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Review Article

BIOGENIC SELENIUM NANOPARTICLES FOR THEIR THERAPEUTIC APPLICATION

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ABSTRACT

Biosynthesis is an eloquent, safe, biocompatible, eco-friendly, and recyclable way of preparing selenium nanoparticles (SeNPs). Selenium occurs in multiple oxidation states, for example, +6, +4, 0, or −2. Selenium (Se) is an essential trace element with a very narrow margin between the lowest acceptable levels of intake and toxicity. Selenium is an essential trace element required for all living organisms. Despite its essentiality, selenium is a potentially toxic element to natural ecosystems due to its bioaccumulation potential that is why it is biologically available in the environment. Selenium is a trace element commonly found in materials of the earth's crust, and it is essential for humans, animals, and plants. Oxyanions of selenium, that is selenite and selenate, are biologically available. Selenium in the form of selenate ion (SeO_4^{2-}) is more toxic to most organisms than selenite (SeO_3^{2-}). Contrarily, elemental selenium (Se^0) is inOsoluble and less toxic in comparison to other forms of selenium. Nanoselenium (Se^0) in the range of 100–500 nm has similar bioavailability to other forms of selenium into plants, animals, humans, and microorganisms. Biologically synthesized SeNP has many biological applications in the field of medical and pharmaceutical research to combat threats to human health. Biogenic SeNPs have anticancer (cytotoxic) activity, antioxidant activity, and antimicrobial activity. Researches are going on with special interest of SeNPs. Conjugation of antibiotics with SeNPs enhances their anticancer efficacy. SeNPs have also applications in nanobiosensors and environmental remediation.

Keywords: Selenium, Nanoparticle, Bioavailability, Anticancer, Antimicrobial.

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INTRODUCTION

Selenium was first discovered in 1817 in the form of precipitate which is red in color, as an elemental form of selenium. Selenium (Se) is a naturally occurring metalloid element which occurs naturally in all type of environments [1]. Selenium is considered as a finite and non-renewable resource on the earth. Biosynthesis is an eloquent, safe, biocompatible, eco-friendly, and recyclable way of preparing selenium nanomaterials [2]. The unique properties of nanoscale materials have given rise to extensive research activity directed toward nanoparticle (NP) fabrication [3], characterization, and applications [4]. To reveal more favorable NP activity, some researchers look to nature for methods to produce NPs with novel properties or enhanced function. Nanoscience and nanotechnology have attracted great interest over the past few years due to its prospective impact on many research areas of scientific interests such as energy, medicine, pharmaceutical industries, electronics, and space industries [5]. Biologically synthesized NPs show specific and considerably changed, chemical, physical, and biological properties compared to a number of the identical chemical composition, due to their high surface to volume ratio [6,7]. The common source of selenium is crustal part of the earth, occur in association with sulfide minerals such as metal selenide, whereas it is rarely found in the form of elemental selenium [2]. While there is no proof of selenium requirement for higher plants, several reports have shown that when selenium is added at low concentrations, it exerts beneficial effects on plant growth. Selenium may act as quasi-essential micronutrient through altering different physiological and biochemical traits [8]. During the biogenic synthesis of NPs, the microorganisms interact with target ions from their environment and then turn the metal ions into the elemental metal through enzymes generated by the microbial cell activities [9]. NPs show the size- and shape-dependent characteristics which are of great interest in applications such as biosensing and catalysts to optics, antimicrobial activity [5], anticancer activity [10], antioxidant activity [11], environmental treatment, solar cells, computer transistors, electrometers, chemical sensors, and wireless electronic logic and memory schemes [12]. Selenium is used widely for the fabrication of pigments [13]. Selenium has also been utilized for the making of rubber, manufacturing of rectifiers, and as an alloying element to improve the machinability of copper alloys and stainless steel. Advanced science and nanotechnology have provided the development of new methods for the preparation of pure selenium as selenium NP (SeNP). They provide noteworthy potential for technological applications in the fields of medicines, diagnostics, therapeutics, toxicology, electronics, catalysis, etc. NPs also have many applications in different fields such as medical imaging, nanocomposites, nano-biocomposite filters, targeted drug delivery, and hyperthermia of tumors [14-18]. However, there are still limitations in the use of chiral SeNPs as a drug delivery system, and lack of targeting abilities may necessarily cause drug toxicity and unwanted side effects [19]. In addition, the *in vivo* anticancer activity of chiral SeNP-based therapeutic drugs remains undiscovered, and these NPs lack the characteristics of fluorescence, which would allow precise, real-time imaging of drug delivery [19]. For the assessment of the sustainability of nanotechnologies, methods of manufacturing NPs, properties have to be studied. The potential range of sizes, shapes, and compositions of biosynthesized NPs translates into a broad domain of existing and new nanomaterial applications [20]. The formation of NP and the physicochemical parameters such as pH, monomer concentration, ionic strength, surface charge, particle size, and molecular weight are important for drug delivery [16,20]. Further, these NPs have the capability to reverse multidrug resistance to a major problem in chemotherapy. Well-established therapies commonly employed in cancer treatment include surgery, chemotherapy, immunotherapy, and radiotherapy [20]. Nanotechnology deals with small structures and small-sized materials of dimensions in the range of few nanometers to <100 nm [21]. NP research shows a promising way in the war against microorganisms, especially against antibiotic-resistant bacteria [22], whose number has been increasing over the past decades [23]. At the present time, different microorganisms, such as bacteria, yeast, fungi, and some biofriendly agents, have been considered as eco-friendly green biofactories for the fabrication of Se nanomaterials. Sodium selenite is used to control selenium deficiency called nutritional muscular dystrophy or white muscle disease [24]. In ruminants, selenium supplements are transformed partiality in insoluble form by microorganisms in ruminant's body, and its process decreases the selenium absorption in the digestive gastrointestinal cavity [25]. Selenium occurs in multiple oxidation states, for example, +6, +4, 0, or −2 [12]. Oxyanions of selenium, that is selenite and selenate, are biologically available [25]. Elemental selenium is getting special attention toward the different scientific research instead of its counterparts (sodium selenates and sodium selenites). It is primarily a two-step reduction process from SeO_4^{-2} to SeO_3^{-2} to insoluble elemental selenium (Se^0) catalyzed by selenate and selenite reductases [26]. Selenium in the form of selenate ion (SeO_4^{-2}) is more toxic to most of the organisms than selenite (SeO_3^{-2}) [27]. Perversely, elemental selenium (Se^0) is insoluble, less toxic compared to other forms of selenium. Nanoselenium (Se^0) in the range of 100–500° nm has similar bioavailability to other forms of selenium, into plants, animals, humans, and microorganisms. Selenium (Se) is an essential trace element with the very narrow margin between the lowest acceptable levels of intake and toxicity [28]. Selenium is required for all living organisms in trace amount. Despite its necessity, selenium is a potentially toxic element to natural ecosystems due to its bioaccumulation property. Selenium is a trace element commonly found in materials of the earth's crust, and it is essential for humans and animals [29]. Although selenium is found naturally in the earth's crust, especially in carbonate rocks and volcanic and sedimentary soils, about 40% of the selenium emissions to atmospheric and aquatic environments are caused by various industrial activities such as mining-related operations [30].

Biogenic SeNPs of bacterial origin are used to determine their antimicrobial activity [26] against selected pathogens in their planktonic and biofilm states. SeNPs biogenically synthesized by Gram-negative bacteria *Stenotrophomonas maltophilia* [Sm-SeNPs(−)] and Gram-positive bacteria *Bacillus mycoides* [Bm-SeNPs(+)] are found to be active at minimum inhibitory concentrations against a number of clinical isolates of *Pseudomonas aeruginosa*, but did not inhibit clinical isolates of the yeast species *Candida albicans* and *Candida parapsilosis* [31]. Bacterial isolate has the potential to be used as a bionanofactory for the synthesis of stable Se^0NPs as well as for detoxification of the toxic selenite anions in the environment. Selenium is a trace element with both nutritional and toxicological properties. Higher selenium exposure and selenium supplements square measure indicated to shield against many kinds of cancers [32]. Selenium is an essential element for humans and animals provided that the tolerable upper limit of intake is not exceeded. From an animal and human health perspective, it is, therefore, important to reveal the uptake, translocation, transformation, and accumulation of Se within crop plants [33]. Selenium reducing bacteria are ubiquitous and occur in diverse terrestrial and aquatic environments. The properties, size, and morphology of NPs are controlled by changing the incubation temperature, pH, reaction time, metal ion concentrations, and the amount of organic material. This is why; selenium is of great interest to a researcher. The characterization of the nanospheres in relation to size is of great importance, both in industrial and biological activities. The synthesized NPs can be separated easily from the aqueous solutions by a high-speed centrifuge. The synthesized SeNPs have been characterized by ultraviolet-visible optical absorption spectroscopy, X-ray diffraction, and transmission electron microscopy techniques [34]. Plants are also used in the biogenic synthesis of SeNPs. Biogenic synthesis of SeNPs is done by a simple biological procedure using the reducing power of fenugreek seed extract. This technique is capable of producing SeNPs in a size range of 50–150 nm, below ambient conditions. The synthesized NPs are often separated simply from the liquid sols by a high-speed centrifuge [35].

METHODS USED FOR THE BIOGENIC SYNTHESIS OF SENPS

Biogenic synthesis of selenium has been carried out using plant extract of fenugreek seeds, ascorbic acid, sodium alginate, and ethanol. This method is eco-friendly, which is less harmful to the environment [35]. Biosynthesis of SeNP has been done using *Klebsiella pneumoniae.* In this method, selenium chloride has been used in the broth of *K. pneumoniae* [36]. Polysorbate 20 surfactant for the 1st time has been used to synthesize SeNPs [23]. Aqueous *Undaria pinnatifida* polysaccharide solution mixed with ascorbic acid under magnetic stirring. Aqueous sodium selenite solution has been slowly added into the mixtures, to synthesize SeNPs which can induce mitochondria-mediated apoptosis in A375 human melanoma cells [37]. *Tetrahymena thermophila* SB210 has been used for, *in vivo* synthesis of SeNPs. *T. thermophila* cultured in proteose, peptone medium containing 1% (w/v) proteose peptone, 0.1% yeast extract, 0.2% glucose, 0.003% ethylenediaminetetraacetic acid ferric sodium salt, and maintained at 27°C in an orbital shaker. Then, sodium selenite 150 μM (Na_2SeO_3) was used for the synthesis of SeNPs [38]. *Thauera selenatis* (a β-proteobacterium) has been used for the reduction of selenate to synthesize intracellular selenium (Se) deposits that were ultimately secreted as selenium nanospheres of approximately 150 nm in diameter [39]. The bacterial strain CM100B was harvested from coalmine soil, by the enrichment of the soil sample for 1 week with sodium selenite (0.5 mM) followed by the dilution plating method on tryptic soy agar (TSA) medium mixed with 0.5 mM sodium selenite. The pure isolate is routinely cultured on TSA plates containing 2 mM selenite at 37°C [40]. Endosymbiont bacterial strains were isolated from roots of biofortified wheat plants. These strains of bacteria which are more tolerant of selenium were used for biogenic synthesis SeNP [41]. Bacterial strain *Bacillus laterosporus* has been used to reduce selenium ions (selenite anions) to SeNPs by fermentation in Luria-Bertani (LB) enrichment medium [42]. Serum bottles containing LB medium supplemented with Na_2SeO_3 in different concentrations (1–5 mM) were inoculated with 24 h growth cultures of *Staphylococcus carnosus* TM300 to reach an optical density of 0.25. The cultures were incubated at 37°C for 72 h under constant stirring at 180 rpm [43]. A primary stock culture of *Lactobacillus acidophilus* bacteria was used to prepare nanoselenium [44]. *Citrobacter freundii* was used to reduce sodium selenite (1 mM) in solution to synthesize SeNPs [45]. Environmental isolates such as *Burkholderia fungorum* DBT1 and *B. fungorum* 95 were found to be instrumental in the synthesis of SeNPs [46]. A summary of the used methods is being presented in Fig. 1.

APPLICATIONS OF SENPS

Biogenic SeNP as a cytotoxic agent

Cancer is a generalized term for a large group of diseases that can affect any part of the body [47]. One defining feature of cancer is the rapid formation of abnormal cells that grow beyond their usual boundaries [48]. Carcinogens are cancer-causing factors to include physical carcinogens, chemical carcinogens, and biological carcinogens [49]. Cancer disease is one of the leading causes of death at the global level. According to the World Health Organization report, there are 14.1 million people have cancer, and 8.2 million people died of cancer in 2012, with more than half of all new cases occurring in less developed regions of the world. Breast cancer is a global health problem and the most frequent cause of cancer death among women [50]. Mammary carcinogenesis is driven not only by genetic alterations but also by epigenetic disturbances [51]. Selenium could be a promising anti-breast cancer chemical element that has shown the modulation of deoxyribonucleic acid methylation and histone post-translational modifications in different malignancies [52]. Both SeNPs biotransformation and reactive oxygen species (ROS) [53] production are size-dependent. The smaller SeNPs are more active; this is often suggesting that small-sized SeNPs are more effective in inhibiting cancer cell proliferation through a ROS mediated mechanism [54]. Water-soluble natural polysaccharides or modified polysaccharide, such as chitosan (CTS), with low molecular weight, has specific biological activities (anticancer activity, antibacterial activity, antioxidant activity, and immune-enhancing effects) [55]. Nanoselenium has many times lower acute toxicity than sodium selenite in mice [27]. In that, having a selenium deficiency, both nanoselenium and selenite can increase tissue selenium and glutathione peroxidase (GPx) group activity [56]. The biological activities of nanoselenium and selenite were compared in terms of cell proliferation, enzyme induction, and protection against

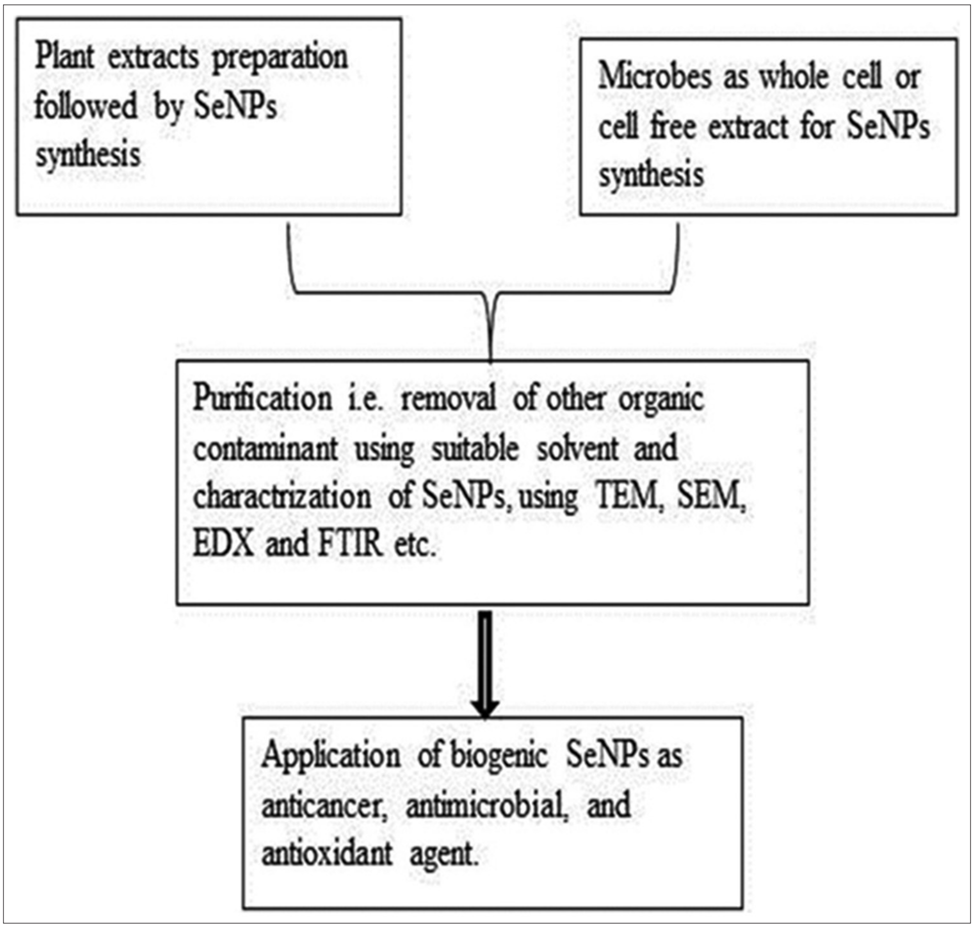

Fig. 1: The common diagram to demonstrate the synthesis of biogenic selenium nanoparticles

free racial-mediated damage in human hepatoma HepG2 cells [28]. Consumption of 200 µg selenium/day in cancer patients reduced mortality and depressed the incidence of many cancers, including lung, colorectal and prostate cancers. Selenium treatment has not proved to protect against the development of basal or squamous cell carcinomas of the skin. However, results from secondary end-point analyses support the hypothesis that supplemental selenium may reduce the incidence of mortality from carcinomas of several sites. SeNP conjugated with CTS has selective cellular uptake with enhanced anticancer efficacy. In a study, mushroom polysaccharides protein complexes were used as a capping agent that produced highly stable SeNPs. SeNP significantly inhibited the growth of Michigan Cancer Foundation-7 human breast carcinoma cells [57]. High level of arsenic (As) in drinking water increases the risk of cancer. SeNP synthesized from the leaf extract of *Terminalia arjuna* cast protection against As (III)-induced cell death and DNA damage by minimizing the production of As (III)-induced ROS [58]. Oral administration of *Lactobacillus brevis* along with SeNPs in a metastatic breast cancer mice model has stimulated the immune response by increasing the interferon production and delayed-type hypersensitivity response [15].

Biogenic SeNP as an antioxidant agent

Biogenic synthesis of SeNPs has been proved beneficial for human [59,60]. A trace amount of selenium is good for human health to remove oxidizing radicals in the body due to the antioxidant activity of elemental SeNPs. Limited works have been done to assay the antioxidant activity [61] of the biogenic SeNPs. Selenium is a micronutrient metalloid which is the main component of many selenoenzymes which are found to protect animal cells from oxidative actions of different radicals [62-64]. SeNPs scavenge ROS [65], such as 1,1-diphenyl-2-picrylhydrazyl, superoxide anion (O_2^-), singlet oxygen ($^1O_2$), and carbon-centered free radicals [63,64]. Selenium is the component of GPx, which protects the cell membrane from oxidative stress [65,66]. Biological properties of SeNPs are determined by NP size. Smaller particles have greater activity. The antioxidant activity of NPs is determined by the production of ROS using human umbilical vein endothelial cells because these cells have more oxidative stress. SeNPs activity is size-dependent where smaller NPs have more scavenging capacity [63]. Selenium (Se) is an essential mineral for good health. Selenium is a structural component of the active center of many antioxidant enzymes and functional proteins. Cellular selenium status plays an important role in the reduction of oxidative stress in the body [67]. An overdose of acetaminophen (APAP), a famous and widely used drug, may have hepatotoxic effects. Nanoscience is an innovative scientific discipline that facilitates specific tools for medical science problems using nano-sized trace elements in hepatic diseases. The administration of nanoselenium in 10–20 nm protected rats liver from APAP-induced liver damage and it is able to restore the cellular structure and avoid its damage [68]. Research related to the antioxidant activity of biogenic SeNP has to be explored to improve the application in living organisms like a human.

Biogenic SeNP as an antimicrobial agent

Antimicrobial activity [69] means the activity of different compounds for inhibition of growth of microbes such as bacteria, fungi, and viruses. Antimicrobial agents are very important in the textile industry, water disinfection, medicine, and food packaging. Organically synthesized compounds which are used for disinfection have some disadvantages, including toxicity to the human body; therefore, the interest in inorganic disinfectants such as metal oxide NPs is increasing. Biologically synthesized and capped with special compounds (proteins and polysaccharides), SeNPs have antimicrobial activity [70]. These SeNPs

Table 1: Synthesis and application of biogenically synthesized selenium nanoparticles

Source	Size	Application	Reference
Spirulina platensis mediated SeNPs	45.7–535 nm	Anticancer activity	[79]
Trigonella foenum-graecum	50–150 nm	Anticancer activity	[35]
Stenotrophomonas maltophilia	170.6±35.12	Antimicrobial activity	[31]
Bacillus mycoides	160.6±52.24 nm	Antimicrobial activity	[31]
Gum Arabic-selenium nanoparticles	34.9 nm	Antioxidant activity	[80]
Bacillus sp.	80–220 nm	Antimicrobial activity	[60]
Bacillus pumilus	10–80 nm	H_2O_2 biosensor	[55]

have an inhibitory effect on many microorganisms such as bacteria, fungi, and nematodes. Nowadays, antimicrobial drugs are becoming less effective to many diseases globally because of drug resistance capability of microbes. This, in turn, has a severe threat to human health across the world [31]. Microbial biofilms, which are characterized by their resistance to the traditional antimicrobial drugs, are considered as a renewable and main source of contamination by the pathogen. The biosynthesized SeNPs have been used to control growth and biofilm formation by foodborne pathogens, including *Bacillus cereus*, *Enterococcus faecalis*, *Staphylococcus aureus*, *Escherichia coli* O157:H7, *Salmonella typhimurium*, and *Salmonella enterica* [71]. Developing more effective antibacterial agents are important for a wide range of applications in various diseases for better public health. However, the emergence of multiple antibiotic-resistant bacteria presents a public health threat. Many developed antimicrobial drugs have limited effective application due to a chemical imbalance, low biocompatibility, and poor long-term antibacterial efficiency. SeNPs conjugated with the quercetin and acetylcholine have been proved a great antimicrobial effect on the pathogen [72]. Probiotics are microorganisms which can improve intestinal microbial balance and provide benefits to human health after consumption in adequate amounts. *Lactobacillus plantarum* and *Lactobacillus johnsonii* cells have been grown in the presence and absence of selenium dioxide, and their cell-free spent culture media are tested for antifungal activity against *C. albicans* ATCC 14053 [69]. Selenium dioxide treated *Lactobacillus* sp. or their cell-free spent stock inhibited the growth of *C. albicans* [69]. Selenium particles extracted from cultures of *S. carnosus* and evidently stabilized by their natural protein coating, for instance, show considerable activity against the nematode *Steinernema feltiae*, bacteria *E. coli*, and *Saccharomyces cerevisiae*. Such natural nano and microparticles were also found more active than mechanically generated selenium particles and can be applied as antimicrobial materials in medicine and agriculture [43]. Antimicrobial tests show SeNPs activity against *S. epidermidis* but not against *E. coli* in low Se concentration of 2 ppm. There is significant suppression of the selenium odor in case of using polysorbate 20 as a surfactant [23]. Selenium and copper NPs exhibit superior antioxidant activity, unique properties, and great potential applications that make them very attractive for developing new composite materials. Polyethersulfone (PES) ultrafiltration membrane has been modified by dispersing nanosized selenium (Se) and copper (Cu) particles uniformly in a PES solution (18% polymer weight) and cast by a phase inversion process. SeNPs were prepared by the reduction of aqueous sodium selenite solution with freshly prepared glucose solution. Spherical SeNPs have been produced in a size range of about 150–175 nm, under ambient conditions. The synthesized NPs can be separated easily from the aqueous solutions by a high-speed centrifuge and can be re-dispersed in an aqueous medium by an ultrasonicator [73]. *S. aureus* is an important bacterium commonly found in numerous infections. *S. aureus* infections were difficult to treat due to their biofilm formation and defined antibiotic resistance. SeNPs were used effectively in the prevention and treatment of disease caused by *S. aureus* [74]. Biosynthesized SeNPs also present on the outer layer of the bacterial cell, mainly consisting of a proteinaceous material that seems to greatly influence the reactivity of SeNPs in terms of antimicrobial and antibiofilm effects. It has been proved that the antimicrobial activity of biologically synthesized SeNPs is significantly more than chemically synthesized SeNPs [75]. There are broad applications of biogenic SeNPs in such scientific research to get better results related to anticancer activity, antioxidant activity, and antimicrobial activity.

Application of SeNPs as nanobiosensors and nanomedicine

Nanotechnology is a promising field of interest in medical research and medical technology. The nanosciences play an important role in the treatment of many diseases using targeted drug delivery systems. Medicines integrated with nanomaterials are used as a biosensor. For the treatment of diseases, diagnosis is must to know the fastest treatment method. Ultrasensitive diagnostic probes are used in place of traditional equipment. The alloyed thioglycolic acid-capped and SiO_2-coated CdZnSeS QD conjugated molecular beacon bioprobes detected extremely low concentrations of norovirus RNA. The additional merits of our detection system are rapidity, specificity and improved sensitivity over conventional molecular test probes [76]. Point of care examining instruments are integral in the health-care system particularly identifying and monitoring the diseases. Its advantage is that it provides rapid and accurate results with low costs [77]. Thus, nanotechnology is proving itself better for the health-care system using NPs. A selenium-resistant bacterium identified as *B. pumilus* sp. BAB-3706 cell-free extract has been implicated in the synthesis of SeNPs. This microbial SeNPs has been a promising source for the development of H_2O_2 biosensor [78]. Table 1 enlists source size and application of SeNPs.

CONCLUSION AND FUTURE PROSPECTS

Over the past 50 years, compelling evidence has accumulated on the beneficial role of selenium in human health. There are very few reports of such biologically synthesized SeNPs and it is still a big challenge for researchers. SeNPs are synthesized by various methods such as chemical, physical, and biological. A biological method that includes whole cell as well as cell-free extract of microbes or extract of plants containing secondary metabolites has been used for the synthesis of SeNPs. Size reduction will also increase the activity of NPs and render them more effective. Biologically synthesized SeNPs are being investigated as anticancer, antioxidant, and antimicrobial agents since biogenic SeNPs are less toxic than selenium salts. Its role in development of biological sensors further adds up to its versatility. Nano selenium possesses strong antioxidant activity so its application in food fortification can be considered. However, application of SeNPs is in its infancy stage, but surely it holds a good promise for curing rather a difficult to cure disease like cancer.

AUTHORS' CONTRIBUTIONS

Awanish and KSP have jointly written the manuscript.

CONFLICTS OF INTEREST

The authors declare that they do not have any conflicts of interest.

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