose of selenium. Selenium used in *vitro* and *in vivo* studies translates to greater doses than necessary when extrapolated for human use. Recent evidence underlines the need of adequate selenium but over consumption by excessive use of selenium supplements need to be discouraged because of selenium toxicity. Toxicity can be dissociated from efficacy by tailoring the structure of selenium containing compounds. Selenium could also be incorporated at appropriate place in molecules already known for their promising anticancer activity [154]. The use of selenium in conjunction with chemotherapy or radiation therapy in various cancers appears worthy of further investigation. Further studies focused towards determination of proper combination need to be carried. As it is true with all other cancer chemopreventive agents, research should be directed to study the effect of heating/cooking on selenium compounds. Furthermore, we need to find out and study comprehensively protective effects of selenium from additives and synergistic combination point of view rather than focusing on individual agent.

Most of the selenium chemopreventive studies have revolved around selenium compounds that are readily available in nature. It's highly critical that this deficiency is overcome by interdisciplinary research and collaboration with chemists. Efforts should be directed to synthesize new compounds keeping in view the fundamental biochemistry and metabolic pathway of selenium compounds. The complexity and diversity of the mechanisms of anti-carcinogenic activity requires deep understanding of the cancer chemopreventive modes. However, in order to get maximal protection consumption of adequate selenium alone is insufficient. All other established means of cancer prevention such as adherence to healthy life style, avoidance of exposures to carcinogenic risk factors should be considered in addition to the appropriate intake of selenium in our food.

ABBREVIATIONS

DMBA	=	7,12-dimethylbenz[*a*]anthracene
p-XSC	=	1,4-phenylenebis(methylene)selenocyanate
BSC	=	Benzylselenocyanate
NAD(P)H	=	Quinone oxidoreductase
GSTs	=	Glutatathione S-transferases
NNK	=	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
AOM	=	Azoxymethane
BP	=	Benzo [a] pyrene
QR	=	Quinone reductase
GPX1	=	Selenoprotein glutathione peroxidase
MSeA	=	Methylseleninic acid
ASC	=	Alkylselenocysteine

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