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REVIEW ARTICLE

An insight into biofabrication of selenium nanostructures and their biomedical application

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Abstract

Evidence shows that nanoparticles exert lower toxicity, improved targeting, and enhanced bioactivity, and provide versatile means to control the release profile of the encapsulated moiety. Among different NPs, inorganic nanoparticles (Ag, Au, Ce, Fe, Se, Te, Zn, etc.) possess a considerable place owing to their unique bioactivities in nanoforms. Selenium, an essential trace element, played a vital role in the growth and development of living organisms. It has attracted great interest as a therapeutic factor without significant adverse effects in medicine at recommended dose. Selenium nanoparticles can be fabricated by physical, biological, and chemical approaches. The biosynthesis of nanoparticles is shown an advance compared to other procedures, because it is environmentally friendly, relatively reproducible, easily accessible, biodegradable, and often results in more stable materials. The effect of size, shape, and synthesis methods on their applications in biological systems investigated by several studies. This review focused on the procedures for the synthesis of selenium nanoparticles, in particular the biogenesis of selenium nanoparticles and their biomedical characteristics, such as antibacterial, antiviral, antifungal, and antiparasitic properties. Eventually, a comprehensive future perspective of selenium nanoparticles was also presented.

Keywords Selenium nanoparticles · Biosynthesis · Biomedical · Antimicrobial activity · Anticancer effect

Introduction

Selenium (Se) was first introduced in 1817 by the Swedish chemist Jons Jacob Berzelius (Skalickova et al. 2017). As a semi-metal element, this chalcogen represented both properties of non-metal and metal element (Burk 1994, Mehdi et al. 2013). Six isotopes of this chalcogen exist together in nature. The mass numbers of its isotopes are almost 74, 76, 77, 78, 80, and 82 (Mehdi et al. 2013). Se resembles sulfur in atomic size, ionization potentials, main oxidation states, and bond energies (Mehdi et al. 2013). This element is stable and does not oxidize at average temperatures. When Se burns, it creates a blue flame, selenium dioxide, and unsightly smell. Se can combine with several elements, such as fluorine, hydrogen, phosphorus, chlorine, bromine, etc. (Burk 1994). Se is present in both form of organic and inorganic. The main organic form is selenocysteine, selenomethionine, while the most abundant inorganic forms are selenite (SeO_3^{2-}), selenate (SeO_4^{2-}), selenide (Se^{2-}), and elemental Se (Mehdi et al. 2013). Selenite is the most toxic form of Se (Wadhwani et al. 2016).

Se is a trace element which is essential for human, meaning that they cannot produce it, and they need to obtain it from their diet (Wadhwani et al. 2016; Skalickova et al. 2017). The biological functions of Se caused by the incidence of selenocysteine amino acid in proteins. Proteins that incorporate selenocysteine in their polypeptide chain are named selenoproteins and they are involved in all

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progenitors of life (eukaryote, archaea, and bacteria). About 100 selenoproteins have been found in mammalian, the most crucial of which are the antioxidant enzymes of glutathione peroxidase, iodothyronine deiodinases, selenoprotein H, selenoprotein K, thioredoxin-glutathione reductase, methionine sulfoxide reductase B1, selenophosphate synthetase, and thioredoxin reductase (Kielczykowska et al. 2018) where Se supplied as their cofactor (Wadhwani et al. 2016). It is feasible for Se to use for the prevention of different diseases containing cystic fibrosis, muscular dystrophy, cardiovascular disease (Weekley and Harris 2013; Skalickova et al. 2017), Alzheimer, leishmaniasis, and cancer (Chaudhary et al. 2014).

Nanotechnology is a cutting-edge field interdisciplinary related to chemistry, fundamental physics, biology, medicine, and material science (Narayanan and Sakthivel 2010). The initial concept of nanotechnology is production of materials of different types at nanoscale level that it presented by Richard Feynman in 1959. Nanoparticles are a broad class of materials that have one dimension less than 100 nm at least (Khan et al. 2019). Nanoparticles usually were synthesized by two approaches including bottom–up and top–down (Wang and Xia 2004). In bottom–up strategy, atoms or molecules were assembled into molecular structures in the nanometer range but in top–down strategy involves the breaking down of the bulk material into nano-sized structures or particles. The importance of these materials cleared when investigators discovered that size might affect the physicochemical properties of the substance (Khan et al. 2019). These physical characteristics created by their large surface area, spatial confinement, large surface energy, and decreased imperfections. Although different chemical and physical approaches broadly generated monodispersed nanoparticles, the stability and application of toxic substances are a paramount concern. The application of toxic compounds on the surface of nanoparticles and non-polar solvents in the synthesis method restricts their utilization in clinical fields. The biosynthesis and usage of selenium nanoparticles (Se NPs) also possess several advantages including biocompatibility, chemical stability, and low toxicity (Wang et al. 2007; Skalickova et al. 2017). Se NPs could be synthesized through physicochemical and biological methods. Se NPs have found applications in medicine as anticancer, antibacterial, antifungal, antiparasitic, antioxidant (Wadhwani et al. 2016), anti-inflammatory, and immune-stimulator (Chaudhary et al. 2014; Hosnedlova et al. 2018).

The aim of this review was investigating the biogenic synthesis and biological applications of Se NPs.

Synthesis of Se NPs

Three various methods can be used for the synthesis of Se NPs, including the chemical, physical, and biological techniques. A summary of synthesis methods for the fabrication of Se NPs is shown in Fig. 1.

Chemical synthesis

Various methods have been used for the chemical synthesis of Se NPs. The most common method is chemical reduction by various inorganic and organic reducing factors, physicochemical reduction, electrochemical techniques, and stabilization with different chemicals (Iravani et al. 2014; Dhand et al. 2015). In general, reducing agents change the ionic form to the zerovalent metal (Iravani et al. 2014). Synthesis by this way in the aqueous solution of inorganic Se used as a precursor. The surface-modified chitosan or carboxymethyl chitosan can lead to an increase in stability and particle size of Se NPs (Chen et al. 2015; Zhang et al. 2015; Skalickova et al. 2017). After fabrication of NPs, their ex-situ characterization performed by several biophysical methods, including electron microscopy (Hosnedlova et al. 2018). Folic acid (Liu et al. 2015), ascorbic acid (Bartůněk et al. 2015), acetic acid (Dwivedi et al 2011), sialic acid (Yin et al. 2015), and carboxylic acid or oxalic acid (Dwivedi et al 2011), as well as benzoic and gallic acid (Bartůněk et al. 2015) can be used for the acid-induced synthesis of Se NPs. Another example of chemical synthesis is the ionic liquid-assisted synthesis of Se NPs by the reaction of ionic liquid (3-methylimidazolinium methane sulfonate) with sodium selenosulphate, a selenium precursor, in the presence of polyvinyl alcohol as stabilizer, in aqueous medium (Langi et al. 2010). Verma and Maheshwari (2018) reported a chemical technique for the synthesis of Se NPs with the chemical reduction of sodium selenite by glutathione and stabilizing using bovine serum albumin. The shape and average size of Se NPs inspected by SEM revealed rod-shaped NPs and size of 74.3 nm (Verma and Maheshwari 2018). An easy wet chemical approach has been employed to synthesize Se NPs with a size range of 40–100 nm, through the reaction of sodium selenosulphate precursor via various organic acids in the aqueous medium, below ambient temperature (Dwivedi et al 2011).

Physical synthesis based on energy supply

Among the physical techniques based on energy supply for synthesis of Se NPs, several important methods, such as pulsed laser ablation (PLA), microwave irradiation, and hydrothermal treatments, have been applied. PLA is a well-known method for nanoparticle production in the case of

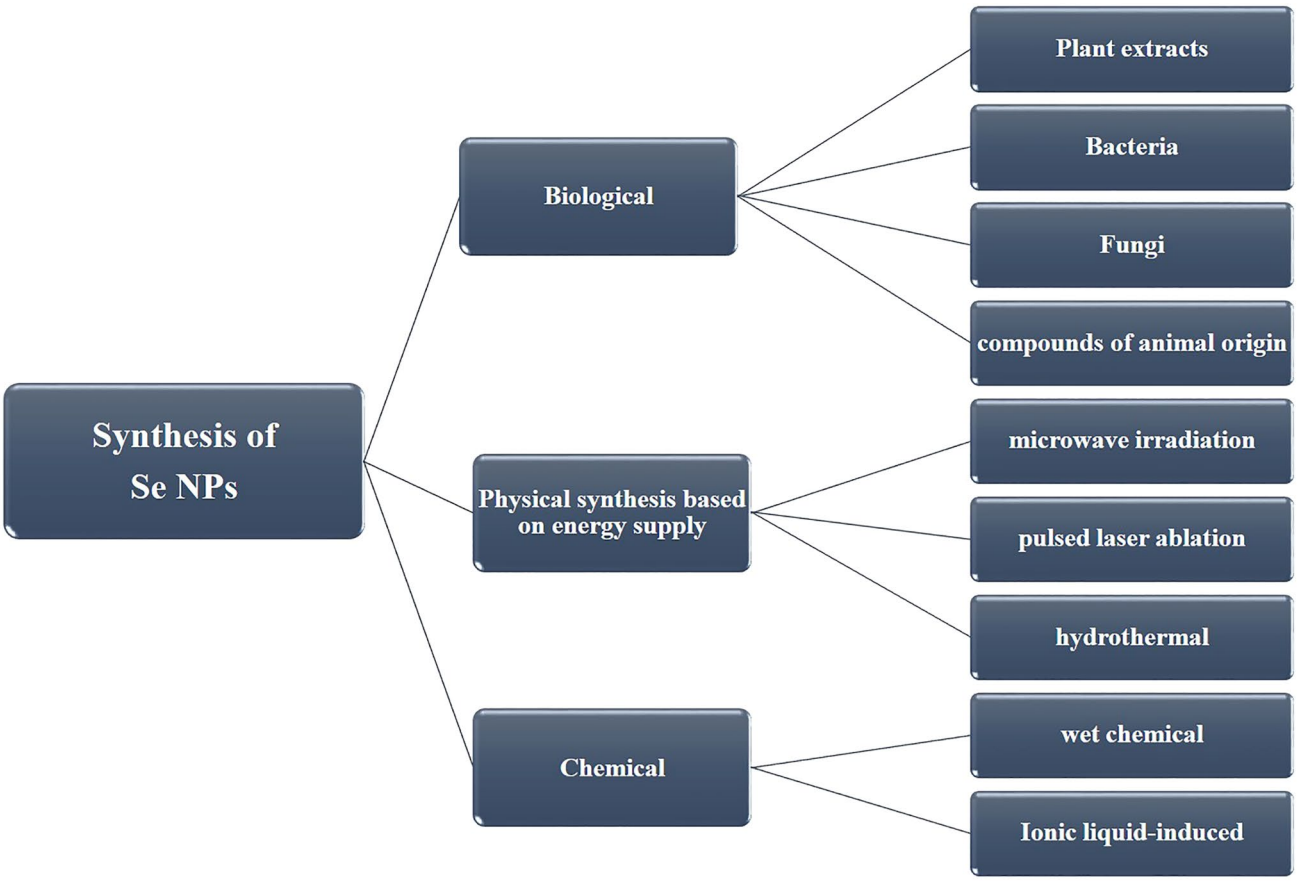


Fig. 1 Different ways for synthesis of selenium nanoparticles

inorganic substances. During PLA, a high-energy pulsed laser beam is concentrated onto the sample, which occurs in micro-explosions near to the surface, and the ejection of nanoparticles (Gera et al. 2020; Baig et al. 2021). The microwave irradiation technique is another synthesis method for nanoparticle fabrication using fast and uniform heating of the reaction medium and consequently provides uniform nucleation and growth conditions for nanoparticles (Joseph and Mathew 2014). The hydrothermal approach has attracted enormous attention owing to its benefits, as environmental friendliness, simplicity, low energy consumption, and inexpensiveness (Shar et al. 2019). Pure Se NPs were synthesized by liquid phase-pulsed laser ablation (LP-PLA) in deionized water (Singh et al. 2010; Guisbiers et al. 2014). PLA displays many advantages for the synthesis of Se NPs in comparison to other techniques like lack of contamination with chemical reagents, low-cost equipment, high stability, and easy collection of nanoparticles (Skalickova et al. 2017). Tzeng et al. (2020) determined a rapid, low-cost, and eco-friendly synthesis method for both crystalline and amorphous Se NPs by laser-induced plasma shock wave for femtosecond at ambient pressure and room temperature. Among other methods, synthesis of Se NPs using reducing selenious acid solution with silk fibroin in the microwave reaction system was reported (Hou et al. 2011). Microwave irradiation for the synthesis of Se NPs utilized Se salts in aqueous solution as a starting reagent. The synthesis of Se NPs by microwave irradiation displayed many advantages in comparison to conventional heating techniques, such as rapid and identical heating, short reaction time, increased reaction speeds, and energy savings (Panahi-Kalamuei et al. 2014). The biosynthesis of microwave irradiated nanoparticles showed minimum particle-size distributions, maximum stability, and the smallest particle size (Długosz and Banach 2020). This method was affected by several factors, such as microwave power, time, stirring rate, temperature, precursor/reducing agent ratio, and pH (Schütz et al. 2018; Mellinas et al. 2019). The most effective factor was associated with NPs size in microwave-assisted green synthesis reported metal precursor microwaves. The low amounts of the metal precursor are required for obtaining smaller size of Se NPs, regardless to the time and microwave power (Mellinas et al. 2019). Synthesis of Se NPs without any polymer or surfactant as stabilizer has been reported via the hydrothermal method by Guangcheng et al. (Xi et al. 2006). Shar et al. (2019) synthesized Se NPs by a hydrothermal procedure

utilizing L-ascorbic acid as a reducing and stabilizing agent and sodium selenite as a precursor (Tzeng et al. 2020). Selenium nanorods were produced using the hydrothermal method by the reaction of glucose with Na_2SeO_3. The diameters of the Se nanorods were in the range of 200–300 nm (Cao et al. 2011).

Biological synthesis

Biological synthesis of Se NPs can be mediated by plants, bacteria, fungi (Wadhwani et al. 2016), and yeast (Narayanan and Sakthivel 2010), and can produce either extracellularly or intracellularly (Fig. 2). Biomolecules play the role of stabilizing and reducing agents. Consequently, the biosynthesis of nanoparticles is biocompatible, because no additional chemical reagents needed in this process (Zhang et al. 2019). The biological synthesis of various metal nanoparticles examines the natural potential of microorganisms and plant extracts for the reduction of metal ions to neutral atoms.

Synthesis by bacteria

The biosynthesis of nanoparticles by bacteria is environmentally friendly (Eszenyi et al. 2011), because fewer chemicals and hazards were used than chemical methods. However, these methods have limitations such as they are longer time than chemical and physical methods and require additional steps for purification of nanoparticles. Nanoparticles synthesized by these methods are not usually uniform sized and have a range of sizes (Iravani et al. 2014). The bacteria used a simple detoxification mechanism for reduction of selenites/selenates to Se NPs (Kessi et al. 1999; Alam et al. 2019). Nevertheless, the accurate mechanism of NPs synthesized using microbes is still not clearly explained, and biosynthesis of Se NPs can be occurred intracellular, extracellular, or through the cell membrane (Alam et al. 2019). Over 16 different species of bacteria were able to reduce colorless selenate and selenite to red color elemental Se with different sizes and shapes (Husen and Siddiqi 2014). Se NPs fabricated by bacteria such as *Bacillus licheniformis* under sodium selenite stress caused to the conversion of toxic selenite ions into non-toxic elemental Se NPs (Sonkusre and Singh Cameotra 2015). *Bacillus* sp. MSh-1 (Forootanfar et al. 2014), *Stenotrophomonas maltophilia* (Cremonini et al. 2016), *Actinomycetes* (Forootanfar et al. 2013; Ahmad et al. 2015), *Bifidobacter* sp., *Streptococcus thermophilus* (Eszenyi et al. 2011), *Staphylococcus carnosus* (Estevam et al. 2017), and *Lactobacillus* sp. (Eszenyi et al. 2011; Sasidharan and Balakrishnaraja 2014; Cavalu et al. 2017) which are shown in Table 1 are among other bacterial strains able to synthesize Se NPs. *Pseudomonas alcaliphila* and *Klebsiella*

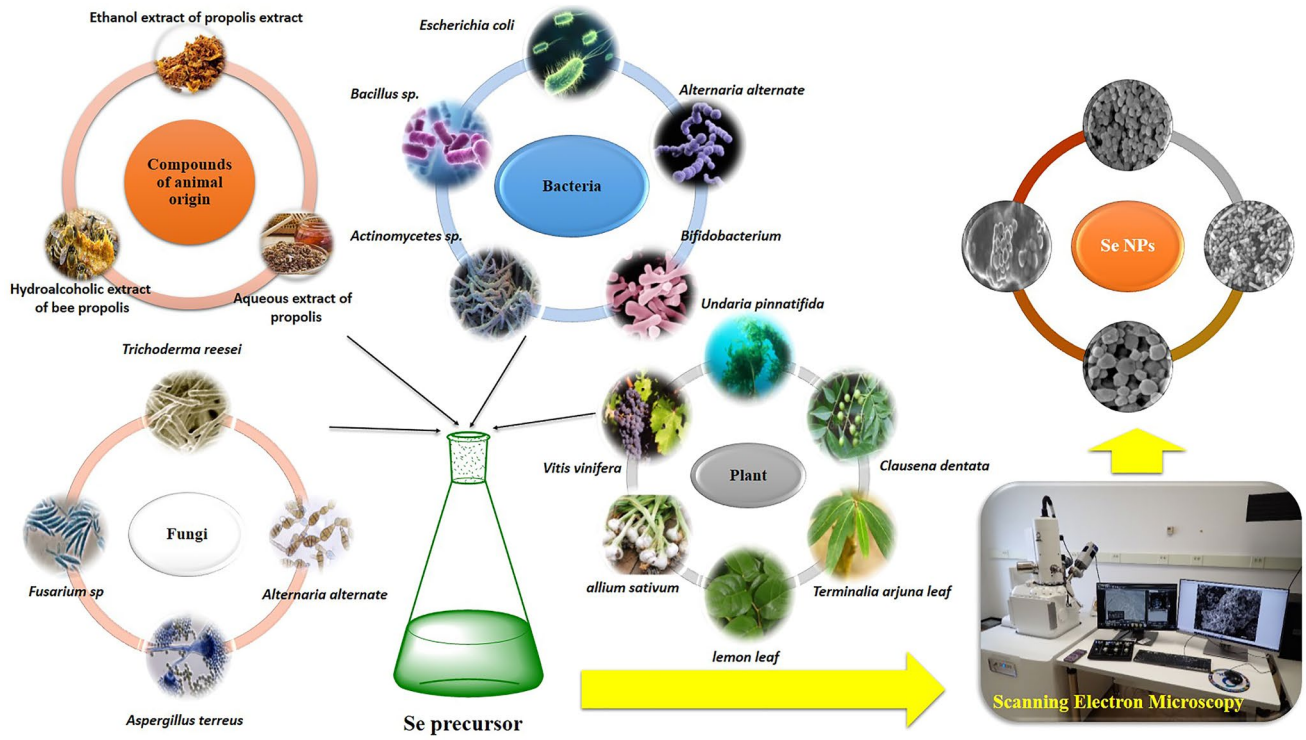
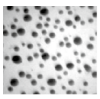
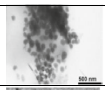
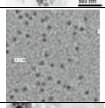
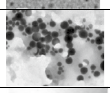
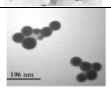
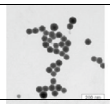
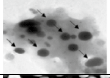
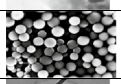
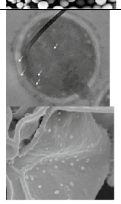
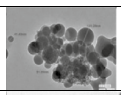
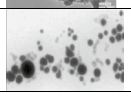
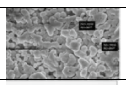
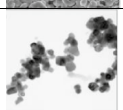
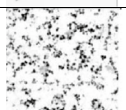
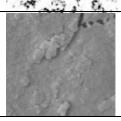
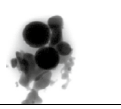


Fig. 2 Application of biological resources for synthesis of selenium nanoparticles

Table 1 Various sources reported to be involved in the biosynthesis of different types of Se NPs

Source	Nanoparticle size	Shape		Reference
Bacteria *Bacillus* sp. MSh-1	~80-220nm	Spherical		Forootanfar et al. (2014)
Ralstonia eutropha	40–120 nm	Spherical		Srivastava et al. (2015)
Lactobacillus acidophilus	2–15 nm	Spherical		Alam et al. (2019)
Pseudomonas aeruginosa ATCC 27853	47–165 nm	Spherical		Kora et al. (2016)
Enterococcus faecalis	29–195 nm	Spherical		Shoeibi et al. (2017)
Azospirillum brasilense	~25–80 nm	Spherical		Tugarova et al. (2020)
Streptomyces minutiscleroticus M10A62	10–250 nm	Spherical		Ramya et al. (2015)
Staphylococcus carnosus	439 nm	Spherical		Estevam et al. (2017)
Fungi *Mariannaea* sp. HJ	45.19 (intracellular Se NP) and 212.65 nm (extracellular Se NPs)	Spherical Spherical		Zhang et al. (2019)
Gliocladium roseum	20–80 nm	Spherical		Srivastava et al. (2015)
Trichoderma sp. WL-Go	20-220 nm	Spherical and Spherical		Diko et al. (2019)
Plants extracts				
Withania somnifera	45– 90 nm	Amorphous		Alagesan et al. (2019)
Ceropegia bulbosa Roxb	An average size of 55.9 nm	Spherical		Cittrarasu et al. (2021)
Zingiber officinale	100-150 nm	Spherical		Menon et al. (2019)
Trigonella foenum-graecum L.	50–150 nm	oval		Ramamurthy et al. (2013)
Compounds of animal origin Propolis extract	279 nm	Spherical		Długosz et al. (2022)

pneumoniae also utilized to synthesize Se NPs by a suitable yield (Husen and Siddiqi 2014). Gerrard et al. (1974) observed Se deposits on the cell wall and cell membrane of *Escherichia coli* by electron microscopy. They have indicated that the bacteria can reduce sodium selenite to elemental Se.

Synthesis by fungi

Five fungal strains have reported as bioresources for the synthesis of Se NPs, including *Aspergillus terreus* (Zare et al. 2013), *Alternaria alternate* (Sarkar et al. 2011), *Lentinula edodes* (Vetchinkina et al. 2013), *Fusarium* sp., and *Trichoderma reesei* (Wadhwani et al. 2016) which are summarized in Table 1. Fungi have many benefits for NP synthesis compared to other microbes and plants. The tolerance of fungal mycelial mesh toward flow pressure, agitation, and other conditions in bioreactors or other chambers compared with plant materials and bacteria is one of these benefits (Narayanan and Sakthivel 2010; Alghuthaymi et al. 2015). In addition, most fungi represent a high resistance toward metals as well as intracellular metal uptake capabilities (Alghuthaymi et al. 2015). They are fastidious grow, easy to handle (Narayanan and Sakthivel 2010), a high wall-binding capability (Alghuthaymi et al. 2015), and easy for fabrication (Narayanan and Sakthivel 2010). Zhang et al. (2019) announced the resistance of fungus *Mariannaea* sp. HJ to selenate ions during growth phase which might ascribe to the capacity of Se NPs synthesis. Liang et al. (2019) investigated the synthesis of Se NPs by several different fungal genera (*Aureobasidium pullulans*, *Trichoderma harzianum*, *Mortierella humilis*, and *Phoma glomerata*) through growth on selenium-containing media (1 mM). Filamentous fungi are capable of extracellular and intracellular synthesis of Se NPs, and they have some advantages over bacteria and other unicellular organisms due to easier bioprocessing and biomass handling (Liang et al. 2019).

Plant-assisted synthesis of Se NPs

Plant-assisted fabrication of Se NPs mostly performed by reduction of selenate to selenite in the presence of plant extracts containing alcohols, phenols, proteins, flavonoids amines, and aldehydes. Low dosages of Se can stimulate the growth of the plants, whereas high dosages of it can cause damage to plants. In addition, biogenic Se NPs demonstrated less toxicity as compared to NPs synthesized via chemical methods (Husen and Siddiqi 2014). As for green synthesis, Se NPs synthesized by plant extracts, such as extract of *Vitis vinifera* (Sharma et al. 2014), *Allium sativum* (Ezhuthupurakkal et al. 2017), *Terminalia arjuna* leaf (Prasad and Selvaraj 2014), *Clausena dentata* plant leaf (Sowndarya et al. 2017), *Undaria pinnatifida* polysaccharide (Chen et al. 2008a, b), and lemon leaf (Prasad et al. 2013) (Table 1). The synthesis of NPs by plant extracts has more benefits than other biological procedures, because it is cheap and does not need any special conditions (Ramamurthy et al. 2013). Biofabrication of Se NPs by plant extracts led to the formation of Se NPs with different size. For example, application of *Vitis vinifera* plant led to the formation of Se NPs with the average size of 3–18 nm, while lemon leaf extract fabricated Se NPs with the size range of 60–80 nm. Phenolic groups present in lignin plants usually serves as reducing agent and oxidation of phenol to ketone has occurred during the redox process. Nevertheless, the plant extract additionally comprises fairly substantial amount of reducing sugars. Hence, they also act as reducing agents and formation of Se nanoballs (Husen and Siddiqi 2014).

Synthesis by compounds of animal origin

Propolis or bee glue is a natural substance collected using honey bees from various plant flowers, and due to its biological features, such as antibacterial, antiviral, and antifungal potentials, antitumor, anti-inflammatory, and antiulcer, it obtained a significant attention from investigators (Shubharani et al. 2019). Various reports showed that propolis is composed of different bioactive compounds (such as flavanones, flavones, alcohols, aldehydes, esters, aromatic acids, etc.) that can synthesize NPS by metal ion reduction to their elements (Kumar et al. 2014; Hatami et al. 2020). Shubharani et al. (2019) investigated the synthesis of Se NPs by hydroalcoholic extract of bee propolis (with size ranged of 52.9–118 nm). They revealed the antioxidant, antibacterial, and antifungal activity of Se NPs biosynthesized with ethanol extract of bee propolis (Shubharani et al. 2019). Se NPs biosynthesized by bee propolis hydroalcoholic extract with the size range of 50–60 nm and six different heating methods, namely, microwave, conventional heating (mild heating by heater and stirrer), ultrasonication, self-assembling, hydrothermal, and UV irradiation (Hatami et al. 2020). Hatami et al. (2020) demonstrated that bee propolis extract, due to the presence of natural reducing and stabilizing agents, had potential application in the biosynthesis of Se NPs. Wali (2019) biosynthesized Se NPs by propolis aqueous extract, and they investigated their biological activity, such as body weight, blood Se-binding protein amount, food intake, catalase, and liver enzymes activities. The body weight and food intake in the Se NPs-treated group significantly increased than the control and selenite-treated groups ($p \leq 0.05$) during 2 weeks of the tests (Wali 2019). The rat group treated with Se NPs exhibited a significant enhancement in Se-binding proteins and catalase associated with normal values of liver enzymes. Therefore, the novel propolis-mediated Se NPs enhanced the availability of the Se to its binding proteins and decrease its toxicity than inorganic selenite (Wali 2019).

Biological applications of Se NPs

Se NPs have wide application in biomedical fields. Se NPs have found biological applications as antibacterial, antifungal, antioxidant, and anticancer agents, etc. (Fig. 3) (Hariharan et al. 2012; Torres et al. 2012; Yang et al. 2012; Yazdi et al. 2012; Forootanfar et al. 2014; Wadhwani et al. 2016).

Antibacterial activity

Bacterial proliferation is a global concerning and rising problem which led to significant damage in various industries. However, a universal solution for limiting bacterial colonization is not discovered yet. Thus, the new approaches for controlling bacterial activity are required, and nanoparticles' synthesis is a great alternative (Díez-Pascual 2018). Se NPs synthesized from a biological resource (by *Saccharomyces cerevisiae*, 30–100 nm size) had shown considerable antimicrobial activity against pathogenic microbes causing nosocomial infection (Hariharan et al. 2012). These pathogenic microbes include *Escherichia coli*, *Staphylococcus aureus*, *Salmonella typhimurium*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Klebsiella pneumonia* which were isolated from hospitals, in India (Hariharan et al. 2012). Se NPs had a high potential broad-spectrum antimicrobial activity (Yip et al. 2014; Stevanović et al. 2015; Wang et al. 2015, 2016; Chung et al. 2016; Huang et al. 2016; Wadhwani et al. 2016; Ionin et al. 2017; Tan et al. 2018). Se NPs can inhibit the growth of both Gram-positive and Gram-negative bacteria (Hariharan et al. 2012). The antimicrobial activity of Se NPs depends on the synthesis method. Piacenza et al. (2017) investigated the antimicrobial effect of two different chemically synthesized Se NP (L-cysteine and ascorbic acid as the reducing agent, size 99.8 nm and 170.5 nm, respectively) compared to spherical biogenic Se nanostructures produced by *Bacillus mycoides* SelTE01 (size 160 nm) on *Staphylococcus aureus* and *Pseudomonas aeruginosa* biofilms grown onto hydroxyapatite-coated clinical surfaces and devices (Table 2). The antimicrobial activity of the chemically synthesized Se NPs was observed at concentration of 2.5 mg/mL, while the biogenic Se NPs were effective at concentration of 0.078 mg/mL.

Staphylococcus aureus causes 25% of all ventilator-associated pneumonia infections. Polyvinyl chloride coated with Se NPs produced by chemical method (size 80–200 nm) may effectively reduce bacterial adherence and proliferation on rat dermal fibroblasts in vitro (Ramos and Webster 2012). In addition, Se NPs synthesized through chemical (using the reduction of sodium selenite by glutathione, size 74.3 nm), and biological (by *Enterococcus faecalis*, size range of 29–195 nm) methods exhibited negative effects on

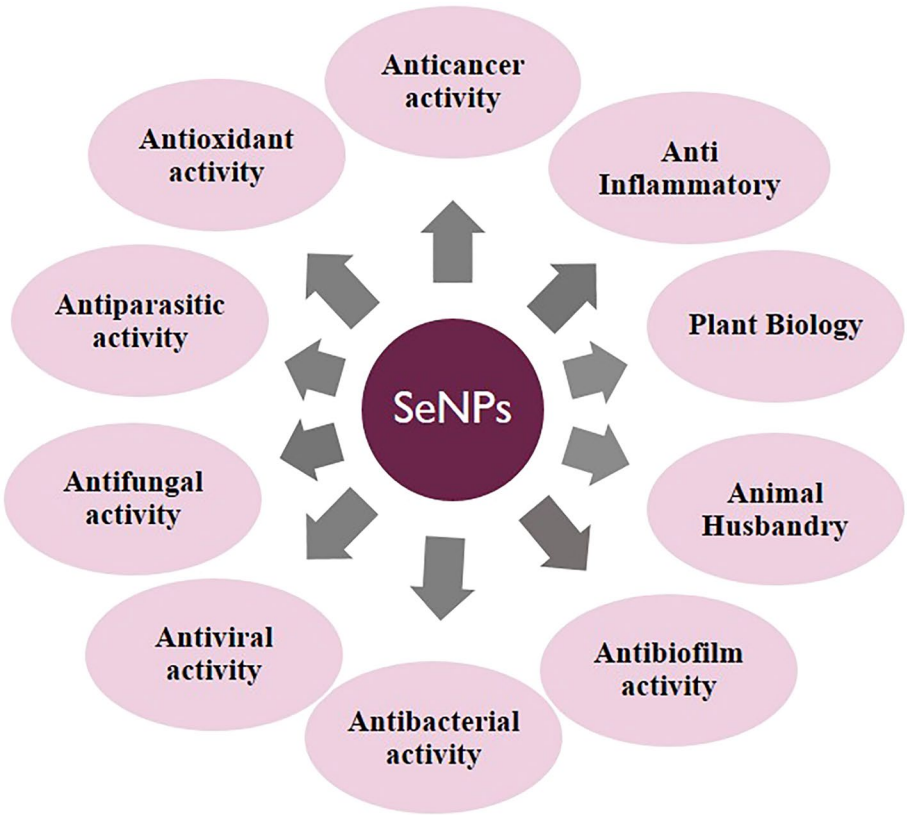


Fig. 3 Biomedical applications of selenium nanoparticles

Table 2 Summary of reviewed studies on Se NPs

Type of Se NPs' synthesis	Resources to synthesize Se NPs	Se NPs' function	Outcome	Refs.
Chemically	L-cysteine and ascorbic acid	Antibiofilm activity	Moderate antimicrobial activity against both *S. aureus* and *P. aeruginosa* strains at the highest tested concentration (2.5 $mg{\cdot}mL^{-1}$)	Piacenza et al. (2017)
Biologically	*Bacillus mycoides* SelTE0	Antibiofilm activity	Antibiofilm activity against both *S. aureus* and *P. aeruginosa* strains at 0.3125 $mg{\cdot}mL^{-1}$ and 0.078 $mg{\cdot}mL^{-1}$	Piacenza et al. (2017)
Biologically	*Bacillus* sp. MSh-1 and sodium selenite	Antibiofilm activity	Se NPs reduced biofilm formation of *P. aeruginosa, S. aureus* and *P. mirabilis* by 34.3%, 42%, and 53.4%, respectively	Shakibaie et al. (2015a, b)
Biologically	Extract of Ginger and sodium selenite	Antimicrobial activity	Se NPs showed significant antibacterial activity against *Proteus* sp.	Menon et al. (2019)
Biologically	*Ralstonia eutropha* and sodium selenite	Antimicrobial activity	Concentrations of 100 µg/ml, 100 µg/ml, 100 µg/ml, and 250 µg/ml Se NPs revealed 99% growth inhibition of *S. pyogenes*, *P. aeruginosa*, *S. aureus,* and *E. coli*, respectively	Menon et al. (2019)
Biologically	*Enterococcus faecalis* and sodium selenite	Antimicrobial activity	Anti-staphylococcal to effective prevention and treatment of *S. aureus* infections	Shoeibi and Mashreghi (2017)
Biologically	Actinobacteria and sodium selenite	Antiviral activity	Se NPs inhibit the viral growth (type-1 dengue virus) maximum in 700 ppm	Ramya et al. (2015)
Chemically	Na_2SeO_3	Antiviral activity	Se@AM decrease toxicity and significantly inhibited the ability of H1N1 influenza at infect host cells	Li et al. (2018)
Biologically	*Ralstonia eutropha* and sodium selenite	Antifungal activity	The Se NPs' concentration 500 µg/ml inhibited the growth of fungi *A. clavatus*	Srivastava and Mukhopadhyay (2015)
Biologically	*Klebsiella pneumoniae* and sodium selenite	Antifungal activity	Se NPs display antifungal activity by inhibition spore germination and these are inhibited dermatophytes like *Malassezia sympodialis* and *Malassezia furfur*	Shahverdi et al. (2010)
Biologically	*Bacillus* sp. MSh-1 and sodium selenite	Antifungal activity	The concentrations of 70 and 100 µg/ml Se NPs exhibited growth inhibition of *C. albicans* and *A. fumigatus*, respectively	Guisbiers et al. (2017)
Biologically	*Bacillus* sp. MSh-1 and sodium selenite	Antiparasitic activity	The results were reported to kill amastigotes and promastigotes of *Leishmania major* and *Leishmania infantum*	Mahmoudvand et al. (2014a, b)
Biologically	*Bacillus* sp. MSh-1 and sodium selenite	Antiparasitic activity	The highest toxicity observed after 72 h against both amastigote and promastigote forms of *Leishmania major*	Beheshti et al. (2013)
Biologically	*Bacillus* sp. MSh-1 and sodium selenite	Antiparasitic activity	Similar outcomes of antileishmanial property of biosynthesis Se NPs showed in vitro against *L. infantum* and *L. tropica*	Soflaei et al. (2012); Mahmoudvand et al. (2014a, b)

Table 2 (continued)

Type of Se NPs' synthesis	Resources to synthesize Se NPs	Se NPs' function	Outcome	Refs.
Biologically	*Bacillus* sp. MSh-1 and sodium selenite	Antioxidant activity	Higher IC_{50} of the Se NPs (41.5 ± 0.9 µg/mL) compared to SeO_2 (6.7 ± 0.8 µg/mL) confirmed lower cytotoxicity of the biogenic Se NPs on MCF-7 cell line	Forootanfar et al. (2014)
Biologically	*Lactobacillus plantarum* and sodium selenite	Anticancer activity	Considerable decrease in the growth rate of tumor in the test mice and enhancement of cellular immunity	Yazdi et al. (2012)
Chemically	Ascorbic acid	Anticancer activity	Functionalization of Se NPs with Spirulina polysaccharides (SPS) inhibit the growth of tumor using inducing apoptosis	Yang et al. (2012)
Chemically	Sodium selenite	Anticancer activity	Suppression of prostate LNCaP cancer cells growth in vitro through caspase-mediated apoptosis	Kong et al. (2011)
Biologically	*Lactobacillus brevis* and sodium selenite	Anticancer activity	Nanored elemental Se NPs decrease tumor-related volume and also demonstrate that levels of TGF-β in these mice decreased and levels of cellular immunomodulatory components significantly increased	Yazdi et al. (2015)
Chemically	SeO_2	Anti-Inflammatory	Se NPs reducing the paw edema in irradiated and non-irradiated rats	El-Ghazaly et al. (2017)
Chemically	Sodium selenite	Anti-Inflammatory	Se NPs induce intracellular toxicity, apoptosis, and necrosis in cancer cells	Pi et al. (2013)
Chemically	–	Anti-Inflammatory	Significant declined antioxidant enzyme such as SOD, CAT, and GPx activities but increased in thiobarbituric acid reactive substances level in RA rats	Ren et al. (2019)
Chemically	Sodium selenite and ascorbic acid	Plant biology	400 mg of Se NPs influence the growth, biochemical characteristics and yield of cluster bean	Ragavan et al. (2017)
–	–	Animal husbandry	Adding Se NPs to livestock feed can improve quality of the tissue and meat and growth requirements	Rajendran (2013)
–	–	Animal husbandry	Se NPs lead the better of fatty acid profile in eggs by reducing the ratio of saturated to unsaturated acids and also significantly increased the level of HDL fraction and decreased the level of total cholesterol and total lipids in plasma and egg yolk	Konkol and Wojnarowski (2018)
Biologically	–	Animal husbandry	Se NPs' addition increases testicular and semen glutathione peroxidase activities and increases male reproductive capacity	Sarkar et al. (2015)

the growth and the percentage of live bacteria (Tran and Webster 2011; Shoeibi and Mashreghi 2017; Verma 2017). In another study, the antimicrobial activity of biogenic Se NPs synthesized by the extract of ginger (size 100–150 nm) was evaluated against six bacterial species of *Klebsiella* sp., *Pseudomonas* sp., *Serratia* sp., *Proteus* sp., *S. aureus*, and *Escherichia coli* (Menon et al. 2019). Se NPs showed significant antibacterial activity against *Proteus* sp. (Menon et al. 2019). The MIC of Se NPs versus *Proteus* sp. was about 250 µg/mL (Menon et al. 2019). The Se NPs biosynthesized by *Ralstonia eutropha* (size 40–120 nm) demonstrated great antimicrobial activity (Srivastava and Mukhopadhyay 2015). The concentrations of 100 µg/ml, 100 µg/ml, 100 µg/ml, and 250 µg/ml of Se NPs inhibited (99%) the growth of *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Escherichia coli*, respectively (Srivastava and Mukhopadhyay 2015). Se NPs synthesized by *Enterococcus faecalis* (size 29–195 nm) can employ as anti-staphylococcal to effectively prevent the *Staphylococcus aureus* infections (Shoeibi and Mashreghi 2017). The antibacterial activity of biogenic Se NPs synthesized by fresh guava leaves (with particle size of 30–50 nm) evaluated against *Enterococcus faecalis* in several groups [group I: distilled water (control), group II: Se NPs (1 mg/ml), group III: calcium hydroxide (1 mg/ml), group IV: 2% chlorhexidine gluconate, group V: 5.25% sodium hypochlorite] using disk diffusion method. The mean zone of inhibition was higher at different concentrations of Se NPs (10–40 µl of Se NPs with concentration of 1 mg/ml was 11.33, 16.50, 21.00, and, 28.50 mm, respectively) followed by sodium hypochlorite (14.67 mm), chlorhexidine gluconate (13.00 mm), and calcium hydroxide (6.83 mm). Guava leaves extract and sodium selenite (as precursor salt) did not show any zone of inhibition which proposes that the antimicrobial activity was only owing to the interaction of Se NPs with the bacterial cell, and not owing to any additional entities that were employed during the synthesis process (Miglani and Tani-Ishii 2021). The disintegration of the bacterial cell wall using the adhesion of NPs is the most common mechanism of antibacterial activity (Escobar-Ramírez et al. 2021). The conjugating quercetin and acetylcholine to the surface of Se NPs adhere to the cell wall, causing damage to the bacterial membrane cell and thereby reaching a significant synergistic effect to prohibit methicillin-resistant *Staphylococcus aureus* (Huang et al. 2016). Huang et al. (2016) reported that the synergistic effects of quercetin and acetylcholine increase the antibacterial properties of Se NPs. The result of various studies exhibited bacteria treated with Se NPs have a cellular contraction and take an irregular shape compared to a control group of untreated bacteria (Huang et al. 2016, 2019; Nguyen et al. 2017; Chandramohan et al. 2019; Escobar-Ramírez et al. 2021). *Pseudomonas aeruginosa, Escherichia coli, Vibrio parahemolyticus*, and *Bacillus subtilis* treated with bio-Se NPs demonstrated holes and pits on the surface, while in *Staphylococcus aureus* treated with bio-Se NPs, some membranes were found to be flattened, wrinkled, and surrounded by cytoplasm, that displayed the leakage of intracellular content (Zhang et al. 2021).

Antibiofilm activity

Bacterial biofilm is a large aggregation of bacterial cells that lives as communities in which these cells stick to each other and often also to a surface. Biofilm is considered as one of the main reasons for chronic infections (Jamal et al. 2018). The studies reported the efficacy of the NPs in decrease biofilm formation, eliminating biofilm, and keeping the antibacterial features even after aging (Díez-Pascual 2018). Biogenic Se NPs produced by *Stenotrophomonas maltophilia* SeITE02 (size 221.1 nm, 345.2 nm and 357.1 nm after 6, 24, and 48 h, respectively) have represented the ability to disrupt microbial biofilms (Zonaro et al. 2015). Biogenic Se NPs synthesized via *Bacillus mycoides* SelTE01 (size 160 nm) displayed the same effective antibiofilm activity against both *S. aureus* and *P. aeruginosa* strains at 0.313 mg/ml and 0.078 mg/ml, respectively (Piacenza et al. 2017). The antibiofilm activity of biogenic Se NPs (produced by *Bacillus* sp. MSh-1, size 80–220 nm) against common biofilm-forming clinically isolates of *S. aureus, P. mirabilis*, and *P. aeruginosa* was evaluated by Shakibaie et al. (2015a, b). The biogenic Se NPs was first produced by *Bacillus* sp. MSh-1 and characterized to individual and spherical nano structure with size range of 80–220 nm (Shakibaie et al. 2010). The results of antibiofilm activity revealed that biogenic Se NPs reduced biofilm formation of *P. aeruginosa, S. aureus*, and *P. mirabilis* to 34.3%, 42%, and 53.4%, respectively, compared to that of controls (Shakibaie et al. 2015a, b; Tan et al. 2018).

Miglani and Tani-Ishii (2021) evaluated the antibiofilm efficacy of biogenic Se NPs produced using guava leaves (with the size range of 30–50 nm) against *Enterococcus faecalis*. The mean percentage decrease in growth of biofilms in different test groups compared to control was higher in Se NPs, sodium hypochlorite, chlorhexidine gluconate, and calcium hydroxide, respectively (Miglani and Tani-Ishii 2021). They were reported that Se NPs inhibited 65% growth of the biofilms. The ability of these groups for inhibition of biofilm formation by *Enterococcus faecalis* was investigated using counting the viable bacteria within the biofilm. The percentage of viable cells at 24 h was 21.38% in the presence of Se NPs, followed by sodium hypochlorite (27.09%), chlorhexidine gluconate (30.03%), and calcium hydroxide (72.20%), compared to control (89.06%) (Miglani and Tani-Ishii 2021). The mean percentage reduction of carbohydrates and protein contents of biofilm compared to control was the lowest in calcium hydroxide followed by chlorhexidine gluconate,

sodium hypochlorite, and Se NPs (Miglani and Tani-Ishii 2021). The antibiofilm mechanism of Se NPs is after adhesion to the biofilm, NPs could penetrate into the pathogen and disrupt the microbial cell well via replacing with sulfur, which induces 50% suppression of *Candida albicans* biofilm at low Se NPs' concentration (Lin et al. 2021).

Antiviral activity

Viral infection considered as a health threat worldwide. Notwithstanding, antiviral drugs that prevent replication of viruses, but many viruses, for example, human immunodeficiency virus, mutate readily and generate resistant strains that they have no effective drugs (Kawai and Akira 2006). The antiviral properties of nanoparticles extensively studied in the past decades. These studies, at least, are divided into two categories. The first category is associated with modified NPs with various organic molecules. The functionalized NPs can be effective on the virus because of interactions among the molecules-receptors and molecules-functionalizer at the virus surface. The second category is related to the antiviral activity of 'pure' (non-functionalized) NPs (Lysenko et al. 2018). It has been shown that Se deficiency plays a critical role in susceptibility to viral infections. Se NPs antiviral activity has its advantages, including less toxicity and excellent activity. The protective effects of supplemental Se explained in mice infected by the H1N1 influenza virus. The mortality of the H1N1 virus-infected Se-deficient mice was three times more than those animals receiving Na_2SeO_3 with a dose of 0.5 mg $Se{\cdot}Kg^{-1}$. Mice with low serum Se concentrations demonstrated a significant reduction in lower levels of IFN-γ and TNF-α and body weight (BW) (Yu et al. 2011). The administration of Se NPs is an efficient approach to improve the immune response in the body.

The actinobacterial synthesized Se NPs (size 10–250 nm) displayed good antiviral activity against type-1 dengue virus. This activity increased with increasing doses, and at the same time, the decrease in viral growth documented. Se NPs maximally inhibited the viral growth at 700 ppm (Ramya et al. 2015). Yinghua et al. (Li et al. 2018) designed surface decoration of Se NPs by amantadine (Se NPs@AM) (produced by chemical method, size of Se NPs and Se@AM were 200 nm and 70 nm, respectively) to reverse drug resistance due to H1N1 influenza virus infection. Se@AM decreased the toxicity and significantly inhibited the ability of H1N1 influenza at infect host cells by suppression of the neuraminidase activity. Functionalized Se NPs using β-thujaplicin (with the size of 80 nm) showed superior antiviral potential to prevent the H1N1 influenza virus (Wang et al. 2020). The action mechanism of antiviral activity from functionalized Se NPs by β-thujaplicin exhibited that it inhibited caspase-3-mediated apoptosis via generating reactive oxygen species (Wang et al. 2020). In vivo antiviral outcomes demonstrated that these Se NPs inhibited Madin-Darby canine kidney cells apoptosis by regulating the AKT and p53 signaling pathways (Wang et al. 2020). They suggested functionalized Se NPs by β-thujaplicin as efficient carriers to gain an antiviral pharmaceutical candidate for H1N1 influenza (Wang et al. 2020). There is a developing association between Se concentration and COVID-19 outcomes. The mechanism of Se on Severe Acute Respiratory Syndrome Coronavirus 2 has been suggested based on previous studies on RNA viruses including the restoration of glutathione peroxidases and thioredoxin reductases, thus decreasing oxidative stress, decrease of viral-induced cell apoptosis, provision of Se for the host's antioxidant requirements, protection of endothelial cells, and decreased blood platelet aggregation (Hiffler and Rakotoambinina 2020; Liu et al. 2021; Martinez et al. 2021).

Antifungal activity

The frequency and variety of invasive fungal infections have significantly increased over the last decades (Van Thiel et al. 2012), and these infections considered a major medical concern in the second half of the twentieth century. Fungal infections are hard to manage due to they tend to become chronic, difficult to diagnose, and hard to root out with antifungal drugs (Casadevall 2018). Guisbiers et al. (2017) reported the first synthesis of Se NPs by femtosecond pulsed laser ablation (size 50–400 nm) in deionized water. These pure nanoparticles used to inhibit the formation of *Candida albicans* biofilms then Se NPs easily adhere on the biofilm, penetrate to pathogen agents, and therefore harm the cell structure by substituting with sulfur (Guisbiers et al. 2017).

The biogenic Se NPs (synthesized by *Ralstonia eutropha*, size 40–120 nm) at concentration of 500 µg/ml inhibited the growth of fungi *Aspergillus clavatus* (Srivastava and Mukhopadhyay 2015). Shahverdi et al. (2010), Wadhwani et al. (2016) evaluated antifungal effect of biogenic Se NPs (produced via *Bacillus thuringiensis*, average size between 50 and 200 nm) against strains of *Malassezia* and *Aspergillus* which are two important clinical fungal genera. Se NPs displayed antifungal activity by inhibition spore germination, and these inhibited dermatophytes like *Malassezia sympodialis* and *Malassezia furfur*. Shakibaie et al. (2015a, b) evaluated the antifungal activity of biogenic Se NPs produced by *Bacillus* sp. Msh-1 versus *Candida albicans* and *Aspergillus fumigatus*. Se NPs demonstrated suitable antifungal activity, and yeast cells were more sensitive than mold cells. The concentrations of 70 µg/ml and 100 µg/ml of Se NPs inhibited the growth of *C. albicans* and *A. fumigatus*, respectively. The

antimicrobial mechanism of NPs reported DNA damage and cell wall disruption. NPs electrostatically interconnect via the cell wall or cell membrane, inducing microbial cell wall destruction (El-Saadony et al. 2021). Consequently, large molecules transmit through the microbial cell membrane and disrupt DNA, finally causing cell death (El-Saadony et al. 2021).

Antiparasitic activity

Parasites are a group of pathogens that are more detrimental to humans than bacteria, and they usually induce chronic infection (Sun et al. 2019). The parasitic diseases created via protozoan parasites and intestinal helminths are one of the most common infections in humans in developing countries (Haque 2007). Biogenic Se NPs (biosynthesized by *Bacillus* sp. MSh-1, size 80–220 nm) showed a significant scolicidal activity versus *Echinococcus granulosus*, which is the agent of cystic hydatid disease. Se NPs can use as therapeutic agents against visceral and cutaneous leishmaniasis, and the results reported to kill amastigotes and promastigotes of *Leishmania major* and *Leishmania infantum*. The 50% inhibitory concentrations (IC_{50}) of Se NPs ranging from 1 to 25 µg/ml (Mahmoudvand et al. 2014a, b; Wadhwani et al. 2016). Beheshti et al. (2013) evaluated the antiparasitic effectiveness of biogenic Se NPs produced by *Bacillus* sp. MSh-1 (size 80–220 nm), against *Leishmania major* in vivo and in vitro. The obtained results displayed the highest toxicity occurred after 72 h against both amastigote and promastigote forms of *Leishmania major* and the IC_{50} of the Se NPs reported to be 4.4 ± 0.6 µg ml^{-1} and 1.62 ± 0.6 µg ml^{-1}, respectively (Beheshti et al. 2013). Similar outcomes of the antileishmanial property of biosynthesized Se NPs (produced by *Bacillus* sp. MSh-1, size 80–220 nm) showed in vitro effect against *L. infantum* (Soflaei et al. 2012) and *L. tropica* (Mahmoudvand et al. 2014a, b). Soflaei et al. (2012) investigated the antileishmanial activities of SeO_2 compared to biogenic Se NPs (produced by *Bacillus* sp. MSh-1, size 80–220 nm) in both amastigotes and promastigotes of *L. infantum*. The results demonstrated a dose-dependent antileishmanial activity for both compounds; although Se NP displayed a greater effect on promastigotes than SeO_2. In another study, Shakibaie et al. (2020) evaluated prophylactic effects of Se NPs against acute toxoplasmosis caused by a single-celled parasite called *Toxoplasma gondii* in the mice. In this experiment, the rate of mortality from an experimental group (receiving Se NPs) compared to a control group (mice did not receive Se NPs) at doses of 10 mg/kg was 100% 10 days after receiving Se NPs. The results of the current study demonstrated the significant efficacy of Se NPs with no important toxicity for curing acute toxoplasmosis in the mice model. Furthermore, Keyhani et al. (2020a, b) demonstrated that the mean number of brain–tissue cysts of *Toxoplasma gondii* was remarkably ($p < 0.001$) reduced in mice treated with Se NPs (biosynthesized using *Bacillus* sp. MSh-1) in a dose-dependent response compared to the control group. The mRNA levels of IFN-γ, TNF-α, IL-12, and inducible nitric oxide synthase were notably raised in mice orally treated with Se NPs (10 mg/kg) compared with the control subgroup ($p < 0.05$). No significant variation ($p > 0.05$) was shown in clinical biochemical factors among the mice in experimental subgroups (treated with Se NPs) compared to control subgroups (Keyhani et al. 2020a, b). In addition, another study showed that biogenic Se NPs (synthesized by *Bacillus* sp. MSh-1) in concentrations of 2.5–10 mg/kg for 2 weeks were able to prevent severe symptoms of toxoplasmosis in mice. These results demonstrated the prophylactic properties of Se NPs with no significant toxicity against chronic toxoplasma gondii infection (Keyhani et al. 2020a, b). Se NPs biosynthesized using *Bacillus* sp. could induce apoptosis of *Leishmania major* via DNA fragmentation (Zhang et al. 2021).

Antioxidant activity

Oxidation is a chemical reaction that generates free radicals, the cause chain reactions that can harm the cells of organisms (Brewer 2011). Most often, the best solution to prevent these harmful effects is addition of antioxidants. Antioxidants are compounds that inhibit oxidation and prevent free radical formation (Brewer 2011). The selenium compounds selenomethionine, selenocystine, and methylselenocysteine can play a significant role in minimizing the free radical concentration to prevent the oxidative damage of DNA in both in vitro and in vivo conditions (Battin et al. 2011). Forootanfar et al. (2014) investigated the antioxidant and cytotoxic effect of biogenic Se NPs produced by marine bacterial strain *Bacillus* sp. MSh-1. The results displayed that at a similar concentration of 200 µg/mL, SeO_2 and Se NPs represented a scavenging activity of $13.2 \pm 3.1\%$ and $23.1 \pm 3.4\%$, respectively. Nevertheless, reducing power assay showed higher electron-donating activity of SeO_2 compared to Se NPs.

Antioxidant activity of Se NPs is dependent on the nanoparticle size; smaller Se NPs have greater activity, and this activity of stabilized Se NPs displayed high activity when compared to selenite and Se NPs without stabilization (Torres et al. 2012). Stabilized biologically produced Se NPs with a size of less than 100 nm can be used as a food additive with antioxidant effects (Torres et al. 2012). In another study, the moderate antioxidant activity of biogenic Se NPs (fabricated by ginger extract, size 100–150 nm) confirmed by comparing the inhibition percentage of 2,2-diphenyl-1-hydrazine (DPPH) radical formation with that of ascorbic acid (Menon et al. 2019). Shinde and Desai (2022) synthesized Se NPs coated with methionine and folic acid

by chemical precipitation approach with size of 50 nm and evaluated its total antioxidant activity in terms of scavenging of DPPH free radicals. An amount of 10 µg/mL of such coated Se NPs could inhibit 41% of DPPH, demonstrating its scavenger function at the lowest concentration (Shinde and Desai 2022).

Xia et al. (2022) indicated that chitosan-stabilized Se NPs have high immunomodulation activity. They reported that immunomodulation activity was correlated to antioxidant activity and lipid metabolism. The chitosan-stabilized Se NPs demonstrated more broad-spectrum impacts on the immune system than an exogenous antioxidant Trolox®. Se NPs has a significant effect on the glutathione system through the promotion of activities and presumably synthesis of selenoenzymes. The biological functions increased using Se NP were almost equal in the healthy and disease individuals that transcriptome analysis on the kidneys and liver and serum proteomics analysis were used to identify molecular pathways. Nevertheless, Se NPs modulates the immune system in various paths, depending on the host condition; in the healthy condition, uptaken Se NPs decline ROS formation to inhibit inflammation and decrease oxidative stress, but Se NPs increase ROS generation during disease conditions. The SOD and NFkβ played an important role in switch changing impact of Se NPs when individuals are under disease, exhibiting the close association between immune and redox regulation (Xia et al. 2022).

Anticancer activity

Cancer or malignancy of cells is one of the health problems around the world (Chaudhary et al. 2014). The six common traits considered hallmarks of cancer cells that including replicative immortality, proliferative signaling, evasion of growth suppressors, invasion and metastasis, angiogenesis, and resistance to cell death (Chaudhary et al. 2014; Nazir et al. 2014). Different diagnostic procedures, such as computed tomography (CT), biosensing, and magnetic resonance imaging (MRI), have been developed in the early detection of cancer (Chen et al. 2008a, b; Muthu and Singh 2009; Janib et al. 2010). Current cancer therapies usually destroy normal cells and therefore represent significant lethal activities and unavoidable side effects. The exceptional capacity of bionanomaterials also opens a novel way for cancer therapy. Se NPs are one of the essential elements with broad pharmacological actions, intrinsic non-toxicity, and significant physiological functions (Wang et al. 2005; Chen et al. 2008a, b; Li et al. 2011; Shi et al. 2011; Duntas 2012; Wang and Webster 2012). Results from human clinical and preclinical experiments (Maiyo and Singh 2017) showed that different forms of Se NPs (produced by fenugreek extract with size of 50–150 nm, ZnS coated quercetin/CdSe with size of 10 nm, single chains lentinan-coated Se NPs with average size of 25 nm, Se NPs functionalized using a novel polysaccharide extracted from *Dictyophora indusiata* with size of 89 nm, novel selenium-substituted hydroxyapatite nanoparticles with size of 160–200 nm, respectively) represented significant anticancer activity (Yang et al. 2012, 2017; Ramamurthy et al. 2013; Jia et al. 2015; Liao et al. 2015, 2016; Yanhua et al. 2016). These compounds can be also used in the diagnosis, treatment, and chemotherapy of cancer and also as drug carriers (Ip 1998; Maiyo and Singh 2017; Tan et al. 2018). Se NPs can inhibit the growth of cancer cells by inducing cell cycle arrest at S phase which mediated with deregulation of the eIF3 (elongation factor 3) protein complex (Hosnedlova et al. 2018). Cell membrane plays a vital role in inducing the cell cycle arrest and Se NPs -induced toxicity in cancer cells, respectively (Pi et al. 2013). Nonetheless, there are different anticancer mechanisms of Se that include three broad categories of (i) chromatin binding and modification, (ii) ROS production and (iii) thiol modification (El-Bayoumy and Sinha 2005; Weekley and Harris 2013; Maiyo and Singh 2017). Yazdi et al. (2012) evaluated the immunostimulatory effect of biogenic Se NPs (fabricated by *Lactobacillus plantarum* with size of 250 nm) on the 4T1-induced breast cancer tumors. The results of tumor growth measurement displayed a considerable decrease in the growth rate of tumor in the test mice when compared to the control group. They attributed such effect to enhancement of cellular immunity and promotion of Th1 immune responses after oral administration of Se NPs.

One way to increase the anticancer activity of nanoparticles and prevention of Se NPs aggregation is the conjugation of Se NPs to organic molecules or drugs (Li et al. 2011; Ramamurthy et al. 2013; Rezvanfar et al. 2013; Vekariya et al. 2013; Ahmad et al. 2015). Functionalization of Se NPs with *Spirulina* polysaccharides (synthesized with chemical reduction method using ascorbic acid by diameter ranging from 20 to 50 nm) inhibited the growth of tumor via inducing apoptosis (Yang et al. 2012). These conjugates also help to specific interactions between carbohydrates and lectins present on the cell surface for targeted delivery of Se NPs to cancer cells (Yang et al. 2012; Wadhwani et al. 2016). Se NPs (synthesized using GSH solution, with average size of 12.4 nm) also demonstrated suppression of prostate LNCaP cancer cells growth in vitro through caspase-mediated apoptosis (Kong et al. 2011; Tan et al. 2018). Furthermore, the results showed when nanorod elemental Se NPs (produced by *Lactobacillus brevis*) administered orally to BALB/c mice bearing 4T1 breast cancer, tumor-related volume was decreased (Yazdi et al. 2015). They also demonstrated that levels of TGF-β in these mice decreased in comparison to the control groups (Yazdi et al. 2015). In contrast, levels of cellular immunomodulatory components (for example, IL-2, IL-12, granzyme B, and IFN-γ) significantly increased in mice treated with both Se NPs and crude antigens of 4T1

cells (Yazdi et al. 2015; Tan et al. 2018). The anticancer mechanisms of Se NPs are not yet fully understood, but the most typical reported pathways are internalization of the NPs, stimulation of autophagy, regulation of the reactive oxygen species generation, and activation of the intrinsic apoptotic pathway (Lin et al. 2021; Spyridopoulou et al. 2021a, b). However, the main mechanism of anticancer activity Se NPs was reported apoptosis in different studies. Se NPs have been demonstrated to cause caspase-mediated apoptosis in various cancer cells, such as melanoma, hepatocarcinoma, cervical, prostate, and breast cancer cells (Li et al. 2019; Alkhudhayri et al. 2020; Spyridopoulou et al. 2021a, b).

Anti-inflammatory

Inflammation is an immune system's defensive response that can be triggered by different factors, involving pathogens, toxic compounds, and damaged cells. The severe and prolonged inflammatory response may involve in progression of many diseases, including cardiovascular diseases, diabetes, cancer, and autoimmune diseases (Liu et al. 2019). Several studies have reported that Se possesses anti-inflammatory properties, and limiting factors including toxicity and bioavailability. El-Ghazaly et al. (2017) evaluated the anti-inflammatory activity of Se NPs (synthesized with a chemical reduction method using SeO_2 with size of 13.4 nm) on inflammation induced in irradiated rats (were exposed to 6 Gy gamma irradiation). They are used the carrageenan-induced paw edema model and were measured paw volume and nociceptive threshold. Se NPs were administered in an oral dose of 2.55 mg/kg. Se NPs reduced the paw edema in irradiated and non-irradiated rats, but it did not change the nociceptive threshold of the both (El-Ghazaly et al. 2017).

The anti-inflammatory effect of Se NPs (folic acid protected/modified selenium nanoparticles with size of 70 nm) was investigated and displayed that Se NPs localized intracellularly in lysosomes and mitochondria of MCF-7 cell (breast cancer cell line) and changed membrane biomechanical properties of MCF-7 cells via disturbing membrane molecules (such as CD44 molecules) and F-actin (Pi et al. 2013). The main mechanism of Se NPs was inducing intracellular toxicity in cancer cells, and it can induce apoptosis and necrosis of these cells (Pi et al. 2013). Furthermore, Se NPs caused down-regulation and disorganization of F-actin, thus, remarkably reducing Young's modulus and adhesion force of MCF-7 cells (Pi et al. 2013). Ren et al. (2019) evaluated the anti-inflammatory activity of Se NPs (Se NPs dispersed in 1% p-coumaric acid with average size of 40 nm) against complete Freund's adjuvant induced rheumatoid arthritis rat model. Their results showed that the symptoms of RA animals which treated with Se NPs (500 µg/Kg body weight) were significantly decreased ($p < 0.001$). They reported some significant decline of antioxidant levels of enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase activities and reduced glutathione, but increased of thiobarbituric acid reactive substances (TBARS) level in RA rats compared to control rats (Ren et al. 2019). Therefore, cyclooxygenase-2 activity, various antioxidant enzyme activities, TBARS, and inflammatory cytokines (TNF-a, MCP-1IL-1b, and IL-6) were significantly reverted to normal levels in treated animals with Se NPs (500 µg/kg) compared with non-treated RA rats.

Se NPs in plant biology

Ragavan et al. (2017) investigated the effect of Se NPs (synthesized by ascorbic acid, size of 50–150 nm) on growth, biochemical characteristics, and yield of cluster bean *Cyamopsis tetragonoloba*. Pot culture of cluster bean treatment with different amounts of Se NPs including 0, 100, 200, 300, 400, and 500 mg was performed and growth biochemical characteristics and yield measured at the end of 60 days (Ragavan et al. 2017). The germination percentage were 100%, 90%, 80%, 90%, 100%, and 100%, respectively. Root length, leaf area, and fresh and dry weight were higher in treatment groups containing 200 mg of Se NPs. The shoot length was lower (12.01 cm) and higher (21.8 cm) in 500 mg and 100 mg treatment group, respectively (Ragavan et al. 2017). Also, the carotenoids, anthocyanin, chlorophyll a, chlorophyll b, and total chlorophyll, protein, L-proline, free amino acids, and leaf nitrate were higher in 400 mg treatment group (Ragavan et al. 2017). The vigor index was higher in 400 mg treatment group. Among the groups, the yield of the cluster bean was lowest in untreated and highest in 400 mg treatment group.

Se NPs in animal husbandry

Some studies have displayed that addition of Se NPs to livestock feed can improve the quality of the tissue and meat and growth requirements (Rajendran 2013). The result showed that average daily gain and final body weight increased in bucks supplemented by different Se forms (sodium selenite, elemental nano-Se or selenized yeast) compared to un-supplemented control groups (Shi et al. 2011). Radwan et al. (2015) reported about adding Se NPs (synthesized using chemical reduction method with size of 80 nm) and sodium selenite to laying hens' nutrition egg production and they observed that feed conversion ratio improved in the nano-selenium groups. Furthermore, in egg yolk of hens receiving Se NPs, lower malondialdehyde content and higher activity of glutathione peroxidase were found (Konkol and Wojnarowski 2018). Se NPs led to the better fatty acid profile in eggs by reducing the ratio of saturated to unsaturated fatty acids and also significantly increased the level of HDL

fraction and decreased the level of total cholesterol and total lipids in plasma and egg yolk of laying hens (Konkol and Wojnarowski 2018).

Se represented a positive impact on the normal reproductive capacity of spermatozoa, normal testicular development, spermatogenesis, and spermatozoa motility, and also incorporated into the mitochondrial protein (Boitani and Puglisi 2009; Sarkar et al. 2015). The two most critical regulating proteins necessary in spermatogenesis are phospholipid hydroperoxide, glutathione peroxidase, and selenoprotein P, which are responsible for carrying Se to the testis (Olson et al. 2005; Imai et al. 2009). Some papers displayed that the supplementation of nano-selenium with 0.3 mg/kg body weight in male boar goats significantly led to better semen glutathione peroxidase activity, testicular Se level, and ATPase activity as compared to control/un-supplemented group (Shi et al. 2010). The results indicated that Se NPs' (provided by Shanghai Stone Nano-Technology Port Co. Ltd., China, with sizes of 60–80 nm) addition increased testicular and semen glutathione peroxidase activities, and testis Se content, and play an essential role in protecting the membrane system integrity. Therefore, Se NPs seem to be able to increase male reproductive capacity more than the other form of elemental Se (Shi et al. 2010).

Conclusion

Fabrication of selenium nanostructures using biological resources, such as microbial strains, herbal extracts, and biological macromolecules, have gained attention during the last decades. Lots of biomedical characteristics, such as antioxidant, cytotoxic, antimicrobial, antiparasitic, anticancer, and immunomodulator activity, compared to that of bulk selenium launched it as a valuable material.

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Declarations

Conflict of interest The authors declare that they do not have any conflict of interest in this study.

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