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REVIEW PAPER

Selenium nanoparticles role in organ systems functionality and disorder

Seyed Mohammad Amini[1,2*], Vahid Pirhajati Mahabadi[3]

[1] Radiation Biology Research Center, Iran University of Medical Sciences, Tehran, Iran

[2] Medical Nanotechnology Department, School of Advanced Technologies in Medicine, Iran University of Medical Sciences, Tehran, Iran

[3] Neuroscience Research Center, Iran University of Medical Sciences, Tehran, Iran

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ABSTRACT

Extensive research on the nutritional and medical application of selenium nanoparticles (SeNPs) was performed in past decades. Besides nutritional values, new characteristics such as antibacterial and anticancer properties depict a bright future for high Selenium (Se) consumption in the coming years. Se is essential for the proper functioning of most of the major body organ systems meanwhile it could be highly toxic and even cancerous. The current knowledge of Se interaction with major organ systems functionality such as the central nervous system isn't well studied and many physiological aspects aren't clear to the science community. Meanwhile, various results were published on increasing organ system functionality through administrated SeNPs. So with the rapid entrance of SeNPs in the medical and nutritional industry, it may cause unintended complications. The intent of this review is to investigate current knowledge of SeNPs interaction with major body organ systems functionality. Investigated pharmacokinetic parameters of SeNPs was also reviewed.

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INTRODUCTION

Se is an essential mineral with a high nutritional value and very important role for majority of physiological interactions in our body [1]. Our body intake of selenium is provided from food or water as a selenite, selenate, selenocysteine and selenomethionine and was carried by different human selenoproteins in the body. Humans with Selenium deficiency are amenable to many Health problems in a way that abnormal selenoprotein function or selenium deficiency could lead to various neurological [2], thyroid [1], muscle [3] and many other physiological disorders [4]. So the need for selenium starts from an embryonic age and continues until old age.

Nanoparticles are gaining lots of attention and concerns in biomedical and industrial application [5, 6]. Especially metal nanoparticles with extraordinary characteristics are capable of many diagnostic[7, 8], therapeutic [9, 10], health [11, 12] and nutrition [13] application. Recently many reports about a different biomedical application of Se nanoparticles were published. With antimicrobial, antioxidant and anticancer properties [14] and lower toxicity in comparison to the selenite (SeO_4^{-2}) or selenite (SeO_3^{-2}) counterpart [15, 16], these nanoparticles have attracted much attention.

As a direct result of higher bioavailability of Se in nanoparticles form in comparison to other Se product, there is a growing need for Se nanoparticles in the livestock industry. Trial studies on animal feeding represents higher body weight gain [17], fertility rate [18], rumen fermentation[19], feed efficiency [20], and antioxidant status [21].

* Corresponding Author Email: *Amini.sm@iums.ac.ir*
Mohammadamini86@gmail.com

Similar to livestock, agriculture industry applied Se nanoparticles for better plants growth and productivity [22]. Furthermore, the extensive use of Se as an antimicrobial agents in hygiene products was recommended by many researchers [23, 24].

Future extensive use of Se nanoparticles may lead to possible harmful effects on human health and the environment. Therefore the present review provides possible pros and cons of Se nanoparticle role in human organ functionality and disorder.

Importance of Se for organ functionality

The discovery of a congestive cardiomyopathy known as Keshan disease and Kashin-Beck disease in certain part of the People's Republic of China, which is deforming arthritis reviled the important role of Se in dietary [25]. But Keshan disease is not the only disorder of Se deficiency. Altogether, many experimental bioassays, epidemiologic studies, and even human clinical intervention trials support that a tiny amount of Se is vital for proper function of many human organs and systems such as Reproductive system [26], Thyroid [27], brain [28], cardiovascular system [29], Jacobson's organ function [30] and many others.

There is much evidence that indicates the direct relation between Se deficiency and increasing the risk of cancer [31, 32]. Molecular scientific bases of Se intake and cancer prevention are not clear but Glutathione peroxidase activity for hydrogen peroxidase breakdown strongly depends on available selenium [33]. Also, mitochondrial electron transport was altered in Se deficiency conditions [34] that could lead to more oxidative stress [35].

Malnutrition may also be associated with microbial infections. In case of Se deficiency, this has been reported frequently by researchers. Different research groups demonstrate that harmless viruses could be virulent in Se-deficient hosts [36, 37]. Boyne *et al*. reported that Se deficiency may have a negative effect on the mice immune system to eliminate Candida albicans [38]. Same results were reported for mice infected with Diplococcus pneumoniae [39] and Listeria monocytogenes [40]. Also, Viral infection leads to high ROS generation [41] and in-fact viral gene expression controls the cellular gene expression via ROS generation which leads to the appearance of cancer cells [42]. It's clear that under low Se condition, general oxidative stress increased and the mentioned process lead to higher viral infection. Also, Se deficiency may cause a decrease in immune system efficiency that provides a chance for opportunistic pathogens [43, 44].

Se toxicity and organ disorder

Se toxicity was well-known in livestock that grazed in high Se soils. These animals developed disorders such as "alkai disease" and "blind staggers" [45]. Alkai disease is characterized by thickening hair and degenerative changes in hooves and blind staggers is characterized by impairment of vision and unsteady steps. In human, acute selenium toxicity usually leads to gastrointestinal disorders such as nausea, vomiting or diarrhoea alongside hair losses and headache [46]. Other acute toxicological symptoms such as bronchitis [47] and hypochromic anemia [48] have been reported. Long-term Se toxicity resembles in acute discolouration of skin and nail [49]. Except for the blood level of selenium, other biochemical indicators of body Se would increase which include: prothrombin time [50], alanine serum concentrations [51] and alanine aminotransferase enzyme activity [52]. Liver histopathological studies reveal sinusoidal damage and nodular regenerative hyperplasia in a rat model with high Se intake [53].

Numerous experimental studies demonstrate the carcinogenic effect of inorganic or organic Se form [54, 55] which is contrary to the cancer-protective activity of Se that was discussed. The same contradictive reports happen to the neuroprotective or neurodegenerative activity of Se. Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease that may be related to high Se intake [56]. Other nervous system abnormality may also be related to Se toxicity [57, 58]. Also, the limited evidence demonstrates Se toxicity in endocrine [48], reproductive [59], immune [60] systems. A direct link between high Se exposure and dental caries is clarified by Hadjimarkos *et al* [61].

Pharmacokinetic parameters of Se NPs

The science of investigating the scale and rate of absorption, distribution, metabolism, and elimination of drugs in the body through rebuts meticulous experimental methods known as a pharmacokinetic [61]. Pharmacokinetic values defined by applying specific parameters include the volume of distribution (Vd), half-life (T1/2), mean residence time (MRT), clearance (Cl), maximum concentration (Cmax), bioavailability (F) and area

under the time-concentration curve (AUC) (Fig. 1). In general metallic nanoparticles pharmacokinetic is different from inorganic or organic metallic ion forms [62].

In the human metabolic cycle, Se exists in various organic or inorganic oxidation states including -2, +2, +4 and +6 [63]. Unlike mentioned oxidative states of Se, pharmacokinetic data of elemental Se (Se^0) is scarce. In nature, some microorganisms reduced selenite (Se^{+4}), or selenate (Se^{+6}) into nanoparticles formed Se^0 [64]. Moderate absorption of Se^0NPs reduced by bacteria in the chicken model was reported [65]. Bioavailability and bioactivity of chemically synthesized Se^0NPs are reported in Rats [66]. The retention of SeNPs and Se-methylselenocysteine (MeSeCys) at the nutritional level in mice blood and other tissues was compared and no significant differences were observed [67]. Similar results were observed for kidney and liver accumulation for Se0NP and selenite [68]. Same results were reported for selenomethionine (SeMet) [69] and selenite [68]. The clearance of SeNPs from the body can be either by renal and hepato-biliary excretion SeNPs or excretion of Se metabolites. In a pharmacokinetic study by Loeschner *et al*. the entrance of Se^0 from Se^0NPs into the metabolic cycle and its subsequent elimination was confirmed by the apprehension of the two urinary metabolites of Se alongside a high amount of stool excretion of Se [68]. The authors don't investigate hair excretion.

Studies that indicate organ functionality with Se Nanoparticles Treatments

Organ functionality strongly depends on Antioxidant defensive capability. The antioxidant defence system is consisting of enzymatic and non-enzymatic antioxidants which are expanded not only inside the cells but also in extracellular environments. The first line of the antioxidant defence system is to restrain the production of free radicals. Reduction of disintegrated hydrogen peroxide and hydroperoxides by water and alcohol is a prime ROS generation mechanism which was suppressed through some selenoproteins and selenoenzymes such as glutathione peroxidase, thioredoxin reductases and etc. In many studies that applied SeNPs, increasing selenoproteins and selenoenzymes activity was reported with lower toxicity in comparison to an organic or inorganic form of Se [62]. SeNPs provides not only higher bioavailability but also they can scavenge free

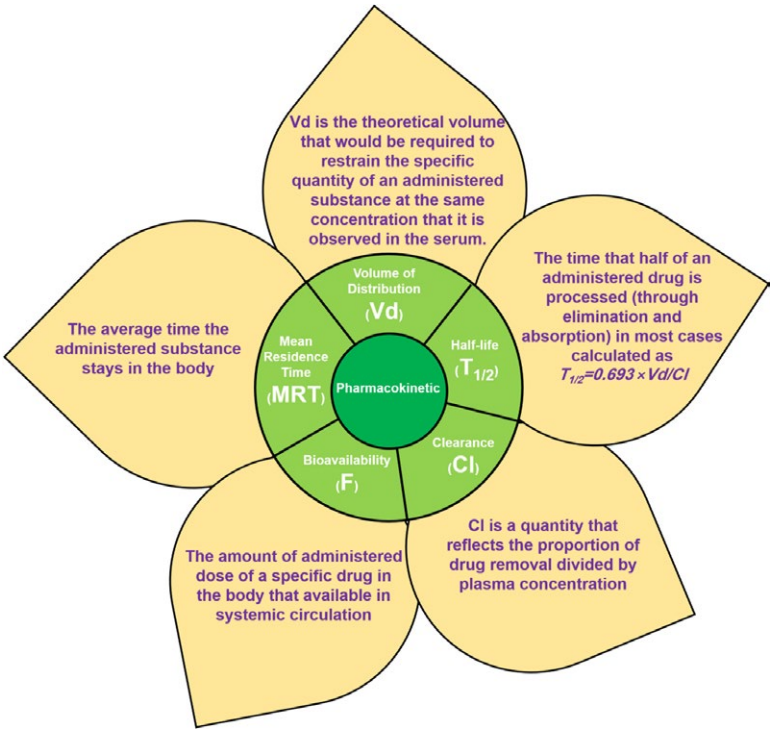

Fig. 1: Pharmacokinetic values

radicals directly [63]. The organ systems in which the effect of selenium nanoparticles on their function is examined is shown schematically in Fig. 2.

Musculoskeletal system: Beside direct interaction with oxidative stress SeNPs could be integrated with other metabolic cycles that are involved with the musculoskeletal system oxidative stress response. For example, increasing oxidative stress can lead to a higher expression of heat shock proteins (HSPs) [64], which is an adjusting process corresponding to the interruption of cellular integrity [65]. The nutritional supplement of SeNPs could increase the expression level of HSP90 in a rest period after extensive exercise. A higher level of HSP expression could increase cells tolerability in stressful condition [66]. The nutritional supplement of SeNPs can significantly decrease the blood urea nitrogen (BUN) and creatinine serum concentration after intense exercise [67]. Both of these compounds can damage cells through oxidative stress [68].

Reproductive system: The main cause of sperm dysfunction is oxidative stress [18]. Some researchers applied SeNPs as a male fertility preservation substance. Increase semen quality and reproductive functionality of male goats was reported by Shi *et al.* through increase activity of testicular GPx and improvement in testicular microstructure and testicular spermatozoa. Moreover, SeNPs treatment leads to higher Se accumulation in testes, and testicular tissue [19]. Fertility preservation in those who have been treated with chemotherapy is major concerns. Rezvanfar *et al.* observed the chemoprotective activity of SeNPs against cisplatin-induced gonadotoxicity. They demonstrate significant improvement in spermatogenesis and semen quality and lessened spermatic DNA destruction alongside cisplatin-induced free radical stress [69].

Endocrine system: Se is necessary for efficient endocrine glands functionality. Many selenoenzymes and selenoproteins are adjusting redox status of endocrine cells and in some cases involved in endocrine hormone metabolism [70]. But few investigations were performed for investigation of SeNPs role in endocrine glands functionality. Hassanin *et al.* demonstrated that accumulated SeNPs in thyroid cell can modify thyroid chromium toxicity in rats [71]. Rezaeian and Sadeghi report investigate the thyroid and sex hormones levels after SeNPs administration in rats. SeNPs administration can increase both thyroids and sex hormones levels not only in

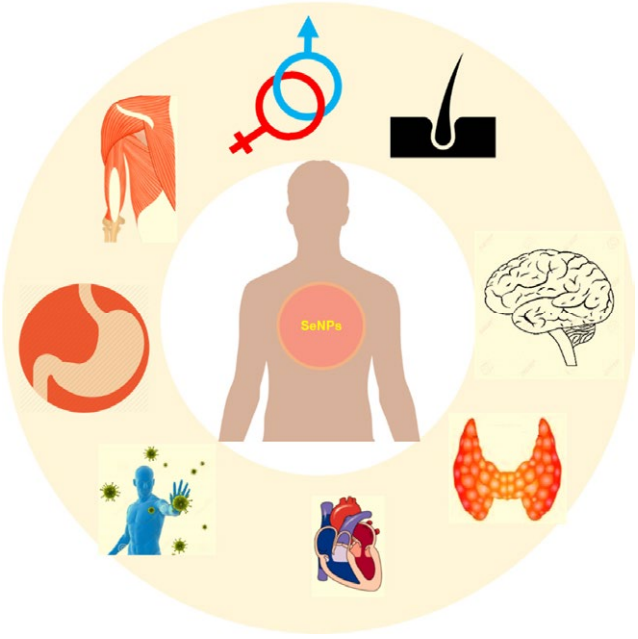

Fig. 2: Schematic representation of SeNPs possible interaction with body organ systems: In this manuscript, current knowledge about SeNPs interaction with musculoskeletal, reproductive, endocrine, nervous, immune, digestive, circulation and the integumentary system was discussed.

normal condition but also in oxidative stress condition [72]. Oral administration of SeNPs can not only minimize diabetic complication but also could enhance pancreatic efficiency. Al-Quraishy *et al* report not only a significant augment of blood serum insulin level was observed but also histopathological studied show a SeNPs protective role in β-cells in the islet of Langerhans [73]. Similar results were provided by a liposomal formulation of SeNPs by Ahmed *et al* [74].

Nervous system: For normal nervous system function selenoproteins are essential. Nervous system damage due to nanoparticle was reported before [75]. A link between selenoproteins functionality and several nervous system disorder was reviewed by Schweizer *et al* [28]. But SeNPs were merely applied for investigation of central nervous system functionality. Nazıroğlu *et al*. review state that SeNPs could be a potential remedial compound for Alzheimer disease treatment [76]. In contrast, Yuan *et al*. studied the impacts of SeNPs on sodium currents on dorsal root ganglion (DRG) neurons activity, applying the whole-cell patch clamp technique. In their report, SeNPs were able to decrease sodium current in a concentration and time-dependent manners which consider possible neurotoxic characteristic for SeNPs [77].

Immune system: It has been demonstrated that Se is generally accumulated in immune response organs such as liver, lymph nodes and spleen [78]. To deal with immunogens, Se treatment can increased antibodies production and expand complement responses through different mechanisms which include various selenoproteins [78]. It has been demonstrated that biogenic SeNPs could be a stimulator for immune system [80]. In particular, expanded neutrophils chemotactic and respiratory burst activities were observed for SeNPs in comparison with sodium selenite [81]. The authors consider the different pharmacokinetics parameters of SeNPs in comparison to selenite for assessment of immune stimulator functionality of SeNPs.

Digestive system: Sarkar *et al*. claimed that SeNPs could be an effective treatment for fatty liver disease [82]. In a separate study induced fatty liver male rats were treated with SeNP, and lower level of free radical and inflammation were reported [83]. SeNPs can improve rumen fermentation in livestock. A diet which contains SeNPs could increase total fiber digestion in sheep [19]. *Lactobacillus* species could be applied for the preparation of selenium nanoparticle-enriched probiotics that represent an antifungal activity against Candida albicans [84].

Circulation system: Selenoproteins and selenoenzymes are essential for blood cells protections against oxidative damages [85]. It has been demonstrated that feeding of SeNPs has a better impact in comparison to sodium selenite upon peroxidative damage in blood cells [21]. SeNPs is also representing a better iron homeostasis capability in compression to other Se forms. In in-vivo compression investigation between SeNPs and sodium selenite, the level of transferrin and transferrin receptor was monitored. Total iron binding capacity (TIBC) in groups that treated by SeNPs is higher than a group that treated with sodium selenite [85]. Se has an essential role in inhibiting cardiovascular problems by augmenting the oxidation stress defence system to combat the oxidative alteration of lipids and subsequent decrease platelets aggregation [29]. SeNPs Ability to protect the cardiac cells from ischemia was demonstrated in an in-vitro experiment by Soumya *et al* [87].

Integumentary system: Se compensates skin-damaging compounds destructive role. It has been used for skin and hair care through cosmetics and health products. It has been demonstrated that SeNPs are able to penetrate in skin tissue and subsequently prevent the lipofusin formation caused by UV-exposure and protect glutathione peroxidase (GPx) activity in mice [88]. Anti-fungal effect of SeNPs was as well as classical antidandruff selenium sulfide with lower cytotoxicity [89].

CONCLUSION

As described throughout this review, because of the extreme role of Se in many selenoproteins and selenoenzymes function, a great deal of research is required to enhance our knowledge of SeNPs interaction in organ functionality and possible role in unwanted disorders. Digestive and integumentary absorption routes of SeNPs is not clearly identified but promising in-vitro and in-vivo results was reported for different organ systems functionality. SeNPs not only represent lower toxicity and higher antimicrobial and antioxidant properties but also it can be used in a larger nutritional amount. Sometimes, some technological profits could be potential problems. Large-scale addition of SeNPs as a livestock food

supply could happen very soon and subsequently human or environmental safety concerns such as long-term toxic and possible carcinogenic effects must be considered through further studies.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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