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RESEARCH PAPER

Biosynthesized Selenium Nanoparticles: An Excellent Bait for Antioxidant Therapy

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ABSTRACT

Nowadays use of antioxidants in the field of medicine are increasing because of health complications induced due to oxidative stress and elevated levels of reactive oxygen species. In addition to traditional antioxidant supplements, selenium should be supplied to the body in sufficient amounts as it acts as an important component for endogenous antioxidant enzymes. Since the dietary supplements for selenium can be toxic sometimes, researchers thought of using selenium nanoparticles for the same. However, the chemically synthesized selenium nanoparticles had many side effects on experimental animals, the green approach for synthesis of selenium nanoparticles using reducing/ capping/stabilizing agents of biological origin like fungi, microbes and plant extracts was investigated by many researchers. Selenium is an antioxidant element itself. Using biological agents of antioxidant nature to get nanoparticles from selenium salt, selenium nanoparticles with enhanced antioxidant properties may be generated. The present review covers the panorama of these studies and proposes green synthesized selenium nanoparticles with enhanced antioxidant potential to be an excellent bait for the therapy for oxidative damage.

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INTRODUCTION

Green nanotechnology has got an incredible attention worldwide due to their simple, economic, biocompatible, rapid, environmentally benign approach with less or no production of pollutants and harmful byproducts. Hence, synthesizing nanoparticles utilizing enzymes, microorganisms, biopolymers and plant extracts attracted many researchers [1-12]. The review encompasses the biogenic synthesis, recent applications of the Selenium nanoparticles (SeNPs) using the plant materials, microbes, fungi sources. It also focuses on potential use of these green synthesized SeNPs in tackling biological complications related to increased oxidative stress due to highly reactive free radicals.

Free radicals and their importance in biology

Free radicals, formed as a byproduct of several cellular metabolic processes, are chemical species having an unpaired electron and are electrically charged. They can readily react with other substances so as to oxidize and neutralize the later [13]. Free radicals are mainly produced

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in mitochondria as a product of reactions like electron chain transport and cause damage to mitochondrial DNA which leads to aging of cells [14]. Exposure to some external factors like X ray, certain chemicals, smoking, pollution etc. also leads to generation of free radicals [15]. The free radicals, also called as reactive oxygen species i.e. ROS, are broadly categorized in to three classes like Superoxide radicals (O_2^-), hydroxyl radicals (OH), and non-radical oxidants like hydrogen peroxides (H_2O_2) and hypochlorous acid (HOCL). The ROS can further lead to production of reactive nitrogen species (RNS) such as peroxynitrite ($ONOO^-$), Nitric oxide (NO) and reactive sulfur species (RSS) after reacting with thiols i.e. thiyl radicals [16]. The reactive oxygen species are been implicated in various normal biological processes like acquired and innate immunity, regulation of cellular signaling cascades etc [17]. However, over accumulation of free radicals results in oxidative stress in a cell. It damages nucleic acids and proteins by lipid peroxidation or oxidation, eventually leading to apoptosis [18]. Free radicals are responsible for many disorders like hypertension, autoimmune disorders, atherosclerosis, cancer, Alzheimer's and Parkinson's disease [19-20]. Antioxidants are hydrophilic/ lipophilic, enzymatic/non-enzymatic compounds that have the ability to counter the production of oxidants resulting in the reduction in amounts, ill effects and the cellular damage caused by these oxidants. Animals can synthesize the antioxidant enzymes and also often obtain antioxidants from various food items [21]. Vitamin A, E, and C are important non-enzymatic antioxidants that are obtained from diet [22]. Radical scavenging enzymes like glutathione peroxidase, superoxide dismutase, polyphenol (Xanthine oxidase) and catalase inhibit activity of oxidative stress generating enzymes [23]. The overall picture of free radical production and damages due to these is depicted in Fig. 1. ROS and RNS are result of various metabolic processes and by activity of ROS generating enzymes such as Nitric oxide synthase and Polyphenols (Xanthine oxidase). Exposure to some of the external factors like UV radiation, environmental stress etc. also play role in production of ROS. Excess amounts of oxidant molecules damage cellular, organelle membranes by damaging the proteins, damage of nucleic acids like DNA and RNA disturb various cellular functions leading to apoptosis. Endogenous and exogenous antioxidants prevent formation of ROS/RNS or transform them into neutral byproducts.

Selenium as an antioxidant molecule

Selenium, a 'P' block nonmetal, has atomic number 34. It was discovered by Jöns Jacob

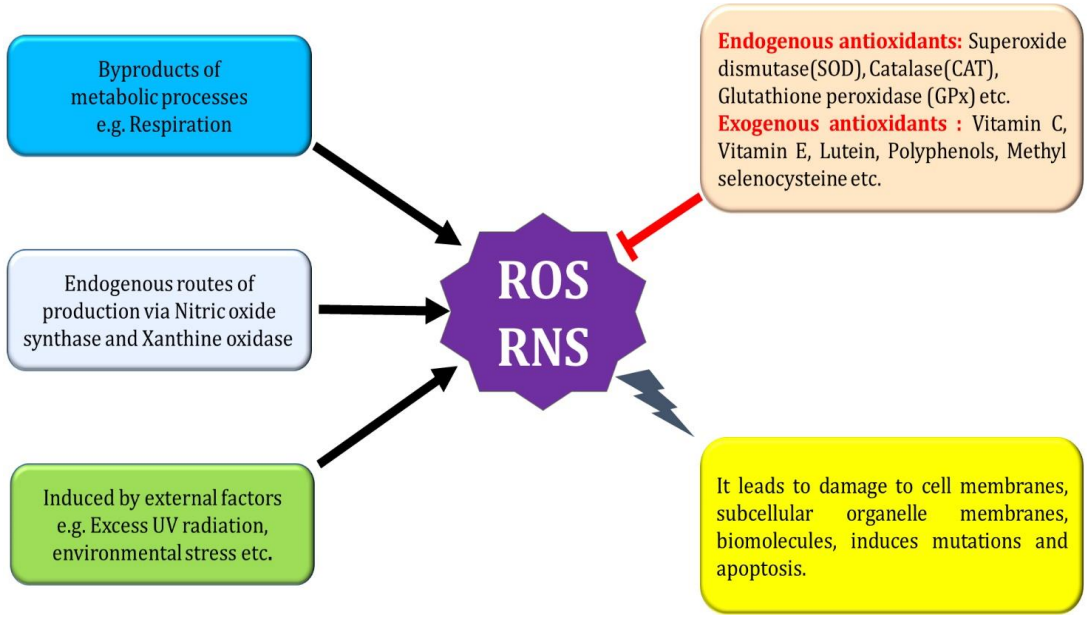

Fig. 1. Review of routes of production and damages caused by oxidant molecules.

Berzelius in 1817. Selenium is extracted from metal sulfide ores such as copper, nickel or lead. It replaces part of sulfur in sulfide ores [24]. Selenium is obtained as a trace element from food sources such as cereals, grains, vegetables etc. by animals. Selenium has been known to possess antioxidant, antimicrobial, antifungal and anti-inflammatory properties [25]. In nature, selenium is present in inorganic forms like selenide, selenate or selenite [26]. Selenomethionine, selenocysteine and methylselenocysteine amino acids contain selenium where selenium has similar function as sulfur [27]. Out of the 30 selenoproteins reported from mammals, human body contains 25 selenoproteins [28]. Selenium is added as a multivitamin and dietary supplement as it plays important roles in carrying out cellular functions. Also, it acts as a cofactor for thioredoxin reductase and glutathione peroxidase; antioxidant enzymes that reduce oxidized molecules. Iodothyronine deiodinase enzyme, contains selenium in the form of selenocysteine, regulates free circulating levels of T3 in blood [29]. The damage of cell membranes and other cellular structures, induced by hydrogen peroxide, is reduced by glutathione peroxidase that degrades hydrogen peroxide. Among the glutathione peroxidase family of four proteins, GSH-Px_1 is one of the most abundant selenoprotein occurring in mammals and its activity is regulated by selenium in liver [30]. Selenium acts synergistically with tocopherol in the regulation of lipid peroxidation. Thioredoxin (Trx), a redox protein, stimulates cell proliferation and regulates redox dependent processes in cells. Over expression of trx is reported in human tumor and cancer cells that inhibit apoptosis and promote tumor growth [31]. Thioredoxin reductase (TR) is a homodiameric selenocysteine containing protein and it reduces Trx levels in tumor and cancer cells. Selenium deficiency is shown to decrease TR activity and promote cell growth [32]. Another selenoprotein 'P' is a major heparin binding protein that works in the oxidant defense system functional at extracellular spaces. Selenoproteins 'W' and 'R', both are involved in oxidant defense mechanism in addition to selenoprotein 'P' [33]. Human body requires selenium ranging from 13-20 milligrams. It is required for sperm motility, reduces the risk of miscarriage and inhibits HIV progression to AIDS [34]. Its deficiency in moderate amounts can lead to infertility, prostate cancer, nephropathy, cardiac diseases, neurological diseases, Kashin-Beck disease, impairment of immune system function etc. [35].

Selenium is present in soil in inorganic forms like selenate and selenite, which gets converted into seleno-amino acids. Selenocysteine is present in antioxidant enzymes like glutathione peroxidase

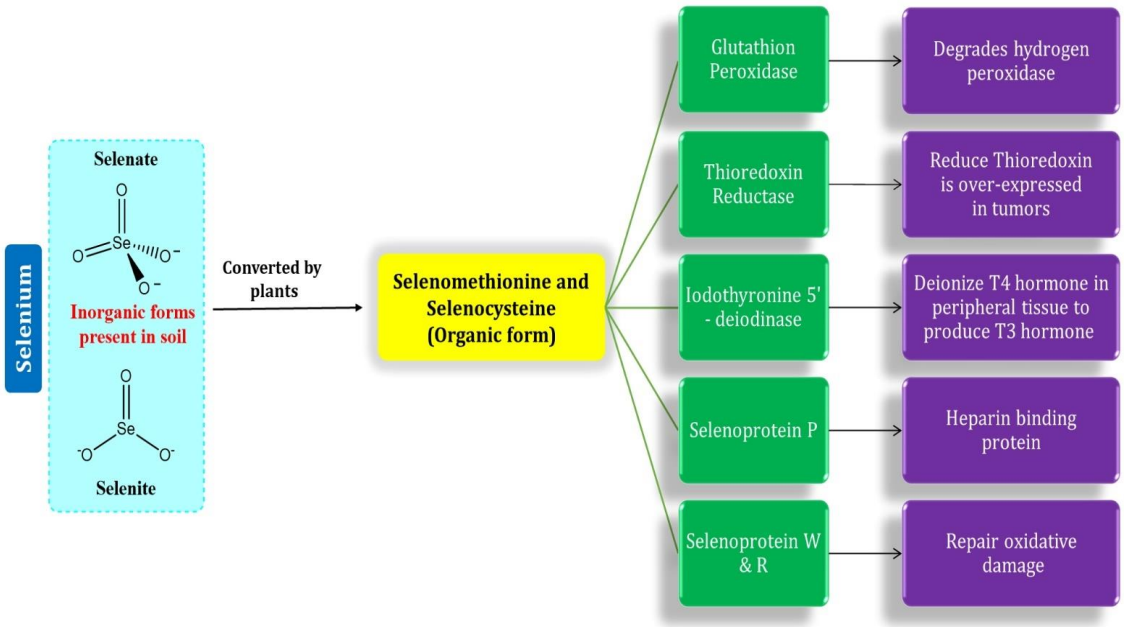

Fig. 2. Biological role of Selenium

and thioredoxin reductase. Other derivatives of selenocysteine are iodothyronine 5'- deiodinase, selenoprotein P, W and R that carryout various functions in body (Fig. 2).

Green synthesis of selenium nanoparticles

Nano scale manipulation of matter is known as Nanotechnology. Nanoscience is the study of structure; physical, chemical and biological properties of such nanoscale material. Thus, Nanotechnology and Nanoscience cover various aspects of physics, chemistry and biology [36]. Nanoparticles are particles between 1 to 100 nanometers in size which act as a whole unit [37]. Nanoparticles may be used to safely deliver element to organ directly with effective absorption even at very low doses. The toxicity of an element, observed at megascale, can be significantly reduced or completely abolished when the same element is reduced to nanoscale. Selenium, being a trace element, is proven to be an excellent antioxidant however sometimes high levels of selenium can be toxic and increase the risk of brain disorders, endocrine system disruption and cancer. High levels of selenium are known to act as a pro-oxidant and thus cause adverse effects [38]. In contrast to selenite, SeNPs (approximately 5-15nm) shows high penetration rates through cellular membranes with enhanced radical scavenging capacity [39]. Use of SeNPs is safer as compared to sodium selenite as sodium selenite causes reduction in levels of antioxidant enzymes and damages liver in mice [40]. SeNPs can be synthesized using various physical, chemical and biological methods. Some of the methods include ionic liquid induced, sol gel, microwave, hydrothermal, solvothermal, sonochemical, vapor phase deposition, solution phase approach, electrokinetic techniques, radiolysis reduction and green methods [10]. Among these, green synthesis of nanoparticles is very effective, low cost, ecofriendly, sustainable and procurable method. Green synthesis involves use of various biological agents like bacteria, fungi, plant extracts, materials of biological origin to reduce metal salts and prepare nanoparticles. In biosynthesis of nanoparticles, plant/bacterial/fungal extracts serve as a reducing and stabilizing agent rather in contrast to chemical method which needs additional agent for reduction and stability. Also, the nanoparticles synthesized so are less toxic as compared to nanoparticles synthesized by chemical methods [41]. There are ample of reports available on the reduction of selenite and selenite to selenium nanoparticles using bacteria, fungi and plant extracts.

SeNP synthesis using bacteria

Uniform sized stable nanospheres of about 300 nm diameter have been generated by selenate and selenite-respiring anaerobic bacteria like *Bacillus selenitireducens*, *Sulfurospirillum barnesii* and *Selenihalanaerobacter shriftii* that were cultured in selenium oxyanions infused medium [42]. *Klebsiella pneumonia* grown in Triptic Soy Broth (TSB) showed highest reduction ability against selenium chloride to synthesis SeNPs [43]. Selenium nanoparticles have been produced under ambient conditions using CM100B (a strain of *Bacillus cereus*) [44], *Zooglea ramigera* [45], *Bacillus subtilis* [46], *Pseudomonas alcaliphila* [47] and *Pseudomonas stutzeri* [48] by reducing selenium oxyanions. Bio-reduction of sodium selenite by *Pantoea agglomerans* strain UC 32 synthesized SeNPs, stabilized using L-cysteine, were smaller than 100nm with higher antioxidant activity than chemically synthesized selenium nanoparticles and selenite alone [49]. Selenium spherical nanoparticles, biosynthesized using *Bacillus sp. Msh -1*, have been shown to possesses inhibitory activity against promastigote and amastigote forms of *Leshmania major*, an endoparasite of human. [50-51]. Further, these nanoparticles exhibited higher antioxidant activity and lower cytotoxicity on MCF-7 cell line in comparison with SeO_2 [52]. SeNPs synthesized using *Bacillus licheniformis* JS2 have shown to inhibit proliferation and induce caspase independent necrosis in PC3, a human prostate adenocarcinoma cell line [53]. *Lactobacillus plantarum* and *L. johnsonil* reduced selenium dioxide to SeNPs that showed antifungal activity against Candida albicans [54]. Antimicrobial and antifungal activity was demonstrated by SeNPS synthesized using *Ralstonia eutropha* [55]. Actinobacteria *Streptomyces minutisclerotius* M10A62, isolated from magnesite mine, have been employed for biosynthesis of SeNPs. These nanoparticles showed antibiofilm, antioxidant and antiviral activity against dengue virus with enhanced wound healing ability [56]. Antimicrobial activity was seen in the SeNPs synthesized using gram-negative *Stenotrophomonas maltophilia* and gram-positive *Bacillus mycoides* [57]. Biogenic

SeNPs synthesized using *Bacillus paralicheniformis* SR14 capped with exopolysaccharides shown better antioxidant properties than chemically synthezied SeNPS [41]. *R. Palustris* reduced SeNPs showed hepatoprotective activity from CCl_4 induced damage in mice by increasing antioxidant enzyme activity and inhibiting oxidative damage [58]. *Acinetobacter sp.* SW30 synthesized SeNPs showed anticancer activity against breast cancer cells with concurrent nontoxic effects on non-cancerous cells unlike chemically synthesized SeNPs [59]. *Enterococcus faecalis* have the ability to tolerate high levels of selenite and synthesize SeNPs. These SeNPs exhibited antimicrobial activity against pathogenic bacteria like *Staphylococcus aureus* [60]. Biosynthesis of SeNPs using *E. coli*, *Pseudomonas aeruginosa*, *Methicillin resistance*, *Staphylococcus aureus* and *S. aureus* have been tried and the SeNPs generated were shown to be non-cytotoxic but with antibacterial activity [61]. *Lactococcus lactis* NZ9000 reduced SeNPs, capped with polysaccharides, shown antioxidant activity and anti-inflammatory activity [62]. Lactobacillus casei 393 reduced SeNPs have been reported to be harmless to human epithelial cells when applied in less amounts. However, these SeNPs had antioxidant and anticancer activities [63]. SeNPs biosynthesized using *Lactobacillus casei ATCC 393* have proven to protect against diquat induced intestinal barrier dysfunction in C57BL/6 mice by decreasing oxidative damage [64]. SeNPs synthesized using Providencia sp. DCX [65] and *Lysinibacillus sp.* NOSK [66] exhibited antibacterial activity. Antioxidant activity was seen in SeNPs synthesized using cell free extract of *Geobacillus* [67]. Necroptosis induction in LNCaP – FGC prostate cancer cells was seen by SeNPs synthesized by *Bacillus licheniformis* [68]. Anti-angiogenic activity, cytotoxicity and inhibition of invasiveness was seen on HeLa cancer cells by the SeNPs synthesized using *Pseudomonas stutzeri* MH191156 [48]. SeNPs synthesized using *Monascus purpureus* ATCC16436, grown on sugarcane bagasse, exhibited antioxidant, anticancer activities against human melanocytes, breast and liver cancer cells as well as antimicrobial and photocatalytic activities [69].

Biosynthesis of SeNPs using fungi

The SeNPs generated using *Bacillus Msh-1* exhibited anti-biofilm activity against isolates from clinical samples of *Staphylococcus aureus*, *Proteus mirabilis* and *Pseudomonas aeruginosa*. As compared to chemically synthesized SeNPs and SeO_2, these nanoparticles were found to be less toxic [70]. *Azospirillum brasilense* (strain Sp7 and Sp245) have been explored for generation of extracellular SeNPs [71]. *Alternaria alternate* [72] and *Aspergillus terreus* [73] have the ability to synthesize SeNPs from sodium selentate. *Lentinula edodes*, a basidomycete reported accumulation of elemental selenium nanoparticles in mycelial hyphae as a red coloured accumulation by reducing inorganic and organoselenium compound [74]. Ultrasound treated *Lignosus rhinocerotis* polysaccharide selenium nanoparticles have been shown to possess higher antioxidant and radical scavenging activities as compared to SeNPs generated without ultrasound treatment [75]. *Fusarium semitectum* reduced SeNPs, besides having antimicrobial and anticancer activities, is shown to be effective against burns, wounds, infections and with higher radical scavenging antioxidant activity [76]. SeNPs synthesized using either *Trichoderma asperellum*, *T. longibrachiatum*, *T. atroviride*, *T.virens*, *T. brevicompactum* or *T. harzianum* were effective against down mildew disease in pearl millet [77]. *Penicillium chryosogenum* PTCC 5031 reduced SeNPs showed antibacterial activity against gram positive bacteria [78]. Intracellular SeNPs synthesized using *Saccharomyces cerevisiae* yeast exhibited antioxidant activity [79]. SeNPs biosynthesized using *Penicillium corylophilum*, with ascorbic acid as a reducing agent, showed antilarval activity towards mosquito, antibacterial activity and cytotoxicity against CaCo2 cancer cells [80].

SeNP biosynthesis using plant extract

There are several reports of production of SeNPs using plant extracts. Researchers have used either any one part of the plants tried or the whole plant, also either dried or fresh samples for the SeNPs generation and checked for their biological activities. Selenium nanoparticles, produced with lemon leaves extract, decreased UVB induced DNA damage in human lymphocytes and its potential use against cancer cells has been proposed [81]. Doxorubicin; a chemotherapy drug, exhibited better anticancer activity against MCF-7 (human breast cancer cell line), when combined with SeNPs reduced by fenugreek seed extract [82]. Later on similar observations have been reported

for SeNPs generated with broccoli extract [83]. Biosynthesis of SeNPs using extract of dried leaves of *Vitis vinifera* [84], *Leucas lavandulifolia* [85], *Allium sativum* [86], *Petroselinum crispum* [87] have been reported. Significant antimicrobial, antioxidant and anticancer (against breast cancer cell lines) activities have been reported in SeNPs biosynthesized using aqueous extract of *Diospyros sentate* leaves [88]. Antitumor activity was detected in Hawthorn fruit extract synthesized SeNPs using Hep G2; human liver cancer cell line [89]. *Withania somnifera* leaves extract reduced SeNPs shown significant antioxidant activity and anti-proliferative effect on human adenocarcinomic epithelial cells of lung alveoli i.e. A549 [90]. SeNPs reduced using alcoholic extract of Psidium guajava (guava) exhibited antibacterial activity and cytotoxic effects on Hep G2 and CHO; Chinese hamster ovary cells [91]. Anticancer activity against MDA-MB-231 cancer cells and antimicrobial activity has been reported in SeNPs biosynthesized using *Ceropegia bulbosa Roxb* extract [92]. Antileukemia activity in *in-vitro* studies on HL60 (human leukemia) cell line was seen in SeNPs synthesized using Cassia auriculata leaves extract [93]. *Asteriscus graveolens* leaves extracts have been used as capping and reducing agents for synthesis of SeNPs. These SeNPs exhibited hemocompatibility and induced apoptosis in HepG2 cells [94]. *Carica papaya* latex used to biosynthesized SeNPs and proven to be anticancer against human breast cancer cell line MDA – MB- 231 [95].

SeNPs synthesized using *Clausena dentata* leaves extract had remarkable insecticidal activity against mosquito larvae [96]. SeNPs biosynthesized using *Ceropegia bulbosa Roxb* extract exhibited anti-larval activity for mosquito larvae and photocatalytic activity for methylene blue dye reduction [92]. *Dillenia indica* leaf broth synthesized SeNPs have been reported as larvicidal for mosquito larvae by disorganizing and breaking of gut region and antibacterial activity against foodborne pathogens [97].

SeNPs bioreduced using *Aloe vera* leaves extract have antioxidant activity [98]. Reduction of SeNPs using green tea extract and capped with *Lycium barbarum* polysaccharides shows high antioxidant activity [99]. Antifungal and antibacterial activities have been reported in SeNPs biosynthesized using *Pelargonium zonale* leaves extract [100]. Potato starch has been known to reduce and act as a capping agent in synthesis of SeNPs with antioxidant potential and antibacterial activity against both, gram positive and negative bacteria [101]. SeNPs reduced using leaves extract of *Azadirachta indiaca* [102], fruit extract of *Emblica officinalis* [103] and root extract of *Zingiber officinale* [104] are thought to be potent antibacterial and antioxidant agents. SeNPs biosynthesized using *Azadirachta indica* have shown cytocompatibility on a murine fibroblast cell line (L929) by MTT assay and antibacterial activity against gram positive and gram negative bacteria [105]. Microwave assisted green synthesis of SeNPs using *Theobroma cacao* L. bean shell extract shown potential antioxidant activity [106]. Selenium nanoparticles synthesized using *Spermacoce hispida* and conjugated with s-allyl glutathione (an analogue of glutathione) showed protective activity for liver and kidney tissues against Acetaminophen; a pain killer, by reducing oxidative stress [107]. Walnut (*Juglans regia L.*) leaves extract, as a reducing agent, was used for synthesis of SeNPs using microwave irradiation which have shown antibacterial activity [108]. Polycrystalline fluorescent SeNPs synthesized using *Ficus benghalensis* leaves extract exhibited photocatalytic activity in methylene blue dye degradation [109]. SeNPs reduced using *Hibiscus sabdariffa* leaves extract proven to show antioxidant and protective effects by upregulation of antioxidant enzymes and glutathione content in testicular tissues of streptozotocin induced diabetic rats [110]. Cytoprotective activity on arsenite (As III) induced human lymphocytes was seen in *Terminalia arjuna* leaves extract reduced SeNPs [111]. *Mucuna pruriens* seed powder extract has been used for reduction of SeNPs with antimicrobial and photocatalytic activity [112]. SeNPs generated using filtrate of *Spirulina platensis* exhibited antimicrobial activity towards gram negative bacteria. On the other hand, it was non-toxic to kidney and liver cell line [113]. The various origins of green synthesized nanoparticles along with their sizes and properties have been listed concisely in Table number 1.

The Fig. 3 is the pictorial presentation of SeNPs generation using either plant extracts, fungi or bacteria as reducing agents. The metal salt solution acts as a precursor for SeNP generation. The biological material is mixed with the metal solution for specific time under specific conditions which results in colour change of the solution.

The change in colour indicates nanoparticle production.

Assays for analyzing the antioxidant potential of selenium nanoparticles

In vitro assays: There are a number of in vitro methods applied by researchers to check the antioxidant potential of nanoparticles. Most commonly used assays are listed below:

DPPH assay: 1, 1-Diphenyl-2-picryl-hydrazyl (DPPH) is a stable free radical. Free electron of nitrogen in DPPH get reduced by hydrogen present in antioxidants. DPPH shows deep violet colour in ethanol solution with maximum absorption at 520 nm. After mixing of DPPH into a reagent that might donate hydrogen atom i.e. antioxidant substance, deep violet colour fades because of the reduction reaction. DPPH slowly reacts with the whole sample prepared in methanol/water as a solvent. This slow action gives enough time to DPPH to react with weak antioxidants also. Because of the stable radical compound DPPH is very accurate, easy to perform and mainly economical method [114].

ABTS assay: It is a very sensitive technique to measure antioxidant potential of a substance. It is applicable for checking hydrophilic and lipophilic antioxidants both. ABTS (2, 2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid)) is oxidized with methemoglobin and hydrogen peroxide, that produce blue coloured cation radical ABTS. Antioxidants stabilize this cation radical ABTS which decreases the blue coloration. In modern version, ABTS is added to sodium or potassium persulfate, which convert ABTS to radical cation of blue colour and absorbs light at 734nm. This is reactive towards most antioxidants that turn ABTS radical cation to colourless neutral form. Evaluation of degree of discoloration shows percentage of inhibition of ABTS cation and by this we can calculate function of antioxidant concentration and reaction time [115].

FRAP assay: Ferric reduction antioxidant power (FRAP) assay is based on electron transfer than hydrogen transfer unlike DPPH and ABTS. Ferric iron Fe^{3+} and 2,4,6-trypyridyl-s-triazine is reduced to its ferrous form Fe^{2+} in the presence of antioxidants in sample by donating electron. On reduction, it develops dark blue colour which has maximum absorbance at 593nm. Samples compared to the iron standards for determining antioxidant capacity of the substance used in the experiment [116].

In vivo Assays: In in vivo methods, the samples that are to be tested are injected or feed to the test animals (mice, rats, etc.) at a definite dosage. Later the animals are usually sacrificed and blood or tissues are used for the assay.

1. Ferric reducing ability of plasma: This assay is similar to FRAP where antioxidant activity is calculated by measuring change in colour, due to reduction of Fe^{3+} into Fe^{2+} using FRAP

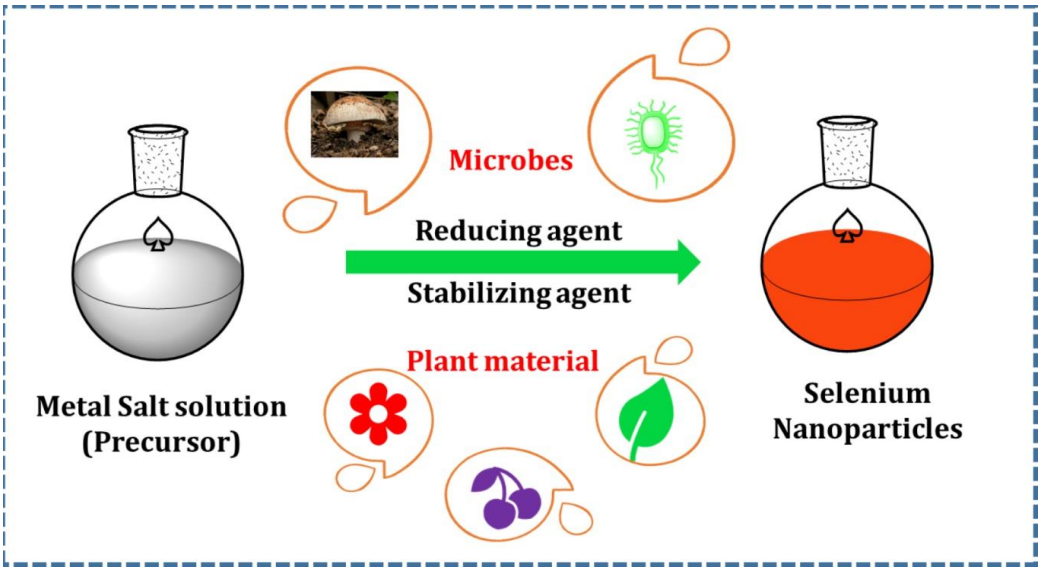

Fig. 3. Biosynthesis of Selenium nanoparticles using Plants/bacteria/fungi

Table 1. Biologically synthesized Selenium Nanoparticles and their activity

SeNPs synthesized using		
Microbes	**Size**	**Activity**
Bacillus paralicheniformis SR14 [41]	~293.73nm	Antioxidant activity
Bacillus selenitireducens, Sulfurospirillum barnesii, Selenihalanaerobacter shriftii [42]	~300nm (nanospheres)	-
Klebsiella pneumonia [43]	100 to 550 nm	-
Bacillus cereus strain CM100B [44]	150-200nm	-
Zooglea ramigera [45]	30-150nm	-
Bacillus subtilis [46]	50-400nm	H_2O_2 biosensor
Pseudomonas alcaliphila [47]	50-500nm	-
Pseudomonas stutzeri [48]	75 nm to 200 nm	Anti –angiogenic and anti-tumor activity
Pantoea agglomerans strain UC 32 [49]	30 and 300 nm	Antioxidant activity
Bacillus sp. Msh -1 [50-52, 70]	80-220nm	Anti-biofilm activity
Bacillus licheniformis JS2 [53, 68]	40-180nm	Anticancer activity
Lactobacillus plantarum L. johnsonil [54]	25-250nm	Antifungal activity
Ralstonia eutropha [55]	40-120nm	Antimicrobial
Streptomyces minutisclerotius M10A62 [56]	10-250nm	Anti-oxidant, Anti-biofilm, wound healing, anti-viral and cytotoxic activities
Stenotrophomonas maltophilia Bacillus mycoides [57]	-	Antimicrobial activity
Rhodopseudomonas palustris [58]	80-200nm	Antioxidant and hepatoprotective activity
Acinetobacter sp. SW30 [59]	79 nm	Anticancer activity
Enterococcus faecalis [60]	29-195nm	Antibacterial activity
E. coli Pseudomonas aeruginosa, Staphylococcus aureus S. aureus [61]	90-150nm	Antimicrobial property
Lactococcus lactis NZ9000 [62]	38-152nm	Antioxidant and anti-inflammatory activity
Lactobacillus casei 393 [63,64]	50-80nm	Antioxidant activity

Providencia sp. DCX [65]	120nm	Antibacterial activity
Lysinibacillus sp. NOSK0 [66]	130nm	Antimicrobial, Anti-biofilm activity
Geobacillus [67]	30-60nm	Antioxidant activity
Monascus purpureus ATCC16436 [69]	46-58nm	Antioxidant, Antibacterial, Anticancer, photo-catalytic activity
Azospirillum brasilense Strain Sp7 and Sp245 [71]	25-80nm	-
Fungi		
Alternaria alternate [72]	30-150nm	-
Aspergillus terreus [73]	47nm	-
Lentinula edodes [74]	~180nm	-
Lignosus rhinocerotis [75]	30-200nm	Antioxidant activity
Fusarium semitectum [76]	32.80-103.82nm	Antioxidant, Antimicrobial and Anticancer activity
Trichoderma asperellum T. harzianum, T. atroviride, T.virens, T.brevicompactum, T. longibrachiatum [77]	49.5-312.5nm	Downy mildew disease control in pearl millet
Penicillium chrysogenum PTCC 5031 [78]	24-65nm	Antibacterial activity
Saccharomyces cerevisiae yeast [79]	75nm	Antioxidant activity
Penicillium corylophilum [80]	29.1 – 48.9nm	Antibacterial, Anti-larval activity
Plants		
Lemon [81]	60-80nm	Prevent DNA damage
Fenugreek [82]	50-150nm	Anticancer activity
Broccoli [83]	50-150nm	-
Vitis vinifera [84]	3-18nm	-
Leucas lavandulifolia [85]	56-75nm	Anti-bacterial activity
Allium sativum [86]	7-45nm	Antioxidant activity
Petroselinum crispum [87]	50-100nm	-

Diospyros Montana [88]	4-16nm	Antioxidant, antimicrobial and anticancer activity
Hawthorn fruit [89]	113nm	Anticancer activity
Withania somnifera [90]	45-90nm	Antioxidant, antimicrobial & photo-catalytic activity
Psidium guajava [91]	8-20nm	Anticancer Antimicrobial activity
Ceropegia bulbosa Roxb [92]	55.9nm	Anticancer, antilarval, antimicrobial and photocatalytic activity
Cassia auriculata [93]	252nm	Antileukemia activity
Asteriscus graveolens [94]	20nm	Hemocompatibility and anticancer activity
Carica papaya latex [95]	40nm	Anticancer activity
Clausena dentate [96]	46.82-78.88nm	Insecticidal activity against mosquito
Dillenia indica [97]	248nm	Anti-larval, antimicrobial activity
Aloe vera [98]	7-48nm	Antioxidant activity
Green tea (*Lycium barbarum* polysaccharides capped) [99]	83–160nm	Antioxidant activity
Pelargonium zonale [100]	50nm	Antimicrobial and antifungal activity
Potato starch [101]	115nm	Antioxidant, antimicrobial activity
Azadirachta indiaca [102, 105]	35nm , 142-168nm	Antioxidant, antimicrobial activity, Anti-bacterial activity
Emblica officinalis [103]	15-40nm	Antioxidant, antimicrobial activity
Z. officinale [104]	100-150nm	Antioxidant, antimicrobial activity
Theobroma cacao L. Bean shell [106]	1-3nm	Antioxidant activity
Spermacoce hispida [107]	50nm	Antioxidant, hepatoprotective and nephroprotective activity
Juglans regia L. [108]	150nm	Anti-bacterial activity
Ficus benghalensis [109]	64.3nm	Photo-catalytic activity
Hibiscus sabdariffa [110]	33nm	Antioxidant activity
Terminalia arjuna [111]	10-80nm	Cytoprotective activity
Mucuna pruriens (seeds) [112]	90-120nm	Antimicrobial and photo-catalytic activity
Ocimum tenuiflorum [129]	15-20nm	Inhibit growth of CaC_2O_4 urinary stones
Trachyspermum ammi [130]	43.28nm	Antioxidant, anti-rheumatic, anti-inflammatory activity

reagent containing 2,4,6-trypyridyl-s-triazine and $FeCl_2.6H_2O$ in the sample solution at acidic pH which avoid hydrogen atom and increase redox potential. It is for analysis of antioxidants in plasma of animal model [117].

2. Glutathione peroxidase (GSHPx) estimation: GSHPx is a family of enzymes with peroxidase activity which reduce hydroperoxides to water. In the reduction of glutathione to glutathione disulfide, hydroperoxide it acts as a catalyst. Glutathione peroxidase in the blood or tissue is used to measure oxidative stress. Disturbance in antioxidants level lowers activity of glutathione peroxidase [118].

SeNPs as a therapeutic drug for treatment of various disorders occurred due to cellular oxidative stress

Selenium nanoparticles (25nm size) decorated by Gonoderma lucidum polysaccharides (SPS) showed stability for longer periods and are demonstrated to induce anti-inflammatory activity by inhibiting lipopolysaccharide stimulated nitric oxide production in murine Raw 264.7 macrophage cells. It also down-regulated mRNA expression of NO synthase, interleukin (IL)-1 and TNF-α, and inhibited activations of NF-jB, JNK1/2 and p38 MAPKs [119]. Selenium is a component of major antioxidant enzymes i.e. thioredoxin reductase and glutathione peroxidase. So it needs to be present in the body in sufficient amounts. Selenomethionine is a commonly used food supplement for selenium. However, since selenomethionine can be toxic if consumed in higher quantities, biosynthesized SeNPs can be a better alternative to selenomethionine as food supplements [120]. Dextrin stabilized SeNPs showed very less cytotoxicity as compared to bulk selenium at same concentration. Wistar rat having freund's adjuvant induced arthritis, when treated with different concentrations of dextrin-SeNPs, showed significant restoration of levels of antioxidant enzymes in liver, kidney and spleen at the dose of 500µg/kg body weight and exhibited anti-inflammatory activity. These results hint at SeNPs as a potential antiarthritic drug supplement [121]. Amyloidn β plaque deposition is a hallmark for Alzheimer disease. SeNPs of size ranging from 5 to 15nm have been shown to deplete formation of amyloidn β plaque by decreasing ROS production through increased levels of antioxidant enzymes. Therefore, SeNPs can be used as therapeutic treatment for Alzheimer's disease [122]. In the diabetes induced male Sprague Dawley rats, SeNPs were seen lowering blood parameters for diabetic nephropathy like collagen, urea nitrogen, fibronectin and creatinine levels. Simultaneously, these SeNPs were found to elevate the levels of cytoprotective markers like HSP-70 (heat shock protein), SIRT-1 (longevity protein) with modulations in Bax and Bcl-2 (apoptotic proteins) in the rat kidney indicating therapeutic potential of SeNPs in reducing oxidative stress and preventing diabetic nephropathy [123]. Selenium nanoparticles act as an antioxidant at optimal dosages but at higher dose it acts as pro-oxidant. This property makes SeNPs a best anticancer agent as it is non-cytotoxic to normal cells but induce apoptosis by increasing level of ROS and apoptotic proteins in cancer cells only. Thus, SeNPs have potential for local delivery vehicle which may make it a therapeutic component and drug delivery agent for cancer treatment [124]. In another study, SeNPs, reduced using precursor selenious acid and reduced glutathione in the presence of sodium alginate, have proven to induce apoptotic regulatory proteins expression with selective cell death in MCF-7 breast cancer cells [125]. Nanocapsules prepared by decorating SeNPs with Folate-Chitosan (FAC@CurP–SeNPs), expanded to snowflake particle at pH 5.3 that may aid in slow drug delivery for longer periods. Nanocapsule could be future of cancer therapy as they are very efficient with prolonged effects with precise control on drug release within cells [126]. SeNPs are proven to exhibit antioxidant and neuromodulatory activity in pentylenetrazole (PTZ) induced epilepsy mice by delaying onset and increase of NrF_2 and HO-1. These SeNPs also inhibited apoptosis in neural cell of mice hippocampus [127]. SeNPs synthesized by ultra-filtration stabilized by chitosan, have antioxidant and hepatoprotective activities in concanavalin- A (Con-A) induced liver injured mouse by enhancing its redox state [128]. SeNPs green synthesized using *Ocimum tenuiflorum* leaf extract shown to inhibit aggregation and growth of calcium oxalate monohydrate crystals can be potential against calcium oxalate stones [129]. *Trachyspermum ammi* extract, as a reducing agent, used for synthesis of SeNPs has proven to show antioxidant, anti-inflammatory and anti-rheumatic potential by dose dependent reduction in edema [130].

TheFig. 4 explains the role of normal levels of

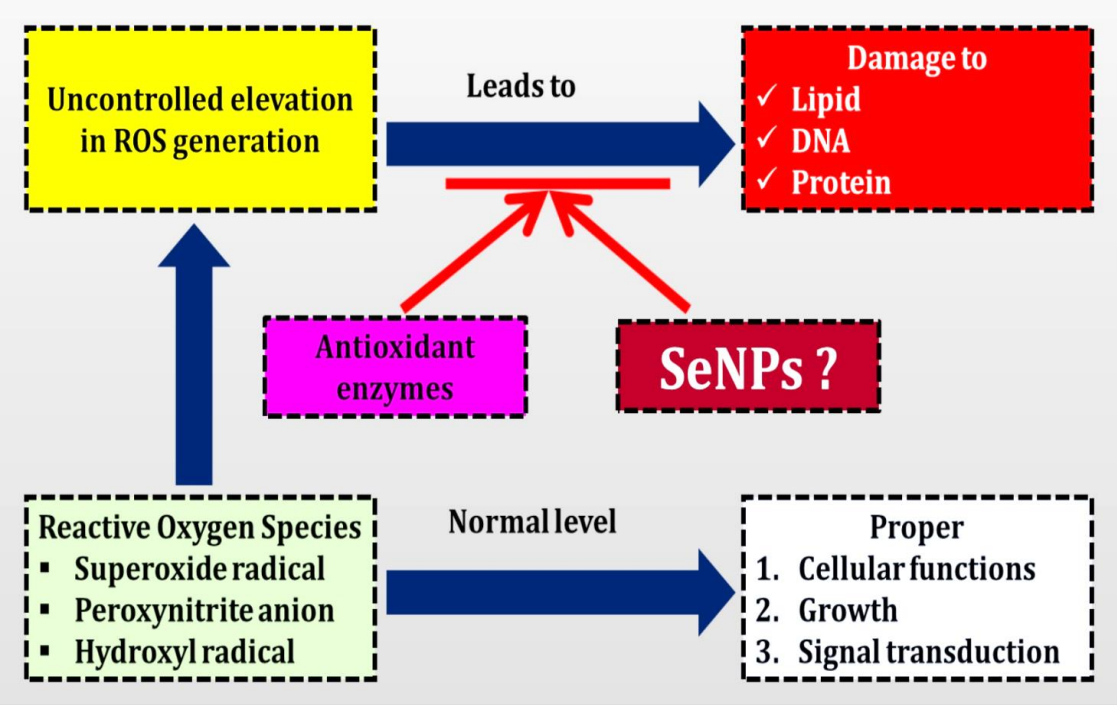

Fig. 4. Potential use of biosynthesized SeNPs as an antioxidant supplement

reactive oxygen species for proper regular cellular functions. However, if the ROS levels are enhanced beyond certain levels, it leads to oxidative stress and damages biomolecules like lipids, DNA and proteins. Endogenous antioxidant enzymes along with other antioxidant molecules are required to handle the oxidative stress and lessens the damages caused due to oxidative stress. On the basis of earlier published work from various laboratories, the authors have proposed green synthesized SeNPs as a better bait for antioxidant therapy and also as a drug delivery vehicle in such situations with less/nil side effects.

CONCLUSION

Selenium is a well-known antioxidant and anticancer agent. Synthesis of nanoparticles is an excellent way to accelerate benefits and lower toxicity, induced by selenium as a bulk element. Chemical reduction of selenium for generating nanoparticles usually ends up in getting nanoparticles with toxic effects at higher doses. To reduce the toxic effects of chemically synthesized SeNPs, green synthesis of SeNPs is a best option to increase antioxidant and anticancer ability of SeNPs without any damage to normal cells. Green synthesis of nanoparticles is a safe, easy and ecofriendly method. These biosynthesized nanoparticles are safe to use as dietary supplements as well. Biological agents can boost antioxidant power of SeNPs that may also act as an efficient drug delivery system. Biosynthesized SeNPs thus have broad future as the potential therapeutic agent in treating various disorders related to oxidative stress and are proposed as best bait for antioxidant therapy in the current scenario.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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