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Selenium Nanoparticles as Delivery System Against Various Diseases

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Abstract

Several obstacles such as drug insolubility, non-specificity, poor bioavailability, high dose requirements, cytotoxicity, blood-brain barrier, drug resistance and biofilm development generally hamper medical conventional chemotherapeutic treatments leading to aggravation of disease-state causing ultimate death of patient. To overcome the biological barriers, nanotechnology-based selenium nanoparticles (SeNPs) have attracted attention recently as drug delivery system as well as nanomedicine in combating several diseases such as inflammation, arthritis, diabetes, infection, neurological disorders, and cancer. The biocompatible, degradable, less toxic, quantum sized with large surface-to-volume ratio, largely differed surface atoms and spherical shaped SeNPs may be surface-functionalized with ligands and / or encapsulated with polymeric vesicle and cargo for biomedical applications to target their payloads to specific cells with controlled release. Moreover, SeNPs have antioxidant, anti-inflammatory, anti-microbial, anti-carcinogenic and immune regulatory activities as a delivery system. Therefore, cargo loaded SeNPs attached with ligands and / or vesicles may be utilized for synergistic bio medicinal applications to get their higher bioavailability and therapeutic efficacies with sustained drug release to specific site/s of interest against diseases. This review elucidates the current advances regarding their synthesis, functionalization, mechanism of action, biomedical applications, toxicity, and elimination as a potent targeted delivery system against different diseases.

Keywords: Diseases; Selenium nanoparticles; Synthesize functionalization; Mechanism of actions; Therapeutic delivery efficacies

Introduction

For any disease development by the exposure of exogenous toxic agent/s into the body, oxidative and nitrosative stresses become prominent over the antioxidant defense and immunity mechanisms to induce cellular damage for making a diseased state [1,2]. Infectious diseases induced by pathogens are associated with inflammation and immune responses resulting in threats to human health. The chronic inflammation-mediated disorders as well as inducted systemic autoimmune disorders lead to progressive damages and pathogenesis of multiple organ systems such as joints, brain, lungs, liver, exocrine glands, muscles, and bones [3-6]. The exogenous toxicant/s-induced chronic inflammatory autoimmune disorder is initiated by the enhanced generations of reactive oxygen and nitrogen species resulting in the oxidative stress, the decline in the antioxidant defense mechanisms and the altered redox signaling involved in the progressions of the various diseased states [7,8]. The frequent usages of drugs with lower targeting-effects lead to promoted drug resistance against infectious diseases [9,10]. The emergence of drug-resistant microbes may form biofilm development owing to the resistant microbial synergy creating serious health complications [11]. As conventional chemotherapy has several disadvantages regarding its drug targeting efficiencies and cytotoxicities, recently, it has given emphasized on nanotechnology-based drug targeting remedies to overpower biological barriers and to get higher biological effectiveness in combating various diseases. In this context, SeNPs have drawn attention as biomedicine and delivery system due to their high biocompatibility, low toxicity, small size, surface charge, high surface area and surface functionalization for ligands and biomolecules [12,13]. Selenium, the essential trace element utilized to maintain human health, binds to proteins to form selenoproteins for exerting antioxidant defense through the activities of glutathione peroxidase, thioredoxin reductase and deiodinase, immune regulation, cell signal transduction and other metabolic processes [4].

Organic selenium such as selenomethionine and ionic selenium such as selenate and selenite are highly bioavailable from food-stuffs or chemicals for their usages or limited usages, whereas elemental selenium is absorbed very less by the gastrointestinal tract owing to its large size [14]. Four oxidative inorganic selenium such as selenate (Se^{+6}), selenite (Se^{+4}), basic Se (Se^{0}) and selenide (Se^{-2}) may be transformed into organic selenomethionine (SeMet) and selenocysteine (Sec) via biological processes, while Sec, located at the functional sites of the enzymes as a cofactor, is used for the enzymatic catalytic activity [15]. The deficiency of selenium may enhance the high morbidity of cancer, cardiovascular diseases, and infectious diseases [7,16,17]. Se NPs may be utilized to boost up the therapeutic efficacies of ionized drug materials, enhance piercing of water-soluble components, peptides, proteins, siRNAs, miRNAs, DNAs, vaccines, and other biological cargos. As Se NPs can produce ROS, their surface-modifications with targeting ligands are needed to consider them as suitable versatile drug delivery system to deliver cargos selectively at target site/s [18]. This review mainly depicts the Se NPs as potential drug delivery system in combating various diseases, based on their biological effectiveness.

Synthesis and surface functionalization of selenium nanoparticles

A few methods for the synthesis and functionalization of SeNPs are described below:

SeNPs may be synthesized by several chemical reduction approaches. SeNPs are prepared mainly through the reduction of precursor sodium selenite by ascorbic acid and stabilized by polysorbate 20 / bovine serum albumin (BSA) / chitosan (Chit) / glucose (Gluc). In brief, (i) 30 mg of sodium selenite ($Na_2SeO_3.5H_2O$) is dissolved in 90 mL of Milli-Q-water. 10 mL ascorbic acid (56.7 mM) is added dropwise to the sodium selenite solution with vigorous stirring. After the addition of each 2 mL of ascorbic acid, 10 µL of polysorbate is added. The visualized color change of the reactants-solution to clear red from clear white indicates the formation of SeNPs after the addition of ascorbic acid. SeNPs are collected by spinning the solution at 12000 rpm. The pellet is re-suspended in double distilled water (DD H_2O) maintaining sterility throughout the preparation for further experimental usages. (ii) Sodium selenite is dissolved in DD H_2O at 0.02 M (12.5 mL). In other flasks, 0.125 M ascorbic acid solutions are prepared (10 mL). Then the solutions are mixed with the solutions of BSA or Chit (5 mL at 0.87% w/w). After that, the prepared sodium selenite solution is added drop by drop. Reaction mixtures are then mixed on a magnetic stirrer (1500 rpm) until the color changes to red orange, while the mass ratio between sodium selenite and BSA or Chit is modified to 1:1. For the SeNPs-Gluc formulation, glucose is dissolved in DD H_2O at 0.055 M (25 mL) following magnetic stirring (1500 rpm) upto 130°C. The 0.017 M solution of 10 mL sodium selenite is added drop-wise promptly after heating started. After ~ 1 h, the color change to orange / reddish indicates the hint of complete reduction and subsequent conversion to Se^{0}NPs. In the course of samples-preparation, reaction vessels are enfolded with aluminium foil for preventing crystallization and photo-oxidation of formed SeNPs, while the colloidal SeNPs-solutions are stored at 4-8°C or lyophilized for future usages.

Biocompatible SeNPs may also be synthesized by green synthesis methods through bioactive plant-extractions in a single-step process with reducing stabilizing agents and herbal capping [19]. The plant-extracted phytoconstituents such as phenols and flavonoids function as stabilizers and reducing agents for the production of nanoparticles [19]. Plant parts such as flowers, leaves, fruits and buds may be utilized to produce SeNPs. The extracts of *Allium sativu, Aloe vera, Catharanthus roseus, Asteriscus graveolens, Clausena dentate, Peltophorum pterocarpum, Diospyros montana, Emblica officinalis, Acalypha indica* and ginger may be utilized to synthesize SeNPs for various biological applications as antioxidant, antimicrobial, free radical scavenger activities, and also as potent carriers for anticancer or other anti-disease-oriented drug or cargos for targeted delivery [19]. In brief, 2 mL of aqueous bioactive plant extract is added drop by drop into 10 mM sodium selenite (10 mL) under the condition of magnetic stirring. After that, the reaction mixture is permitted for the reduction in dark state at 27±2°C on the orbital shaker (120 rpm) for 24 h and followed by the color-change of the synthesized SeNPs. In addition, the extract of green tea together with *Lycium barbarum* polysaccharides (LBP) as a surface capping agent and sodium selenite as a reducing agent may be utilized to produce spherical functionalized SeNPs for biomedical applications [19]. Moreover, SeNPs may also be functionalized with folic acid, transferrin, hyaluronic acid and ferulic acid, monosaccharides such as sialic acid, polysaccharides such as pectin, amino acids such as valine, aspartic acid and lysine, proteins, peptides, antibodies, aptamers, siRNA/miRNA genes, and polymers such as polyethylene glycol, polyvinyl alcohol, poly-lactide, poly(lactide-co-glycolide), polyethylenimine, polyvinyl pyrrolydone, poly-L-lysine and polyacrylic acid [13,20] for biomedical usages.

Characterization of selenium nano-composites

The shape, size, and surface morphology of the nano-composites are determined by transmission electron microscope, scanning electron microscope and atomic force microscope. The elemental compositions and the phase structure of the nano-composites are analyzed by energy-dispersive X-ray diffractometer. The selenium contents of the nano-composites are determined by utilizing inductively coupled plasma optical emission spectrometer. The outcomes of protein concentration on the nano-composites' hydrodynamic size are observed utilizing dynamic light scattering. The zeta-potential of the nano-composites is measured for finding the surface charge on the NPs by using Zetasizer Nano ZS. Different stabilizing and reducing functional groups of reagents and plant metabolites used in the fabrication of nano-composites are detected by Fourier Transform

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Infrared spectrometer. The nature of the nanomaterials is explored by using Raman microscope. The possible changes of protein's conformation by the induction of SeNPs are monitored through the circular dichroism measurements by using JASCO spectropolarimeter. The bio-reduction of selenium selenite in the formation of SeNPs observed through the color change is monitored by using UV-visible spectrophotometer.

Mechanism of actions of selenium nanoparticles

The pharmacological outcome and toxicity of SeNPs depend on their redox state, concentration and the type of selenium compound utilized. Supra-nutritional dosages of SeNPs through the activities of methyl selenocysteine and selenomethionine inhibit many cancers such as prostate, lung and colorectal cancer causing G2/M cell cycle seizure and inducing apoptosis in cancerous cells by mitochondrial signaling pathway [21-23]. The key se ion behind the toxicity is selenite (Se^{+4}) needed to be reduced to selenium (Se^{0}) by biogeochemical cycles, while SeNPs act as antioxidant at low sub dosages and becomes pro-oxidant at high doses [24]. After cellular exposure, the pro-oxidant form of SeNPs reduces the nano-selenium through thioredoxin and glutaredoxin –intervened redox signaling leading to the production of Se^{2-} anion via the utilization of $NADPH^{+}$ H^{+} to trigger the generation of ROS, disrupting the cell membrane, damaging proteins and DNA, and resulting to signaling apoptosis of the cells through endoplasmic reticulum stress-induced activations of MAPK/Erk, Wnt/β-catenin, NFκB, PI3K/Akt/mTOR and caspase-3 as anti-microbial and anti-carcinogenic effects [25-27]. SeNPs have capabilities to target macrophages and to regulate macrophage polarization for initiating innate immunity to inhibit microbial activity by the regulation of the cytokines production [28].

Moreover, SeNPs may function as immunomodulatory agents for inhibiting tumor growth by the enhancement of anti-tumor immune reactions such as the regulation of tumor-associated macrophages and the activation of specific T cells [29,30]. Furthermore, at sub-optimal dosages, SeNPs and their systemic compounds-forms such as selenomethionine, methyl selenocysteine, Di selenide selenocysteine, selenodiglutathione and glutathione selenylsulfide as antioxidants may scavenge free radicals by reducing oxidants produced in cells to protect DNA from oxidative damage [31].

Biomedical applications of selenium nanoparticles

On the basis of suitable properties such as nano size, high spatial confinement, ease surface functionalization, high surface-to-volume ratio, large surface energy, high bioavailability, low toxicity, pro-oxidant, anti-oxidant and immunomodulatory activities, SeNPs have attracted attention as nanoparticulated delivery system to target cargos to specific site/s against various pathological conditions such as oxidative stress injury and inflammation, rheumatoid arthritis, diabetes, microbial infection, neurodegenerative diseases and cancer (Figure 1).

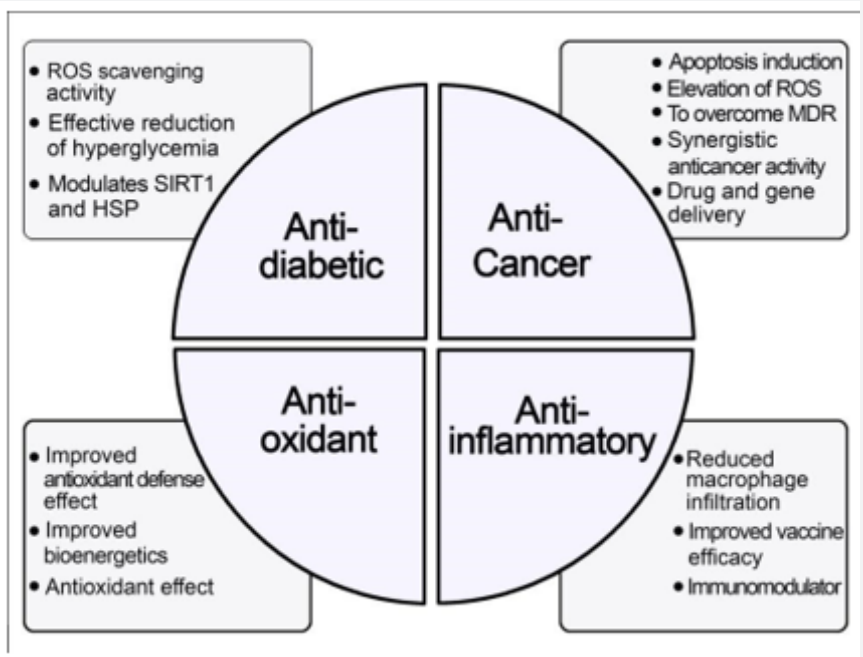

Figure 1: Therapeutic activities of selenium nanoparticles. As antioxidant, SeNPs mainly can scavenge ROS and improve antioxidant defenses, whereas as pro-oxidant, SeNPs chiefly can trigger ROS production leading to endoplasmic reticulum and mitochondrial damage as well as DNA damages.

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Anti-oxidant and anti-inflammatory applications

Inflammation, the immune system's response to foreign bodies, germs, and irritants, is mediated by macrophages to cause acute and chronic disease stages. For free radical generations in oxidative and nitrosative stresses, both ROS (O_2^-, H_2O_2, OH) and RNS (NO,$ONOO^-$) lead to protein oxidation, nitration, lipid peroxidation and DNA damage causing inflammatory gene expressions and cell membrane damages mainly through the induction of TNF-α, the activation of NF-κB and the production of COX-2, while the selenoenzymes such as glutathione peroxidase, thioredoxin reductase, and the thiol anti-oxidant such as glutathione act as antioxidant system to protect the inflammation. In this context, nanoselenium may stimulate the selenium-dependent enzymes to form the selenophosphate and selenocysteinyl tRNA for neutralizing free radicals as well as reducing inflammation [32]. It has been shown that SeNPs may prevent cisplatin-induced gonadotoxicity and nephrotoxicity via the antioxidant capability where free radical toxic stress, spermatic DNA damage and renal injury have been reduced [33,34]. A few investigators have exhibited that SeNPs have been used to restore SOD, T3, T4, catalase and GSH levels and cellular injuries as antioxidant activity against chromium-induced thyrotoxicity [19]. In an experiment, it has been indicated that SeNPs as protective functionality have diminished anastrozole-induced osteoporosis and bone toxicity [19]. A few studies have implicated that SeNPs have protected the male animal reproductive system from aflatoxin B1induced toxicity such as aberrant spermatozoa and the DNA fragmentations [13]. A few other researchers have exhibited that SeNPs have decreased carrageenan-induced inflammatory indicators such as ROS, TNF-α, IL-1β, PGE2, MDA and thiobarbituric acid reactive substances [13]. The usage of silymarin-loaded SeNPs at low concentration against trinitro benzene sulphonic acid (TNBS)-induced colitis has exhibited their anti-inflammatory activities to inhibit MAPK and NF-κB and to decrease TNF-α level, whereas pro-inflammatory cytokines (TNF-α and IL-6), NF-κB signaling, phosphorylation of JNK1/2 and p38MAPK1 have been inhibited by polysaccharide-modified SeNPs [19].

Rheumatoid arthritis (RA), the chronic disease distinguished by joint inflammation and tissue injury and promoted by enhanced ROS production, is progressed by the elevated inflammatory moderators such as TNF-α, IL-6, IL-1β, PGE2, C-reactive protein and MCP-1 [13]. A few investigations have exhibited that catalase-loaded, FA and HA –functionalized SeNPs have been utilized to target activated macrophages associated with atherosclerosis and rheumatoid arthritis through their FR-β and CD44 receptors to destroy high levels of H_2O_2 productions [13]. In another experiment, tripterine-loaded SeNPs have been used as synergic antioxidant and anti-inflammatory effects against inflammation and joint swelling to reduce NO, cytokines and inflammatory mediators [13]. In other experiment, anti-Tfr receptor monoclonal antibody decorated PEGylated SeNPs have been utilized against stroke to protect neuronal cells by the reduction of cellular swelling caused by the abnormal entry of Na^+ ions [13]. Moreover, SeNPs have been applied to treat pulmonary fibrosis to reduce the levels of cytokines such as TNF-α and TGF-β1, the infiltration of inflammatory cells such as fibroblasts [13].

Anti-diabetic applications

Diabetes mellitus, the metabolic disorder owing to the high blood glucose level regulated and controlled by the pancreas-secreted insulin hormone for transforming cellular glucose into energy, is caused and progressed by the endothelial dysfunction-induced oxidative stress leading to failures or damages of the systemic organs [19]. The type-I diabetes may result from autoimmunity, viral infections, genetic disorders or acute poisoning due to less pancreatic insulin secretion in the body, whereas the type-II diabetes due to improper usages of insulin by the body is caused by the lack of exercise and improper diet resulting insulin resistance [19]. The antioxidant and α-glucosidase inhibitor RTFP-3 polysaccharide functionalized with SeNPs have been utilized as anti-diabetic agents in the enhancement of both ABTS and DPPH radical scavenging activity, the decrement of mitochondrial oxidative stress, the activation of pancreatic islet of β cells and the reduction of caspase activation (caspase -8/-9 and 3) [13]. A few investigators have shown the usages of SeNPs in streptozotocin (STZ)-induced type-I diabetes to get hypoglycemic effect with the enhancement of serum insulin concentration and reduced oxidative damages [35]. Another study has exhibited that the *Catathelasma ventricosum* polysaccharides (CVPs)-decorated SeNPs have been utilized to get anti-diabetic activity against

STZ-induced diabetes [36]. The other research group have implicated that chitosan-stabilized SeNPs have been used against STZ-induced diabetic animal to get anti-diabetic activity [37]. A few researchers have shown that liposomal SeNPs treated against STZ-induced rats, have preserved anti-diabetic activity (glucose depletion and enhanced insulin secretion) associated with inhibition of pancreatic inflammation, repression of oxidative stress and enhancement of the antioxidant defense system [38]. Other investigations such as usages of BAY 55-9837 peptide stabilized SeNPs and vasoactive intestinal peptide receptor-2 (VPAC-2) agonist peptide-coupled chitosan-designed SeNPs against type-II diabetes have reported to enhance insulin secretion and decrease glucose level [20,19]. Metformin-loaded SeNPs have shown their synergistic effect against STZ-induced diabetes to increase ROS scavenging and insulin secretion through the activation of pancreatic islet of β-cells, to ameliorate antioxidant defense system and to decrease hyperglycemia [13].

Anti-microbial applications

With the increased release of selenium ions and owing to the capability for adsorbing proteins, SeNPs may disrupt the cell membranes, restrain the multi-drug resistant biofilms, reduce the free intracellular thiols and regulate the microbial genes exhibiting

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their efficient microbicidal activities [39]. Several researchers have exhibited the anti-microbial effect of SeNPs against antibiotic resistant Gram-positive bacteria such as *Staphylococcus aureus* and Gram-negative bacteria such as *Escherichia coli* to destroy bacterial cell walls and biofilm formation and reduce exo-polysaccharide synthesis [39]. Several other researchers have shown the synergistic anti-microbial effects of lysozymes / gelatin / quercetin / acetylcholine / polymer -loaded / coated SeNPs to damage the cellular integrity through the production of ROS stress, autophagy, apoptosis and PI3K/Akt/mTOR signaling pathways [39,19,13]. A few investigators have implicated that SeNPs / chitosan decorated SeNPs have shown their antifungal biofilm inhibition through the penetration into the pathogens disrupting cellular structures with the substitution of sulfur and their cytosolic absorption via sulfate permeases transporters to generate toxic ROS leading to DNA breakages, protein misfolding's and fungal enzymatic dysfunctions [39,13,19]. A few other investigators have demonstrated that SeNPs or oseltamivir/ amantadine/ribavirin decorated SeNPs have elicited their anti-H1N1 influenza viral activities through the inhibition of cellular apoptosis by obstructing DNA fragmentation and chromatin condensation along with the arrest of ROS-mediated actuation of p53 phosphorylation, Akt, cleaved PARP, caspase-8, Bax, p38 and JNK signalings, and the inhibition of hemagglutinin and neuraminidase activities for viral glycoprotein transport into host cells [39,13]. A few experiments with oseltamivir / siRNA-enterovirus VP1 loaded PE1-capped SeNPs have elicited their anti-enterovirus 71 (EV71) activities through the suppression of EV71 proliferation by the inhibition of caspase-3- induced apoptosis and ROS production [39,13]. Moreover, selenium species exposed against hepatitis B virus (HBV) and SARS-COV-2 have shown to suppress HBV protein expression, transcription, and genome replication, and to inhibit COVID-19-infected Vero cells through the covalent binding of COVID-19 Virion Mpro via cell membranes [39]. Furthermore, SeNPs have also been used as anti-parasitic activities against leishmaniasis, schistosomasis and toxoplasmosis to kill the parasites through the enhancement of immune mediators such as IFN-γ, TNF-α, IL-12 and iNO, and the decrement of IL-10 [39,13].

Anti-carcinogenic applications

The uncontrolled cell-divisions and their spreadings to the surrounding tissues lead to cancer or cells-malignancies characterized by proliferative signaling, angiogenesis, resistances to cell death, evasions of growth suppressions, invasions and metastasis, and replicative immortalities [19]. Owing to the intrinsic anticancer activities, SeNPs coupled with higher selectivities to carcinoma cells may exhibit targeted deliveries with reduced systemic toxicities and increased chemotherapeutic efficacies [40]. The internalized endocytosed SeNPs as pro-oxidants may increase ROS levels in cancer cells resulting in apoptotic cellular death and cell cycle arrest at the S-phase via initiation by elF-3 protein deregulation [19]. The conjugated SeNPs associated with intracellular proteins and cysteine-containing enzymes may accumulate ROS inside the cancer cells leading to their destructions [19]. Lysine / Ruthenium –decorated SeNPs have shown their targeting anticancer activities [19]. Human serum albumin coated Dox-loaded mesoporous SeNPs have shown their effective antitumor activities [19]. Negatively charged polysaccharide. (Hyaluronic acid)-functionalized SeNPs have exhibited their significant antitumor activities [19]. Curcumin / paclitaxel –loaded SeNPs have shown their antiproliferative activities against cancer cells through the induction of apoptosis, and oridonin-loaded GE11 peptide-conjugated SeNPs have shown their inhibitory tumor growth by the suppression of tumor angiogenesis [40]. NAS24 / 5TR1 aptamer-functionalized epirubicin-loaded SeNPs have exhibited their inhibited tumor growth in cancer-bearing animal [40]. Dox-loaded liposomal SeNPs have shown their sustained drug release to the carcinoma cells with the synergic anticancer effect [40]. Sialic acid / folic acid –conjugated SeNPs have implicated their active targeted receptor-mediated anticancer activities through apoptosis-induced activation of caspase-3 and proteolytic cleavage of PARP [20,13]. PEG / BSA / chitosan conjugated SeNPs have shown their enhanced therapeutic inhibitory efficacies against cancerous cells [13]. Moreover, triphenylphosphin-functionalized SeNPs have exhibited their cellular mitochondrial targeting as anticancer activities through the induction of ROS generation and the mitochondrial dysfunction [13].

Anti-neurodegenerative applications

Elevated oxidative stress and free radical production in neuronal cells cause a high O_2 consumption, poly-unsaturated fatty acid, and a reduction in enzymatic antioxidant activities leading to the generation of systemic neuro-degenerative diseases, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, epilepsy, cerebral ischemia, and traumatic brain injury [19]. Modified SeNPs as a cofactor in GPx have shown their direct antioxidant effect on the neuronal cells by scavenging H_2O_2 to prevent efficiently oxidative damage as well as decrease in the neuro-degenerative diseases [19]. Cerebral or ischemic stroke caused by the shortness of blood flow in the brain may be protected by the treatment of monoclonal antibodies (OX26) functionalized SeNPs through the targeting various cellular signaling and regulating oxidative defense system, inflammatory reactions, apoptosis, and the cellular metabolic states [19].

Immunomodulatory activities of selenium nanoparticles

SeNPs have exhibited their potent immunomodulation with the regulation of different immune cells and modifications of few crucial immuno signaling incidents [39]. Au decorated SeNPs have shown their activations on anti-tumor immunity significantly with the killing of cancerous cells under the presence

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of tumor-associated antigens and the effective transformation of the tumor associated macrophages (TAMs) from M2 to M1 phenotype supported by the T cell activation for tumor rejection and phagocytosis of the tumor cells [39]. SeNPs have also shown their innate and acquired immune modulations against cancer through the cytotoxic upregulated expressions of NKG2D, CD16, and IFN-γ molecules in γδ T cells and downregulated expression of PD1 molecule in γδ T cells to enhance the killing of cancer cells with the inhibition of tumor growth [39]. Chitosan decorated SeNPs and SeNPs have implicated their immunomodulatory activities against bacterial infectious diseases through the enhancement of immunity and disease resistance with the stimulation of concanavalin A (ConA) and lipopolysaccharide (LPS) and the up-regulation in IL-2 and IL-12 productions, and through the inhibition of Mtb-lysosome escape and the promotion of the host antibacterial immunity by the induction of the host cell autophagy, apoptosis, and M1 anti-bacterial polarization to increase intracellular Mtb killing efficiency significantly [39].

Pharmacokinetics and toxicity of selenium nanoparticles

For therapeutic usages, NPs should be checked for their selective suitability as nanomedicine through pharmacokinetic investigations such as absorption, distribution, metabolism, excretion, and toxicity studies. For oral intake, the absorption of NPs is obstructed by two gastrointestinal barriers namely the intestinal mucosa and the surrounding mucus, while NPs can move via the intestinal epithelium through paracellular and transcellular transportation with endocytosis depending on the surface hydrophobicity, size, and electric charge of the NPs. The lipid containing epithelium of the digestive tract may absorb higher hydrophobic and nanosized NPs, while the distribution and absorption of selenium from SeNPs to organs and their excretion have shown the same outcomes as Se (IV) utilized via the oral route in rats, and the high doses of SeNPs / Se (IV) have shown high relative metabolic amounts in the kidneys and liver in comparison to low doses based on dose and form of selenium [32]. In blood, selenium is transported via selenoprotein P (Sel P) and extracellular GPx, while its nutritive deficiency <40 mg/day, normal range 30-55 mg/day, and toxic levels >400 mg/day [32]. Usually, SeNPs have exhibited their less toxicity, decreased liver impairment and short-term side effects *in vivo* [32]. The dosages of 2.5, 5, 10 and 20 mg/kg of SeNPs have revealed no significant side toxicity in liver, spleen, kidneys and serum indicating their less toxicity and more bioavailability with potent biological characteristics [32].

Conclusion and future perspectives

The naked SeNPs may be utilized as biomedical agents at low concentrations for their antimicrobial and anticarcinogenic features with low cytotoxicity [41]. The tunable positively or negatively charged SeNPs loaded with cargos or biomolecules by covalent or non-covalent bonds conjugated with C=O, COO^-, C-N or NH groups of active pharmaceutical ingredients may enhance their superior adsorptive capability to load, stabilize and deliver cargos to the specific site/s of interest with lower cytotoxicity [40]. However, selenium has a narrow therapeutic window dependent on its dietary deficiency or excessive intake leading to severe symptomatic several diseases with drug resistance. Therefore, SeNPs may be loaded with needed cargos, anchored with ligands, and coated with vesicular system to reduce their cytotoxicity and deliver the minimal ingredients to the targeted site/s maximally with sustained release to get effective biological efficiencies against various diseases. In this context, detailed investigations are required to apprehend the bridge between nano-selenium and the selenium, and the molecular sequences related to their therapeutic differences and toxicity-effects correlated with their biocompatibility. Moreover, further long-term exposure-studies are required for getting maximum *in vivo* targeting biological efficacies of the ligand-attached cargo-loaded SeNPs with optimal formulation, dosage, biocompatibility, biodistribution, pharmacokinetics, biodegradability, toxicity, elimination, and administrative routes specifically oral and intravenous before their clinical transformations as nanobiomedicinal delivery system.

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