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Therapeutic applications of selenium nanoparticles

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ABSTRACT

Nanoparticles (NPs) serve to reduce the toxicity, enhance bioactivity, improve targeting, and provide versatile means to control the release profile of the encapsulated moiety. Among different NPs, inorganic NPs of metals like Ag, Au, Ce, Fe, Se, Ti and Zn possess a significant place owing to their unique bioactivities in nanoforms. Selenium (Se) is an essential trace element. It is incorporated into selenoproteins as selenocysteine (Sec) representing the most important part of the active center of their enzymatic activities. Many selenoproteins have oxidoreductase activity and, thus, regulate the physiological redox balance. Se has a narrow therapeutic window and the toxicity margins are very delicate whereas the nanoparticles of Se (SeNPs) possess remarkably reduced toxicity. SeNPs have been explored in various oxidative stress and inflammation mediated disorders like arthritis, cancer, diabetes and nephropathy with potential therapeutic benefits. SeNPs constitute an attractive carrier platform to ferry various drugs to the site of action. Herein we have discussed the significance of nanosizing on the pharmacological activity of Se. The role of SeNPs in pharmacological protection against various inflammatory and oxidative stress mediated conditions is presented. However, it is largely unknown how SeNPs may affect the pharmacokinetics and pharmacodynamics of selenoproteins. Most of the available studies were poorly designed without any comparison to the other Se sources. In the future, detailed studies with inclusion of an appropriate source of Se should be carried out with emphasis on understanding the role of selenoproteins in the observed pharmacological activity.

1. Introduction

The emergence of nanotechnology in the last three decades has changed the perception of drug discovery and development by opening many hidden doors in disease pathophysiology and treatment options [1,2]. Nanotechnology deals with submicroscopic particles with at least one dimension less than 100 nm. The adage, “small is the new big”, rightly fits to describe the role played by nanotechnology based delivery systems in modern-day therapeutics. A variety of nanostructures, including polymers, dendrimers, liposomes, metal nanoparticles (Ag, Au, Ce, Cu, Eu, Fe, Se, Ti, Y, etc.), silicon and carbon based nanomaterials have been used as successful therapeutic agents and drug delivery carriers [3–10]. The unique features of nanoparticles (NPs) like the small size, high surface area, surface charge, surface chemistry, solubility and multi-functionality make them remarkably unique. NPs have proven their case very strongly as drug carriers by tremendous success in the delivery of the therapeutic molecules. Nanomedicine is the application of nanotechnology based techniques and methods in medical research and clinical practice for the treatment, diagnosis, monitoring and control of biological systems [11]. NPs solve many of the biopharmaceutical and pharmacokinetic (PK) problems associated with many drugs in a variety of disease classes. NPs boost the therapeutic efficiency of ionised drugs; improve the penetration of water soluble compounds, proteins, peptides, vaccines, siRNA, miRNA, DNA and other biological therapeutics. Surface modification of nanoparticles with targeting ligands makes the drug delivery system much versatile and can selectively deliver at target site [12].

Metal nanoparticles of Ag, Au, Ce, Fe, Se, Si, Ti and Zn have a special place in the area of nanotechnology as they offer a unique opportunity not only as theranostic agents but possess tremendous potential as carriers for chemotherapeutic agents, proteins, siRNA etc. Among these nanoparticles, selenium nanoparticles (SeNPs) are one of the most extensively studied. Selenium (Se) metal was discovered by Jöns Jacob Berzelius in 1817 [13]. The term Se was coined from the Greek root ‘Selene’ which means moon. Its atomic number is 34 and belongs to the Group-6 of the periodic table. It was discovered as a byproduct of sulphuric acid synthesis. Se is a semi solid-metal, usually observed as a red colored powder, black in vitreous form and metallic gray in crystalline form, resembling sulphur and tellurium [14]. Se exists in different oxidation states like 2^+, 4^+, 6^+, and 2^-. Se has

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"zero" oxidation state, is colorless, non-toxic, biologically inert material. Some of the critical roles played by selenoproteins are immunomodulatory activity and orchestration of sperm motility [15]. There are 25 selenoprotein genes in human genome. Se is incorporated as selenocysteine (SEC) in various antioxidant enzymes like glutathione peroxidase (GPX), thioredoxin reductase (TXNRD) and selenoprotein P (SELENOP). Se acts as the redox centre of all these enzymes and is essential for their biochemical activity. Some of the other important Se containing compounds are sodium selenite, selenomethionine and monomethylated Se which can act as anticancer agents (mainly chemopreventive) by different mechanisms [16].

A large number of reports indicate the role of Se in the induction of cancer cell apoptosis with minimal side effects on normal cells [17–19]. Anticancer effects are observed at doses close to the toxic levels [20]. Thus, the pharmacological effect and toxicity is critically dependant on the concentration, redox state and the type of Se compound used. Supranutritional doses of Se reduce the incidence of many cancers which includes lung, prostate and colorectal cancer [21]. It causes G_2/M cell cycle arrest and induces apoptosis in cancer cells by mitochondrial pathway [22]. Methylselenic acid and methylselenocysteine supplementation decrease the incidence of lung, colon and liver cancer effectively [23]. High doses of Se may cause toxic effects. The key Se ion behind toxic effects is selenite (Se^{+4}) which is required to be reduced to selenium (Se°) by biogeochemical cycles. Thus, Se is a double edged sword which is antioxidant at sub nutritional doses and becomes prooxidant at supranutritional doses [24]. Fig. 1 outlines various applications of Se based molecules for therapeutics.

A large number of reports suggest unique biomedical applications of SeNPs ranging from antioxidant activity to anticancer effects and are attributable mainly to its redox modulatory property. However, the detailed review of molecular effects of SeNPs is hitherto absent from the current literature. In the present review, we have made an attempt to fill this gap by providing a comprehensive survey of various pharmacological activities with emphasis on the molecular mechanism of such reported activities. In addition, the underlying mechanisms behind the reduction in toxicity of Se upon nanoparticlization have been explored to provide a possible explanation for this unique phenomenon owing to the fact that Se is toxic and the margin of safety is very narrow.

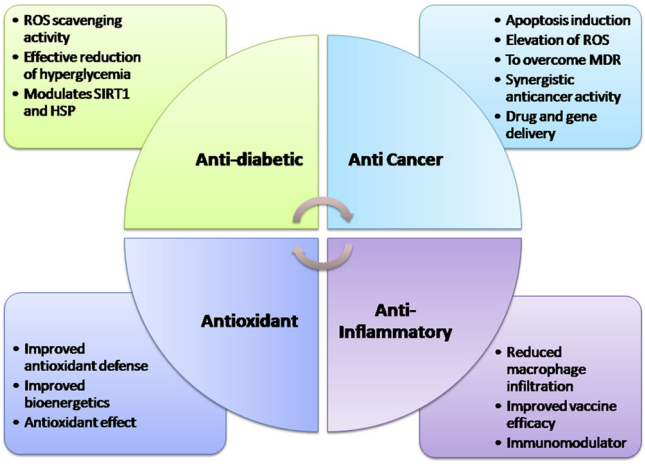

Fig. 1. Therapeutic applications of selenium nanoparticles (SeNPs). SeNPs possess various therapeutic benefits including anticancer, antioxidant, anti-inflammatory and anti-diabetic action. The anticancer activity is largely due to its prooxidant properties in these cells triggering reactive oxygen species (ROS) synthesis leading to mitochondrial and endoplasmic reticulum damage which in turn leads to DNA damage.

2. Selenium nanoparticles (SeNPs)

2.1. Origin and the relevance of nanoselenium

The concept of nanomedicine emerged as a new rising star in the area of therapeutics as this novel platform offers unique advantages. Nanomedicine based approaches envisage modalities to address the complex issues associated with conventional forms of drugs and their dosage forms. A widely accepted advantage of nanomedicine is the enhanced safety. In case of Se, the major hurdle from bench to bedside translation is the small therapeutic window with low margin of dosage error and the use of Se in the form of nanoparticles has substantially answered the toxicological concerns associated with Se. Various methods have been reported for the synthesis of SeNPs like the biological or synthetic methods. A detailed description of various methods used for the synthesis of SeNPs can be found in previously described reviews and is beyond the scope of the present review [25–27]. Se is an integral part of various selenoenzymes like GPXs, TXNRDS, deiodinases (DIO) which are required for multiple biochemical reactions including the physiological antioxidant defense system [28]. It has unique antioxidant and pro-oxidant effects depending on the dose, duration and the oxidation state [16]. The use of SeNPs dramatically reduces the death incurred by acute toxicity associated with Se up to four times in a rodent model [29]. Moreover, the liver injuries associated with the high dosage of Se are substantially reduced by using SeNPs as evident from the biomarkers of hepatotoxicity [30]. Although surprising, the inherent question to be answered is, how the SeNPs attenuate the toxicological outcome associated with Se? To answer this question, understanding the redox state of Se is of utmost importance as the oxidation state of Se lies at the heart of the observed biological effects and the toxicity elicited. The most important organic forms of Se are selenomethionine, selenocysteine, and methylselenocysteine, and inorganic as selenite and selenate. Se exists in various oxidation states like selenate (SeO_4^{2-}, +6), selenite (SeO_3^{2-}, +4), selenide (Se^{2-}, +2) and the Se (Se°). The controlled interplay of different oxidation states of Se may provide a plausible reason for the reduction of toxicity upon nanosizing. The bioavailability and the aqueous solubility of different oxidation states of Se define its toxic response. However, to date there is no sound evidence as to what really happens behind the observed reduced toxicity of SeNPs.

SeNPs exhibit attractive anticancer activity and reduced toxicity concerns compared to different Se species. SeNPs have been used in many disease conditions including cancer, diabetes, inflammatory disorders, liver fibrosis, and drug induced toxicities [31–34]. SeNPs scavenge the free radicals *in vitro* in size dependent manner (5 nm–200 nm). Bo Huang et al. showed that small sized (5–15 nm) SeNPs have better free radical scavenging capacity and prevented the oxidation of DNA. The SeNPs showed superior effects at < 0.5 mM concentration compared to free Na_2SeO_3 which exhibited IC_{50} > 2.5 mM [35]. SeNPs show better bioavailability, biological activity compared with inorganic and organic Se compounds. However, poor cellular intake is the main drawback of SeNPs. Significant attempts have been made to overcome this problem by conjugation of targeting ligands on the exterior surface of nanoparticles. This provides a beneficial platform for anticancer therapy. Surface capping agents control the size, stability, improve the cancer selectivity, enhance cellular uptake and also improve the bioavailability and biological activity of SeNPs. Introduction of amphoteric ligands such as polyethylene glycol (PEG) has been shown to substantially assist in nanoparticle synthesis [36]. In another study, SeNPs were conjugated with a custom synthesized cyclic peptide which showed improved penetrability in SK-OV-3 ovarian adenocarcinoma cell line [37]. Thus, SeNPs can be potentially used as nanosized delivery tools for differentially charged biomolecules and anticancer drugs as well.

2.2. Role of selenoproteins in the pharmacological activity of SeNPs

Se is a unique trace element which exerts pleiotropic pharmacological activities mediated via its incorporation into selenoproteins. Some of the selenoproteins are necessary enzymes and even require SEC in their active sites [16,38,39]. Various reports indicate an indirect antioxidant effect of Se via activation and regeneration of Vitamin C and Q10 by selenoproteins. Modification of signaling proteins by thiol oxidation is one of the most important ways by which selenoproteins affect the function of protein kinases, phosphatases and transcription factors like NFκB [39]. Selenoproteins play important role in adipocyte and enterocyte differentiation [40]. The TRX plays a critical role in the activation of NLRP3 inflammasome which leads to activation of interleukin 1β [41]. GPXes catalyze the reduction of hydroperoxides by oxidizing GSH [42]. Similarly, other selenoproteins are involved in orchestrating various physiological functions. Earlier excellent reviews have been published on the physiological roles of selenoproteins and can be referred for detailed description [40,43–48]. It is unknown how SeNPs affect the pharmacokinetics and pharmacodynamics of selenoproteins. Considering the number of activities demonstrated for the pharmacological activities of SeNPs, it is surprising to note that most of the studies failed to examine and establish correlation with the dynamics of selenoproteins. Detailed studies are thus warranted whereby comparison of SeNPs with its elemental counterpart can be established in correlation with selenoproteins. In addition, studies designed with important selenoproteins like selenocysteine may aid in understanding the biological differences between SeNPs and its various inorganic compounds. Time and concentration dependant alterations in the expression of these selenoproteins in presence of SeNPs and inorganic Se compounds may help in deciphering various unanswered questions related to the biology and toxicology of SeNPs. Such studies may even help in understanding why SeNPs are safer compared to the inorganic forms.

3. Therapeutic applications of SeNPs

Based on the improved properties of SeNPs over Se, they have been explored in various disease conditions. SeNPs offer improved bioavailability with the added advantage of decreased toxicity. The prooxidant, as well as the antioxidant effects provide different avenues for exploration in a variety of pathological conditions. In the present section, we highlight the use of SeNPs for various therapeutic purposes including the conventional antibacterial, anticancer, anti-diabetic, and anti-inflammatory activity. In addition, the progress in targeting strategies and advanced applications has also been summarized.

3.1. Anticancer activity

Cancer is one of the most devastating disorders of the 21st century, creating a major concern among clinicians and researchers. The ever growing problem of drug induced toxicity and resistance has doubled the trouble. Many different treatment strategies are being tried to fight the war against cancer and a plethora of strategies have been attempted. Nanotechnology has significantly improved our approach of personalized medicine whereby the targeting has improved and at the same time the toxicity can be suppressed. Various inorganic nanoparticles have been investigated to induce cytotoxicity in cancer cells and one of the successfully tried nanoparticles is SeNPs. SeNPs based approaches have shown hope in fighting with the drug resistance problem and in mitigating toxicities associated with chemotherapeutic agents. SeNPs offer an excellent platform to ferry chemotherapeutics to the target site. SeNPs exhibit differential activity against malignant cells and normal cells (Fig. 2). The putative mechanism of SeNPs against various cancers is described in Fig. 3.

3.1.1. Bare or unfunctionalized SeNPs

Wang et al., proved the efficacy of SeNPs in killing intraperitoneally injected H22 hepatic cancer cells. Interestingly, the NPs were found to preferentially localize inside the cancer cells and caused production of reactive oxygen species (ROS) thereby causing cytotoxicity [49]. In vivo efficacy of SeNPs in hepatocarcinoma was proved by Ahmed et al., where SeNPs were found to alleviate N-nitrosodiethylamine induced hepatocarcinoma. SeNPs significantly reduced DNA damage as evident from the decreased ratio of 8-hydroxy-2-deoxyguanosine and 2-deoxyguanosine. Moreover, genetic analysis of the treated and the diseased animals revealed that SeNPs increased the expression of aldo-ketoreductase1B10 (Akr1b10), ING3 (interacts with p53 and induces apoptosis) and decreased the levels of Foxp1 gene (Forkhead box, class O; involved in proliferation of hepatic stellate cells) [50]. Luo et al., showed that SeNPs exhibit anti-proliferative activity in MDA-MB-231 cells in a dose (10–40 μmol/L) dependent manner. SeNPs effectively arrested the S phase in MDA-MB-231 cells at 10 μmol/L [51]. Kong et al., observed that SeNPs reduced the growth of LNCaP prostate cancer cells by degradation of androgen receptors which are required for the normal function of prostate cells. SeNPs activated the Akt/Mdm2 pathway, decreasing the transcriptional activity of androgen receptors by regulating its mRNA and protein expression [52]. In the case of lung cancer, pretreatment of SeNPs inhibited the incidence of lung cancer induced by ferric nitrilotriacetate. SeNPs decreased the lipid peroxidation, inflammation (TNF-α) and C reactive protein levels [53]. Vekariya et al. reported the activity of chemically synthesized SeNPs, where the NPs were found to modulate estrogen receptor-alpha signaling in MCF-7 breast cancer cells and led to increased expression of cytochrome C, Bax, and P-p38 compared to MDA-MB 231 cells [54]. In a separate report, SeNPs were found to significantly reduce the adhesion force, induce apoptosis and necrosis in MCF-7 cells and decreased the expression of CD44; caused disorganization and dysregulation of intracellular cytoskeleton F-actin in MCF-7 cells [55]. SeNPs inhibit the matrix metalloprotein-2 expression which is mainly involved in tumor invasion, metastasis and angiogenesis in fibro-sarcoma cell lines (HT-1080) [56].

SeNPs showed promising anti-proliferation activity and inhibition of HeLa cells during S phase [51,57]. In another study, SeNPs were synthesized intracellularly from haloarchaeon *Halococcus salifodinae* BK18 with the involvement of enzyme NADH-dependent nitrate reductase. In HeLa cells, SeNPs showed remarkable antiproliferative activity and no toxicity to normal HaCat cell lines [58]. Although effects of SeNPs look appealing in these cells lines; however to make a concrete conclusion, *in vivo* studies are mandatory which are hitherto not much explored. In addition, exploring the role of SeNPs in three dimensional (3D) tumor spheroid models may help to delineate the possible mechanism [59]. Moreover, 3D models may benefit in exploring the possible tumor mechanisms as these models mimic the *in vivo* conditions much closer compared to the two dimensional (2D) systems.

3.1.2. Stabilized SeNPs

The naive SeNPs suffer from the issue of stability which leads to compromised in efficacy and physicochemical characteristics of the NPs. Various attempts have been made to improve the stability and biocompatibility of these promising anticancer NPs. In the case of melanoma, SeNPs decorated with *Spirulina* polysaccharide to enhance biocompatibility and increase residence time owing to bioadhesive properties were proved as a chemotherapeutic agent in A375 melanoma cell lines. The NPs induced apoptosis, hallmarked by increased sub G1 cell population, chromatin condensation; DNA fragmentation and phosphatidylserine translocation thereby inhibiting the cell proliferation [60]. In a similar study by Chen et al., SeNPs fabricated in the polysaccharide of *Undaria pinnatifida* to enhance stability, induced apoptosis in A375 melanoma cells with the involvement of oxidative stress and mitochondrial mediated apoptotic pathway [61]. Surface capping of SeNPs with water soluble polysaccharides-protein complexes

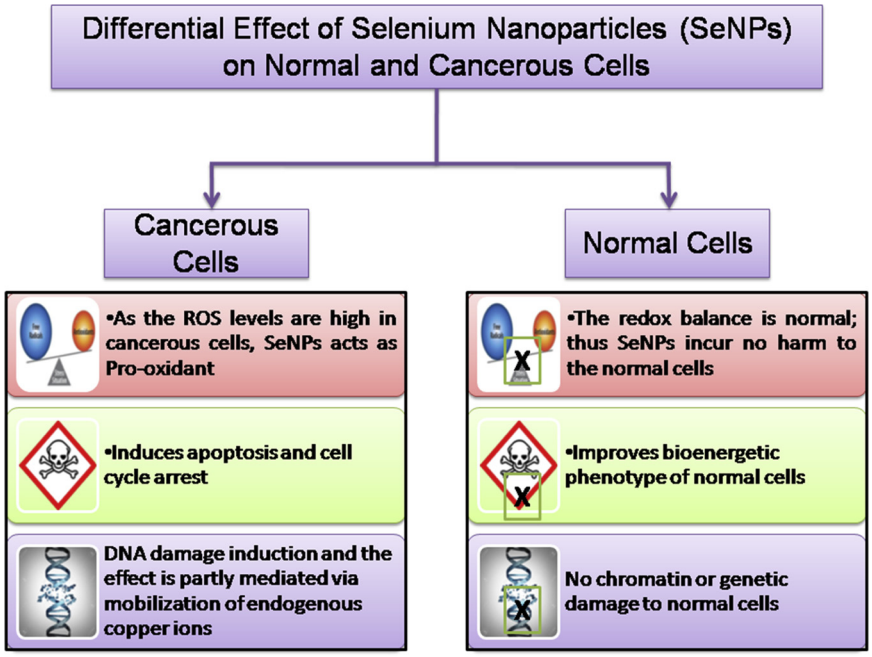

Fig. 2. Differential activity of SeNPs on cancer cells and normal cells. SeNPs show prooxidant behavior inside malignant cells owing to distinct osmotic and redox state of cancerous cells. The nanoparticulate form of Se provides controlled release behavior with improved cellular bioavailability. This unique difference between cancer cells and normal cells leads to reduced toxicity of SeNPs compared to their inorganic counterpart although the basic mechanism of cellular death incurred remains the same.

of *Polyporus rhinoceros* significantly enhanced the endocytosis of NPs which in turn led to enhanced anticancer effect as evident from the increased DNA damage, caspase 3/8 activation, and cellular growth arrest in G2/M phase in lung cancer cells [62]. One study showed that mushroom polysaccharide-protein (PSP) complexes capped SeNPs with higher stability and prolonged residence time are good candidates for therapy of breast cancer. High stability of PSP SeNPs was found to be due to physical adsorption of hydroxyl groups of polysaccharides and imino groups of proteins on the surface of SeNPs. It induced apoptosis in MCF-7 cells via cleavage of PARP and activation of caspase-7, 8 and 9. Mitochondrial mediated intrinsic apoptotic pathway played a major role in SeNP-PSP mediated apoptosis [63]. The anti-glioblastoma activity of *Gracilaria lemaneiformis* polysaccharide (GLP) functionalized SeNPs has been reported, where the combination proved better than the parent NPs. GLP augmented the cellular uptake of SeNPs and specific binding to the αv-β3 integrin receptors over expressed on U87 glioma cells compared to C6 cells. GLP-SeNPs induced apoptosis in U87 glioma cells by activation of p53, MAPKs and Akt pathways [64].

Surface charge is an important determinant of cellular uptake and applications of SeNPs and NH_3^+ groups of chitosan were found to enhance stability of SeNPs in aqueous solutions. NH_3^+ groups bind to the phosphoryl groups of phospholipid components in cell membrane increasing the cellular uptake of SeNPs. SeNPs decorated with chitosan were found to induce comparatively higher apoptosis in A375 melanoma cells in a dose dependent manner, compared to liver (HepG2) and osteosarcoma (MG-63) cells and no toxicity to normal human kidney (HK-2) cells indicating selective targeting [65]. Selective cellular uptake is a major problem associated with anticancer drugs. Estevez and co-workers compared the effect of chitosan stabilized SeNPs with inorganic Se compounds: selenomethionine, selenocysteine,

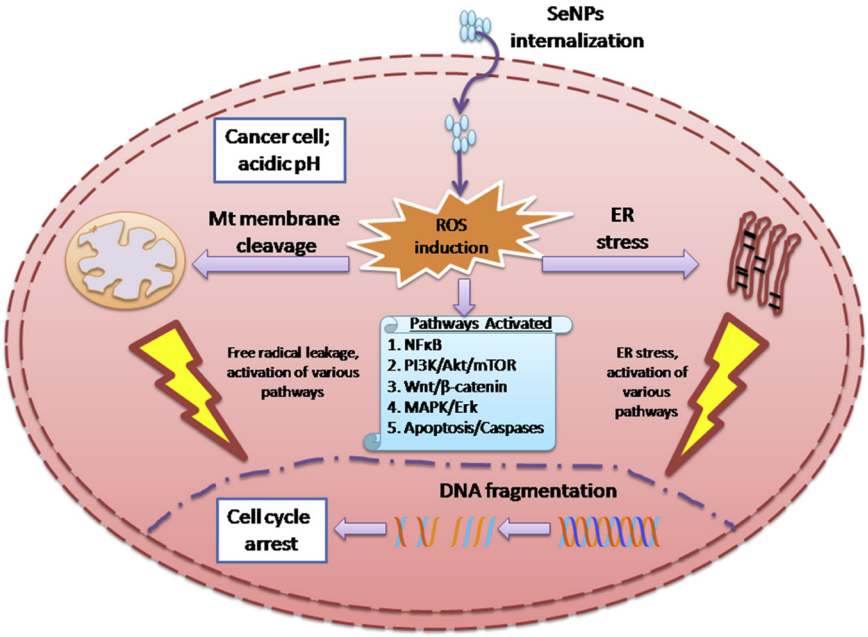

Fig. 3. Putative mechanism of anticancer activity of SeNPs. SeNPs are believed to internalize via receptor mediated endocytosis. The malignant cells have an acidic pH state with redox imbalance. This microenvironment of malignant cells leads to prooxidant conversion of SeNPs triggering the further formation of free radicals which on one side causes mitochondrial membrane disruption causing leakage of mitochondrial (Mt) proteins and on the other side leads to endoplasmic reticulum (ER) stress. Damage to Mt membrane leads to leakage of various proteins and triggers apoptosis via activation of caspases. This cellular stress state orchestrates activation of multiple molecular pathways including the NFκB, PI3K/Akt/mTOR, Wnt/β-catenin, MAPK/Erk and apoptotic pathways. The NFκB pathway stimulates the inflammatory and oxidative stress signaling and disrupts cellular homeostasis. The PI3K/Akt/mTOR, MAPK/Erk, VEGF and Wnt/β-catenin pathway are important in oncogenic signaling and their modulation by SeNPs causes impaired cellular proliferation and hampers the growth promoting signaling in the vicinity of tumor microenvironment. In addition, SeNPs have been shown to slow down the angiogenic signaling in cancer cells which further checks the growth and proliferation. Amalgamation of these disruptive cellular events initiates DNA damage causing cell cycle arrest ultimately culminating as cell death.

methylselenocysteine, Se^{+4} and Se^{+6} on hepatocarcinoma cell lines. Mechanistically, the NPs caused dysregulation of eukaryotic translational factor (eIF3m and EiF3d) required for cell proliferation and oncogenesis [66]. Yu et al., reported that structure transformable nanocapsules prepared by the decoration of SeNPs with folate-chitosan, to form small shell nanocapsules. The NPs were found to selectively endocytose inside cancer cells [65]. Studies reported that amino acid functionalized SeNPs provide better stability and biocompatibility. Amino acid surface decorated SeNPs showed ROS mediated apoptosis in a dose dependent manner in MCF-7 cell lines. Compared to aspartic acid, lysine and valine decorated SeNPs exhibited higher apoptosis [67]. Collectively, these reports indicate the potential of stabilized SeNPs to become an attractive future option of these difficult to treat cancer types. However, more detailed *in vivo* studies are desired to support the proof of concept. In addition, analytical techniques to estimate the change in selenoprotein concentration should be employed along with the biological evaluation of SeNPs so as to establish a concentration and time dependant correlation.

3.1.3. Functionalized SeNPs

The ability of a therapeutic system to recognize and to distinguish cancerous cells from the normal imparts specificity. Thus a unique ability to target tumors is necessary for active targeting. Enhanced site specificity by targeting various peculiar features of the tumor stroma increased the efficacy of the treatment and at the same time reduces side effects. A variety of functionalization strategies have been employed for targeting the tumor tissues. ATP is an endogenous energy compound which acts as a neurotransmitter that can selectively bind to the purinoceptors present in various cancers including hepatoma cancer cells. Zhang et al., synthesized ATP decorated SeNPs which could specifically bind to purinoceptors in the tumor. ATP functionalized SeNPs caused dose dependent apoptosis and showed significant cancer cell death [68]. Luminescent Ru (II)-thiol conjugated SeNPs selectively inhibited the tumor growth and angiogenesis in a HepG2 xenograft tumor mice model, with less toxic effects. It impressively inhibited tumor growth by inhibiting the mitochondrial membrane potential and produced ROS in a dose dependent manner with higher tumor-targeted fluorescence indicating the superiority of SeNPs as a theranostic agent [69]. Lack of targeting causes nanoparticle induced side effects, which can be overcome by functionalization of nanoparticles with small molecules. Folic acid receptors are over expressed in many cancer types and have been widely explored for active targeting to cancer cells. Folic acid modified SeNPs induced S phase arrest and mitochondrial mediated apoptosis in MCF-7 cells. SeNPs induced ROS production, and disrupted mitochondrial membrane potential and activated mitochondrial mediated apoptotic pathway [70] and disorganize the cytoskeleton by decreasing the expression of F-actin [55]. Folate functionalized SeNPs were found to be endocytosed effectively inside the HepG2 cells and elicited remarkable anticancer effects. Moreover, the inclusion of ruthenium polypyridyl imparted fluorescent properties to the NPs facilitating the cellular tracking of NPs. SeNPs overcame multidrug resistance (MDR) by inhibition of ATP binding cassette MDR proteins [71]. Transferrin (Tf) is one such strategy which has been explored extensively for better target ability of nanoparticles via surface decoration owing to the fact that Tf receptors are over expressed in tumor tissues. Li et al. harnessed this property of Tf and showed enhanced accumulation of Tf functionalized SeNPs inside HeLa cells.

Sialic acid is an electro negatively charged monosaccharide that targets the selectins present in the plasma membrane of cancer cells. Sialic acid was found to promote the cancer targeting, cytotoxicity and cell penetrating abilities of SeNPs in HeLa cells. As reported by Zheng et al., sialic acid evidently enhanced the Se concentration in cancer cells 338% more compared to normal control cells. It selectively caused loss of cellular adhesion, cell shrinkage and promoted the formation of apoptotic bodies. The approach showed low toxicity to normal cell as observed in human kidney (HK-2) cells. Sialic acid coated SeNPs induced apoptosis via the activation of caspase-3 and proteolytic cleavage of PARP [72].

PEGylation is a well-known strategy to modify the pharmacokinetic and pharmacodynamic properties of nanoparticle based formulations. PEG-nanolized ultra SeNPs showed stronger cytotoxic activity in drug resistant R-HepG2 cells, than normal HepG2 cells. PEG200 is a surface modifier which increased the cellular uptake of SeNPs. Interestingly, the PEG-SeNPs complex was uptaken by resistant R-HepG2 cells via endocytosis. The cytotoxicity assay proved that PEG-SeNPs complex exhibited superior cytotoxicity in R-HepG2 cells compared to normal HepG2 cells and very less cytotoxicity to HK-2 normal kidney cells, thus indicating preference of PEGylated SeNPs for killing the resistant cancer cells. Moreover, PEG enhances internalization of the NPs by promoting endocytosis and may provide enhanced circulation time if given *in vivo*. The results of normal kidney cells indicated the safety of the used SeNPs [36].

Gene therapy offers a versatile platform to inhibit the disease progression molecularly. However, delivering siRNA/miRNA has been challenging and various nanotechnology based systems have been used to effectively deliver genes. In an attempt to explore the viability of SeNPs to deliver genes, Li et al., loaded heat shock protein-70 (Hsp-70) siRNA inside polyethyleneimine modified SeNPs to kill HepG2 cells. Interestingly, the NPs exhibited impressive transfection efficiency with significant cancer cell death by inducing ROS and apoptosis (via p53 and Akt) [73]. Thus, this study opened new avenues and possibilities to be explored with the NPs based on this essential trace element. However, the major drawback of these preclinical studies has been lack of in vivo studies. In addition, none of the studies tried to establish any correlation with kinetics of selenoproteins. Until the experimental designs are improved with emphasis on in vivo efficacy of the formulations, such studies may only continue to report various activities of SeNPs but are actually of little value concerning the question of clinical translation.

3.1.4. SeNPs in combination with other drugs

Conjugation of NPs with chemotherapeutic agents may aid in the efficacy of the cargo as NPs elicit better cellular internalization. Most cancers develop multi-drug resistance and systemic toxicity which can be overcome by the combination of drugs at low concentrations. Various drugs have been used either in combination with SeNPs or in the form of complexes/conjugates of SeNPs. 5-Fluorouracil (5-FU) coated SeNPs exhibited enhanced anticancer activity in A375 cells. Surface functionalization with 5-FU induced apoptosis in dose dependent manner with the involvement of ROS which was confirmed by activation of caspase 9 and depletion of mitochondrial membrane potential in addition to increased DNA damage and nuclear condensation [74]. SeNPs in combination with irinotecan increased antitumor activity in *in vitro* and *in vivo* as well. In human ileocecal adenocarcinoma (HCT-8) cells, the combination of Irinotecan and SeNPs induced p53 mediated apoptosis and partially caspase mediated apoptosis. SeNPs increased the activity of caspase-7, 8 and 9. Both intrinsic and extrinsic apoptotic pathways were involved in SeNPs mediated apoptosis [75]. The combination of adriamycin and SeNPs proved to be a potent approach to cancer chemotherapy. This combination exhibited synergistic anticancer activity at small concentrations compared to the drugs alone in Bel7402 hepatic cancer cell lines [76]. Similarly, anti-hepatocarcinoma effects were observed in HepG2 cells with anisomycin-loaded functionalized SeNPs, where the NPs arrested the cell cycle progression at G0/G1 phase [77]. SeNPs were also shown to enhance radiosensitivity on A375 cells and combined therapy elicited synergistic activity [78]. X-ray responsive PEGylated SeNPs were shown to effectively reduce HeLa cell growth and provided effective anticancer activity [79].

Biomolecules present in plants like flavonoids, terpenoids, vitamins, and polysaccharides are used for reduction, synthesis, and stabilization of NPs. SeNPs synthesized from quercetin and gallic acid were shown to

possess antioxidant, antimicrobial and antitumor activity [80]. Bimetallic Se-Ag nanoparticles showed promising antitumor activity against Dalton lymphoma cells [81]. SeNPs (25 μg/mL) in combination with doxorubicin (2.5 μg/mL) showed superior apoptotic effect in MCF-7 human breast cancer cells compared to individual drugs. SeNPs also show significant antitumor activity in MCF-7 cell induced *in vivo* xenograft model [82].

Thus, surface decoration of SeNPs with various carriers and ligands might be a fruitful strategy to improve the selectivity and efficacy and at the same time to reduce the toxicity. These studies indicate potent anticancer activity of SeNPs, their conjugates and functionalized products against a wide array of cancer types. However, the clinical translation has not been possible yet as most of the studies were carried on two dimensional *in vitro* cell culture models. Detailed anticancer studies on three dimensional (3D) cell culture and *in vivo* models may ease the path of SeNPs to reach the clinic [59]. So the emphasis on *in vivo* translation of anticancer effects is the need of the hour and more detailed studies with possible mechanistic profiles in preferably nude mice models may add value and improve the possibility of clinical translation of this promising metal NPs.

3.1.5. Drug and gene delivery

Nanomedicine has emerged as a boon to the present day pharmaceutical applications. Multifunctional NPs have made a paradigm shift in the synthesis and biomedical applications of nanomedicine for tailored applications like targeted therapy, diagnosis and combating MDR. SeNPs serve as an attractive platform for drug and gene delivery and growth has been rapid in the last five years. They have been utilized as drug carriers for anticancer agents; for delivering genes to the target site and for active immunization via carrying antigens. Se and Au NPs stimulate both cellular and humoral components of the immune system and induce proinflammatory cytokines. Nanoparticles stimulate the release of interferon-γ from splenocyte. Colloidal particles encourage the antigen presentation to the reticuloendothelial system [83].

Multidrug resistance is one of the teething problems in chemotherapy. The observed resistance to various drugs may occur due to the mutation in the drug efflux pumps. The most widely known cause of resistance is mediated via overexpression of ATP binding cassette including P-glycoproteins (P-gp) and MDR proteins like breast cancer resistance protein (BCRP). Another major cause of drug resistance is the involvement of hidden cancer stem cells (CSCs) which lead to an even bigger threat for cancer therapy. Thus novel delivery vehicles with attractive theranostic properties are welcome to strengthen the armamentarium against cancer. SeNPs are potential drug carriers and numerous evidence indicate its potential vitality as a valid carrier. Polyamidoamine dendrimer-modified SeNPs simultaneously delivered cisplatin and siRNA. It induced cell apoptosis through the PI3K/Akt/mTOR and MAPK/ERK pathways in A549/DDP cells. In nude mice model, polyamidoamine modified SeNPs significantly delivered the siRNA and cisplatin to tumor, without any systemic toxicity [84]. PEG functionalized SeNPs proved to be effective delivery carriers of crocin for pH responsive delivery. The novel NPs could effectively kill lung cancer cells *in vitro* and proved their efficacy *in vivo* as well in nude mice model via synergistic anticancer activity [85]. Mesoporous SeNPs were reported as carrier for the delivery of doxorubicin for targeting breast cancer with reduced toxicity and enhanced anticancer efficacy [86]. Curcumin loaded SeNPs were reported with promising anticancer activity and were found efficacious against Ehrlich's ascites carcinoma mouse model via induction of apoptosis and reduction of NF-kB signaling and EMT [87]. Curcumin functionalized SeNPs were reported for enhanced chemopreventive activity [88].

The utility of small interfering RNAs (siRNA) has shown great promise in treating a variety of diseases including many types of cancer, while their ability to silence a wide range of target genes underlies their effectiveness, the application of therapies remains hindered by a lack of an effective delivery system. Xia et al., reported successful targeted delivery of siRNA using RGDfC-conjugated functionalized SeNPs against liver carcinoma. The anti-Oct-4 siRNA loaded SeNPs activated Wnt/β-catenin signaling and triggered Bcl-2 mediated apoptosis. In addition, the NPs were proven safe as evident from the results of organ histology [89]. Layered double hydroxide supported SeNPs were functionalized with dual siRNAs against anti-P-gp and anti-β-tubulin III for combating MDR in breast cancer. The targeted NPs effectively induced cellular apoptosis, changed morphology, enhanced cellular ROS levels via the expression of Bcl-2/Bax, activation of caspase-3, PI3K/Akt/mTOR and MAPK/ERK pathways [90]. However, as mentioned earlier the major lacuna lies in the area of correlation in terms of selenoprotein levels as it is essential to establish the real pharmacodynamics of therapeutics and the role of these proteins behind the observed protective effects.

3.2. Protective role of SeNPs in drug induced toxicity

Cisplatin is one of the most widely used anticancer drugs for treatment of various cancers including testicular cancer, head cancer, ovarian cancer and neck cancer but it produces severe toxic effects. Major toxicities associated with cisplatin are nephrotoxicity and genotoxicity mediated via activating inflammatory pathway ultimately causing profound oxidative stress leading to organ damage. Other previous studies have shown that several natural and synthetic antioxidants such as vitamin C, lycopene, N-acetyl cysteine show nephroprotective action on cisplatin induced nephrotoxicity. One study reported that 11-mercapto-1-undecanol (MUN) decorated SeNPs decreases cisplatin induced nephrotoxicity in human kidney HK-2 proximal tubular cells. Co-treatment of SeNP-MUN with cisplatin decreased the activation of caspase-3 and exhibited nephroprotective action by inhibition of ROS. So, the combination of anticancer drugs with SeNPs may be a better strategy to reduce toxicities associated with cytotoxic anticancer drugs. However, the effects were not compared to any inorganic Se compound [34]. Razvanfar et al., showed that SeNPs decrease the cisplatin induced reproductive toxicity, improved sperm characteristics, sperm DNA integrity and serum testosterone [91].

SeNPs showed a protective effect on chromium induced thyrotoxicity. SeNPs reduced the $K_2Cr_2O_7$ induced oxidative stress in thyroid gland, restored the T3, T4, superoxide dismutase (SOD), catalase, and GSH levels in treated animals. Furthermore, SeNPs preserved the cellular structure, prevented the cell damage and inhibited changes observed in thyroids [92]. Anastrozole is used for the treatment of breast cancer, and bone toxicity is the limiting factor in clinical usage. Results of *in vitro* studies on human osteoblasts indicated decrease in cell death by SeNPs treatment (5 μg/mL). In addition, SeNPs were found to reduce Anastrozole induced osteoporosis and increased bone density at the studied doses (0.25, 0.5 and 1 mg/kg). Thus, this study with SeNPs highlighted the protective effect on ovariectomized rats by reducing the risk of osteoporosis and bone cell death and this may become a potential treatment for osteoporosis in future [93]. Sirous et al. compared the activity of selenite and SeNPs in healthy sheep. SeNPs increased the number, activity, survivability of white blood cells. SeNPs showed superior antioxidant activity than sodium selenite by reducing the thiobarbituric acid reactive substances (TBARS) levels in plasma. Se is a component of various antioxidant enzymes which might be responsible for the observed protection from oxidative damage in blood cells [94]. SeNPs were reported to alleviate cadmium chloride induced neuro and nephrotoxicity via reduction of oxidative stress and apoptosis [95]. Fig. 4 depicts the putative mechanism of action of SeNPs against drug induced organ and genotoxicity. Thus, it may be potentially used for preventing occupational health hazard associated with this highly toxic metal in various industries. Though there are multiple reports suggesting the beneficial role of SeNPs, most of the studies were not compared to any inorganic Se source, thus making it difficult to establish a viable correlation in terms of Se concentrations reached and the corresponding effect on selenoprotein synthesis.

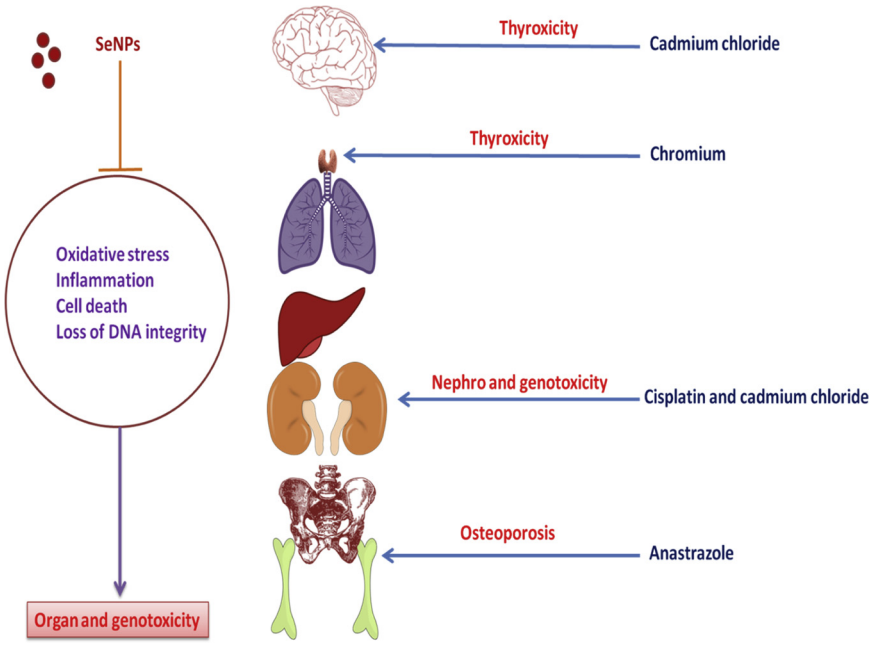

Fig. 4. Modulation of drug induced toxicity by SeNPs. SeNPs have been shown to attenuate the drug induced organ and genotoxicity by modulation of oxidative stress, inflammation, apoptosis and DNA fragmentation. SeNPs were found to reduce the thyrotoxicity caused by cadmium chloride and chromium. Furthermore, SeNPs have been found protective against cisplatin induced nephrotoxicity and anastrazole induced osteoporosis.

3.3. Role of SeNPs in inflammatory diseases

Inflammation is one of the most important initial steps in the pathobiology of a plethora of diseases. Combating inflammation by using novel strategies is one of the fertile areas and a large number of research groups worldwide are exploring the utility of such interventions. One study reported that a combination of silymarin and SeNPs at low concentration (120 mg/kg silymarin + 2 μg/kg SeNPs) is a good candidate for reducing experimental trinitro benzene sulphonic acid (TNBS) induced colitis in rats. The combination showed superior benefits compared to SeNPs alone at 2 mg/Kg. SeNPs were found to inhibit the MAP kinase, NFκB and reduced TNF-α levels. Combination exhibited excellent antioxidant and anti-inflammatory property. However, clinical studies are warranted for the safety and efficacy of the new intervention [96]. SeNPs decorated with *Ulva lactuca* polysaccharide with enhanced stability and prolonged residence time effectively reduced dextran sodium sulphate induced colitis via inhibition of proinflammatory cytokines (IL-6 and TNF-α) and NFκB signaling [97]. In another study, SeNPs were reported as anti-inflammatory agents in multiple models including carrageenan induced paw edema with and without irradiation using 6 Gy gamma radiation. SeNPs (0.5, 1, and 2.55 mg/kg) could effectively alleviate paw edema of non-irradiated and irradiated rats in a dose dependant manner [98]. But, detailed mechanistic studies are warranted along with comprehensive toxicological profiling for ascertaining the clinical utility of SeNPs.

Natural polysaccharides have better bioavailability, bio-compatibility and less toxicity. Hydroxyl groups of polysaccharides prevent the aggregation of NPs by intermolecular hydrogen bonds. Anti-inflammatory activity of polysaccharide modified SeNPs may be due to the inhibition of NF-κB pathway via inhibitory protein Iκ-B subunit. It also inhibited the phosphorylation of JNK1/2, p38 MAPKs [99]. Photodynamically active SeNPs with photosensitive and macrophage-targeting bilayers were proved to be an effective way to combat macrophage mediated inflammation, a major cell type involved in acute and chronic inflammation. The dual coating based on a photosensitizer (rose bengal) and thiolated chitosan was found to provide a theranostic platform for fluorescence imaging and treatment of induced macrophages via H_2O_2 depletion [100].

Melatonin-SeNPs showed a protective effect on immunological liver injury induced in mice by BCG and LPS. SeNPs and melatonin form a novel complex, with synergistic antioxidant activity and reduce the oxidative stress induced by BCG/LPS. Previous studies reported that melatonin protects the liver injury by its direct antioxidant action and immunoregulatory activity. Melatonin-SeNPs treatment (5, 10 and 20 mg/Kg) increased the activity of antioxidant enzymes like SOD, GPX activity, decreased serum ALT, AST, NO, MDA levels, liver pathological abnormalities, proinflammatory cytokines and splenocyte proliferation [33,101]. Biogenic SeNPs synthesized from L. *plantarum* strain showed immunostimulatory effect in BALB/c mice with 4T1 breast cancer cells. SeNPs oral treatment significantly enhances the proinflammatory cytokines such as Th 1, cytokines IFN-γ, IL-2, IL-12 and TNF-α and also increases the delayed hypersensitivity reaction. SeNPs reduced the tumor volume and increased the survival of mice treated with SeNPs due to increased immune response [102]. Fig. 5 shows the proposed mechanism of action of SeNPs against inflammatory disorders. However, most of these studies also indicated therapeutic benefits of SeNPs

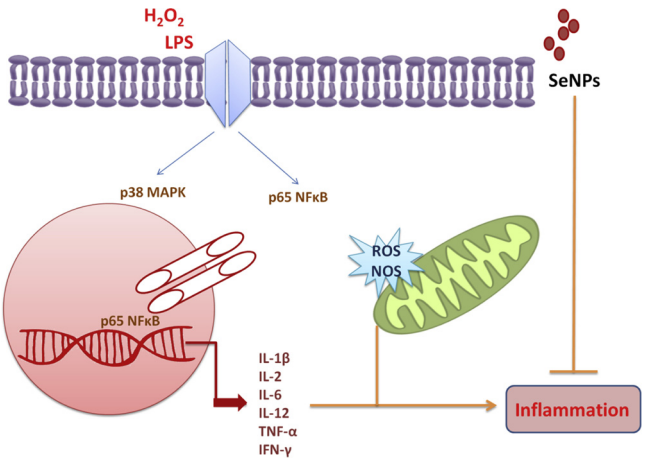

Fig. 5. Anti-inflammatory effects of SeNPs. SeNPs are effective in perturbing the inflammatory response incurred by H_2O_2 or lipopolysaccharide (LPS). SeNPs owing to their antioxidant activity, were shown to scavenge the ROS and RNS. Modulation of the p38 MAPKs and NFκB has been indicated as the mechanism of anti-inflammatory activity whereby it reduces the expression of inflammatory cytokines like IL-1, IL-2, IL-6, IL-12, TNF-α and IFN-γ. ROS-Reactive oxygen species; RNS- Reactive nitrogen species; MAPK- Mitogen activated protein kinase; NFκB- Nuclear factor kappa-light-chain-enhancer of activated B cells.

without comparison to any inorganic Se source. In addition, lack of simultaneous evaluation of pre, post and concurrent treatment strategy hinders in evaluating the proper pharmacological effects. Detailed toxicological studies are must to hasten the pace of clinical development of SeNPs.

3.4. Diabetes and associated complications

Kumar et al. studied the protective effect of SeNPs on progression of diabetic nephropathy. SeNPs exhibited biological activity in streptozotocin induced diabetic nephropathy by reducing oxidative stress and increasing the activity of cytoprotective protein Hsp-70, longevity protein Sirt1 and modulated the expression of apoptotic protein Bax and anti-apoptotic proteins Bcl-2 in apoptotic kidney. However, the effects were not correlated either with selenoprotein concentration or a standard inorganic Se source [32]. BAY 55-9837 it is a long peptide with 27 amino acids found to be beneficial for type 2 diabetes mellitus (T2DM). To increase the plasma half-life and decrease the renal clearance rate, this protein was conjugated with chitosan stabilized SeNPs. Conjugation increases the apparent size of the protein, thereby enhances the $t_{1/2}$. Conjugation of small molecules with nanocarriers increases the $t_{1/2}$ of therapeutics. SeNPs were found to reduce the apoptosis of pancreatic β-cells by its antioxidant activity. Stable BAY 55-9837 -SeNPs with 200 nm size were found to stimulate insulin release from pancreatic cells [103].

Vasoactive intestinal peptide receptor 2 (VPAC2) agonist peptide-conjugated chitosan modified SeNPs were found to show selective activity against type-2 diabetes. The NPs were reported to enhance proliferation, glucose uptake and insulin uptake along with reduction in intracellular oxidative stress [104]. In a recent breakthrough, SeNPs were proposed as a plausible vehicle for oral delivery of insulin. The NPs were reported to have synergistic antidiabetic activity with promising antioxidant, improved pancreatic islet function and promoted glucose utilization [105]. Fig. 6 describes the various plausible targets modulated by SeNPs in pharmacological models of diabetes. Thus, such a novel delivery carrier may become an attractive tool for future therapy of insulin dependent diabetes with improved therapeutic outcomes. However, it is too early to decide the clinical fate of these NPs owing to the lack of sound proof of preclinical toxicology. In addition, more detailed pharmacodynamic studies with inclusion of inorganic Se source and measurement of selenoproteins need to be planned for further understanding the molecular mechanism behind the observed protection.

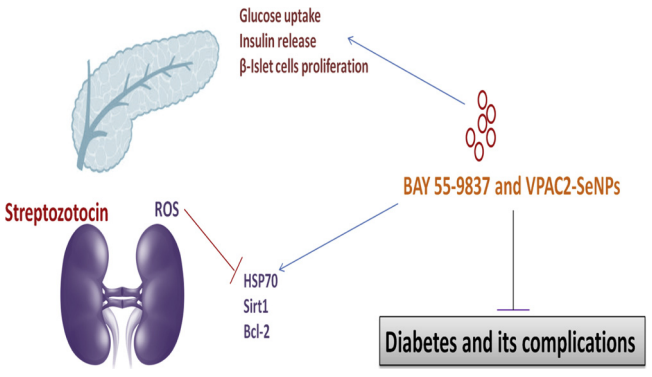

Fig. 6. Anti-diabetic activity of SeNPs. SeNPs possess antidiabetic properties independently as well as in combination with other agents. SeNPs in combination with BAY 55–9837 and VPAC-2 was found to effectively combat the hyperglycemia. SeNPs have been shown to improve insulin release and β-cell proliferation. The proposed mechanisms for its ability to fight against diabetes and associated complications include the ROS scavenging ability and modulation of SIRT1 and HSP70.

4. Future directions

Nanotechnology driven formulation approaches hold a substantial potential in the 21st century drug discovery and developmental programs. The evidence is not hidden from anyone and there are numerous nanotechnology based products in the market. Nanoparticles of Se, an essential trace element required as a cofactor for various enzymes, has emerged as an important tool in theranostics of not only cancer but for combating wide array of maladies ranging from bacterial, fungal and viral infections, inflammation, neurodegenerative disorders, diabetes, drug induced toxicity etc. Indeed SeNPs hold significant rationale behind the majority of reported studies. However, there is still a long way forward in deciding the therapeutic window owing to the higher toxicity potential of Se. Detailed studies are needed to understand the bridge between the Se and nano Se and the molecular events that are responsible for the therapeutic differences. High throughput platforms may be developed to ascertain the cytosafety and cytotoxicity of the intended NPs. In addition, detailed mechanistic studies are further warranted although there are few detailed studies available in cancer. Moreover, it is essential to understand the kinetics of various selenoproteins in presence of either SeNPs or inorganic sources which may enhance our current understanding of pharmacological effects of SeNPs. However, the activity in other disease categories is hitherto not much explored. The drug delivery properties of SeNPs have been scarcely used for natural products which often suffer from the problem of poor pharmacokinetics though possess attractive pharmacological efficacy [106–110]. In addition, the area of gene delivery remains grey and extensive studies should be carried out to harness the clinical relevance of this promising essential element. NPs with higher transfection efficiency are desired. In future multifunctional SeNPs may be designed with enhanced tumor penetration by using tumor penetrating peptides like iRGD, with improved uptake by functionalization with lactoferrin and simultaneous drug loading and theranostic properties. It would be interesting to explore sustained release microparticulate formulations for encapsulation of SeNPs which may further improve the safety and therapeutic profile [111,112]. Though SeNPs have been explored in inflammatory disorders, it would be interesting to see how they fare in fibrotic disease which are an outcome of chronic inflammation [108,113]. However, the interaction of SeNPs with genes and chromosomes is warranted with studies pertaining to their genosafety [114].

5. Conclusion

Se is an essential trace element with pleiotropic pharmacological activities. In the present review, we highlighted the importance of SeNPs over their elemental counterpart. SeNPs have shown promising results as a unique platform for drug and gene delivery. The multifunctional NPs based on functionalization with various receptors and simultaneous loading of genes and drug holds a substantial potential for cancer therapy. In addition, SeNPs have proven their case well in diseases where inflammation is the major route of pathogenesis including diabetes, bone toxicity, colitis and drug induced toxicity. SeNPs have been shown to effectively combat drug induced toxicities and genotoxicity. SeNPs were found to modulate the inflammatory disorders and diabetic complications via attenuation of p38 MAPKs, NFκB, SIRT1 and HSP70. In conclusion, SeNPs possess all the properties required for clinical translation except their detailed safety owing to the small therapeutic window. Thus extensive preclinical safety studies are the need of the hour before SeNPs can see the light of the day.

Conflict of interest

The authors declare that there is no competent conflict of interest.

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