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Mini Review

Selenium nanoparticles: Small is the new big: Mini review

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Abstract

Nanotechnology is the study of developing peculiar particles (1-100 nanometres (nm)) of matter at an atomic, molecular, and supramolecular scale. These nanoparticles possess unique properties such as large surface area, fewer side effects, bioavailability, decrease the toxicity, and prolonged drug release. Some inorganic metals nanoparticles like Ti, Se, Zn, Ag, Ce, Au, and Fe play possess antonymous bioactivities. Selenium is the essential trace element and essential micronutrient in the biological system. There are 25 selenoproteins in the human body possessing oxidoreductase activity; therefore, regulating the physiological redox balance in the organs system. Selenium nanoparticles (SeNPs) have exclusive properties and bioactivities as compared to traditional selenium supplements. Therefore, SeNPs have been attracted worldwide interest as a therapeutic agent and food additive. In this review, we have discussed the therapeutics applications of selenium nanoparticles.

Introduction

Nanoparticles (NPs) are the submicroscopic particles with size range in between 1- 100 nm possessing peculiar properties such as small size, large surface area, surface chemistry, surface charge, multi-functionality, and solubility. They have played a considerable role in the drug delivery system, therapeutics, disease pathophysiology, and treatment privilege [1]. NPs have the property of boosting the therapeutic potential of ionized drugs and also enhance the invasion of water-soluble compounds, vaccines, DNA, proteins, peptides, miRNA, siRNA, and more biological therapeutics [2]. The inorganic nanoparticles of Ti, Se, Zn, Ag, Ce, Au, and Fe play essential roles as theranostic agents and carriers for proteins, chemotherapeutic agents, etc. Among them, selenium nanoparticles attract more attention because of its high bioavailability and lower toxicity [3,4]. Selenium (Se) belongs to Group-6 in the periodic table with atomic number 34. It is a semi solid-metal and present in 2+, 4+, 6+, and 2- oxidation states. Se with zero oxidation state (Se^0) is a colorless, non-toxic, biologically inert material [5]. Selenium is present as selenocysteine in 25 human proteins and enzymes and plays a protective role in several disease conditions, e.g., hypercholesterolemia, some cancers, and cardiovascular disorders [6]. Selenium is a cofactor for thioredoxin reductases, and glutathione peroxidases and have exceptional growth modulating properties [7]. The biological activity of SeNPs depends on its size: smaller the particle, more significant is the activity [8]. SeNPs are used as antimicrobial, anti-tumor (both in vitro and in vivo), anticancer, and nutritional supplements [9,10]. SeNPs can be synthesized via physical techniques such as UV radiation and laser ablation; chemically via acid decomposition, catalytic reductions, and precipitation, biologically via microorganisms or plant extracts [11]. The health benefits of SeNPs are anti-aging, antioxidant, antidiabetic, boost immunity, reduces inflammation, improves fertility and brain functions, anti-asthma, anti-arthritic, treats muscular dystrophy, antiviral, and regulates thyroid [12].

Role of SeNPS as antioxidant

SeNPs possess the antioxidant capability due to selenoenzymes present in the Glutathione Peroxidase (GPXs), Thioredoxin Reductase (TR) and Iodothyronine Deiodinases (IDD). They are less toxic, more productive, and increase the activity of selenoenzymes (for combating oxidative stress) as compared to selenocysteine, Se-methyl, selenomethionine, and selenite [13]. SeNPs scavenge ROS, such as superoxide anion (O_2^-), 1,1-diphenyl-2-picrylhydrazyl, singlet oxygen ($^1O_2$), and carbon-centered free radicals [14]. Zhang, et al. (2007) have been reported that the activity of glutathione peroxidase (GPx) in the liver of weanling pigs significantly becomes higher when the animals were administered Nano-Se diet (concentration range of 0.50 and 1.0 mg Se·kg-1) as compared to an inorganic form of selenium [15]. In another study, it has been observed that the administration of nanoselenium (10–20nm)

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Ameliorated acetaminophen (APAP)- induced liver damage in the rats and restored the cellular structure [16]. Similarly, the SeNPs have been shown a protective effect against $K_2Cr_2O_7$ induced oxidative stress in some thyroid gland by preventing cell damage and found to restore the levels of catalase, GSH, superoxide dismutase, T3, T4 in the treated animals [1].

Role of SeNPS as an anticancer agent

The anticancerous property of SeNPs is due to the induction of glutathione S-transferase (GST) by selenium [4]. SeNPs mitigates the problems of drug resistance and toxicities connected with chemotherapeutic agents. SeNPs have the potential to suppress the growth of cancer cells via the induction of cell cycle arrest at S phase [17]. Cancer cells selectively incorporate SeNPs via endocytosis, and then these SeNPs induces the apoptosis of cancer cell by triggering apoptotic signal transduction pathways [18]. SeNPs have been observed to inhibit the growth of prostate LNCaP cancer cells moderately via caspases mediated apoptosis *in vitro* [19]. Furthermore, it has been observed that SeNPs, along with *Lactobacillus Brevis*, stimulates the immune response via enhancing the production of interferon and delayed-type hypersensitivity response in a metastatic breast cancer mice model [20]. Sonkusre, et al. [2014] have shown that introduction of biologically synthesized SeNPs (concentration as low as 2 µg $Se{\cdot}mL^{-1}$) are competent enough to suppress the proliferation and induce caspase-independent necrosis in human prostate adenocarcinoma cells (PC3). In addition to their anticancer potential alone, SeNPs when used in combination with 5-Flourouracil (5-FU) has been shown to enhanced the anticancer potential of the drug in A375 human melanoma cells. The Figure 1 demonstrates the mode of SeNPs action as an potential anticancer agent and carrying out the apoptosis.

Role of SeNPs in drug delivery

SeNPs have been used as a drug delivery system for anticancer drugs/agents, for active immunization via carrying antigens and also for genes to the appropriate site [1]. The selective/effective uptake and drug accumulation at the target site are possible because of the nanosize of these particles. SeNPs have been found to deliver siRNA against specific oncogenic gene [22] Yang, et al. have been observed that the usage of several surface decorators increases the cellular uptake and anticancer potential of nanoparticles. In their study, they functionalized SeNPs with *Spirulina* polysaccharides (SPS). They found that SPS surface decoration markedly increased the cellular uptake and cytotoxicity of SeNPs against various cancer cell lines. The SPS-SeNPs was observed to suppress the growth of cancer cell via apoptosis, as manifested by an increment of the sub-G1 cell population, fragmentation of DNA, condensation of chromatin, and translocation of phosphatidylserine [23]. Zheng, et al. (2015) have been reported that polyamidoamine dendrimer-modified SeNPs efficiently deliver the siRNA and cisplatin to A549/DDP cells for reversal multidrug resistance. This combination induces apoptosis of cells via PI3K/Akt/mTOR and MAPK/ERK pathways in A549/DDP cells [24].

Furthermore, the mesoporous SeNPs has proven to be as a carrier for the delivery of doxorubicin for targeting breast cancer with lesser toxicity and improved anticancer potential [25]. Xia, et al. (2017) have reported that the delivery of siRNA using RGDfC-conjugated functionalized SeNPs is successful against liver carcinoma. It activates Wnt/β-catenin signaling and sparks Bcl-2 mediated apoptosis [26]. The Figure 2 illustrates the modification of SeNPs and using them as a source of drug delivery.

Role of SeNPS in reducing inflammation

Inflammation is the earliest step in the onset of a disease/injury leading to accretion of body fluids, white blood cells and release of prostaglandins and several inflammatory mediators [28]. Se helps in decreasing the inflammatory responses

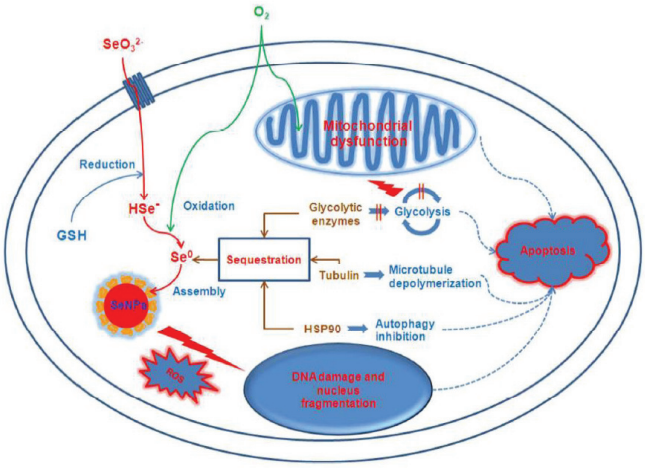

Figure 1: The mechanism of SeNPs as an anticancer agent [adapted from Bao, et al. 2015 [21]].

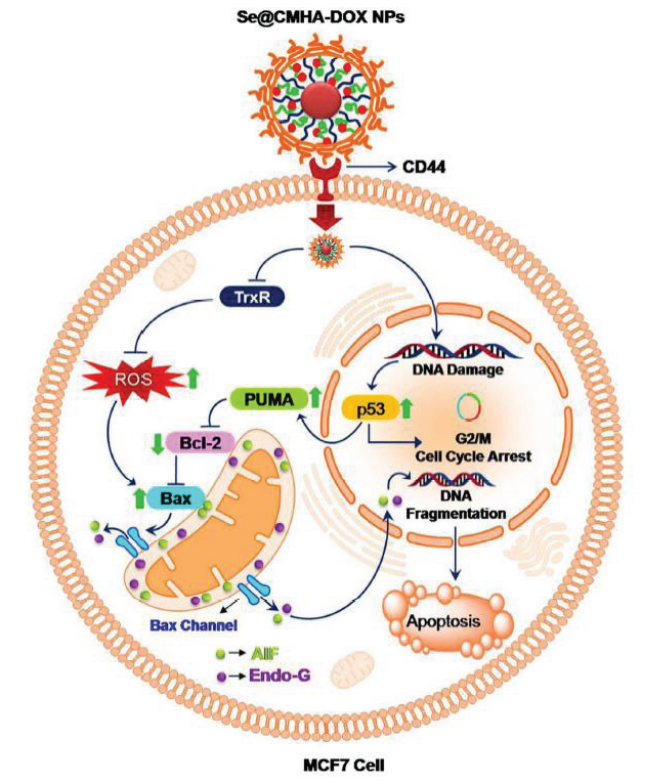

Figure 2: Role of SeNPs in the drug delivery [adapted from purohit, et al. 2017 [27]].

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in autoimmune/inflammatory diseases by increasing the antioxidant function of selenoproteins thus leading to decrease in the expression of many proinflammatory cytokines such as IL-6 and TNF alpha [29]. It has been observed that SeNPs decorated with Ulva lactuca polysaccharide sigficantly inhibited the proinflammatory cytokines (IL-6 and TNF-α) and NFκB signalling in dextran sodium sulphate induced colitis [30]. Similarly, it has been recently found that SeNPs decreases the expression of genes of pro inflammatory mediators like TNF-α, PGE2 and TBAR in inflammation induced irradiated rats [31]. Combined treatment of melatonin-SeNPs have been shown to reduce the pathological abnormalities in liver, proinflammatory cytokines, proliferation of splenocyte, and levels of serum ALT, AST, NO, MDA in immunological liver injury induced by BCG and LPS in mice. Further, the combination also enhanced the activities of SOD and GPX thus decreasing the oxidative stress and inflammation [32].

Role of SeNPS as antimicrobial

SeNPs possess the antimicrobial activity thus inhibiting the growth of microbes such as bacteria, fungi, and viruses. Biologically synthesized SeNPs (from bacterium *Ralstonia eutropha)* has been showed to possess antimicrobial activity at a concentration of 100, 100, 250, and 100 µg/mL by inhibiting 99% growth of *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli*, and *Streptococcus pyogenes* respectively. Furthermore, it has been observed that SeNPs at a concentration of 500µg/mL inhibits the growth of pathogenic fungi *Aspergillus clavatus* [33]. It has been reported that selenium dioxide treated probiotics that is *Lactobacillus plantarum* and *Lactobacillus johnsonii* or their cell-free spent stock inhibits the growth of *C. albicans* thus demonstrating their antifungal activity [34]. The antiviral activity of SeNPs has been investigated on H1N1 influenza virus and was found that the combined use of oseltamivir and amantadine-loaded SeNPs strongly inhibits the generation of ROS and activation of p53 phosphorylation and AKT [35-37].

Conclusion

Selenium is an essential trace element participating in many physiological processes of the organism and possesses tremendous pharmacological activities. Nanoparticles of Se are more productive and more appropriate for supplementation. Se NPs have low toxicity and high bioavailability, due to which they are used in various therapeutic applications such as drug delivery system, as anticancer drugs, as an antioxidant, against drug-induced toxicities, as anti-inflammatory and antidiabetic. The future aftermaths of SeNPs seem to be very favorable in enhancing the potency of existing treatments and the development of new therapies/remedies.

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