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Selenium nanoparticles: a review on synthesis and biomedical applications

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Selenium is a trace and essential micronutrient for the health of humans, animals, and microorganisms. Recently, selenium nanoparticles (SeNPs) attracted the interest of many researchers due to their biocompatibility, bioavailability, and low toxicity. Therefore, due to their higher bioactivity selenium nanoparticles are largely being used in various biomedical applications. Generally, selenium nanoparticles can be synthesized by physical, chemical, and biological methods. However, the biologically synthesized SeNPs demonstrate greater compatibility with human organs and tissues. The effect of size, shape, and the method employed for their synthesis on their applications in biological systems has been explored by many researchers. This review discusses various synthesis methods employed for their preparation and highlights their applications in the biomedical field such as in the treatment of fungal, bacterial, and parasitic infections, cancer, and diabetes. They can also act as chemopreventive agents, anti-inflammatory agents, and antioxidants.

1. Introduction

Elemental selenium (Se) has great importance in the fields of physics, chemistry, and biology. Naturally, selenium exists in two forms: inorganic (selenite and selenate) and organic (selenomethionine and selenocysteine). Selenium is found in the form of both crystalline and amorphous polymorphic structures in nature. Monoclinic and trigonal selenium are the crystalline forms. Monoclinic selenium (m-Se) is red in color and contains rings of Se_8. Based on different packings, it exists in three allotropic forms (α, β and γ). Trigonal selenium (t-Se) is black in colour and the most stable crystalline form at room temperature. Red amorphous (a-Se), black amorphous and vitreous selenium are the non-crystalline forms of selenium.[1] The crystal structures of t-Se and m-Se are presented in Fig. 1(a and b), respectively.[2] Selenium, a part of selenoproteins and selenocompounds within the human body, plays a critical role in reproduction, DNA synthesis, thyroid hormone, metabolism, and protection from infections and oxidative damage. It has many industrial and commercial applications. Due to its high photoconductivity and low melting point, it possesses great catalytic activity towards organic hydration and oxidation reactions. Selenium is an essential trace element in the human body but the margin between its usefulness and toxicity is very slender. The United Kingdom group of vitamins and minerals recommended the daily intake of selenium by women and men should be 60 μg and 70 μg, respectively.[3] A daily intake of more than 400 μg could be toxic which leads to a disorder known as selenosis.[3–5] Selenium plays a key role as a biochemical component of glutathione peroxidase, an enzyme responsible for the protection of essential SH-groups and for the decomposition of peroxides, thereby acting as an antioxidant. The bactericidal activity of selenium is because of its capacity to catalyse the oxidation of intracellular thiols, causing death of microscopic organisms.[6–8] Selenium, as one of the fundamental minor components, is affirmed to improve the action or restore the activity of the seleno-catalyst and glutathione peroxidase in prevention of free radical harm to cells and tissues *in vivo*.[9–12] It is widely utilized in nutritional supplements as well as a potential nutrient in fertilizers.[13] A selenium free diet leads to malfunctioning of the liver and hemolytic processes. Se deficiency leads to many diseases such as Kashin–Beck disease,[14]

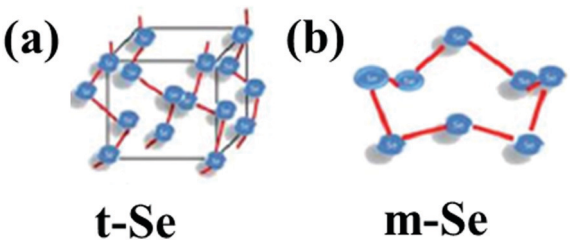

Fig. 1 General representation of the crystal structure of (a) t-Se and (b) m-Se. Reproduced from ref. 2 with permission from The Royal Society of Chemistry, copyright 2015.

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neurological disorders,[15] and chronic degenerative diseases.[16] Selenium supplements can prevent diseases, such as viral infections,[17] immune system dysfunction,[18] and neural function loss.[19] The recent boom in nanotechnology furnished an indefinite number of applications of metal nanoparticles in biomedicine. Metal NPs of Au and Ag, have immense medicinal benefits but are costlier to synthesize, whereas the synthesis of Se nanoparticles (SeNPs) is economical and they can be integrated with other biological agents to enhance their biological properties. Vahdati *et al.*[20] demonstrated the synergistic antimicrobial effect of SeNPs and lysozymes. Due to their higher surface-to-volume ratio at the nano-level, the surface of the particles is more exposed which leads to an enhanced activity of selenium more profoundly in the nano-regime. SeNPs show promising potential as antioxidants, cancer therapeutic agents, and drug carriers in biological applications.[21] Several studies have supported their anticancer,[22] antioxidant,[21] antimicrobial,[23–25] and anti-biofilm properties.[26] Use of nano-Se medication in the therapy of Huntington's disease has given promising results.[27] SeNPs possess unique semiconducting, photoelectric and X-ray-sensing properties, and are used in photocells, photocopying, photometers, and xerography.[28] Their importance in renewable energy devices has also been greatly mentioned.[29] Additionally, selenium nanoparticles (SeNPs) are environmentally important because of their mercury capturing properties.[30]

The absorption profile of selenium indicates that nano-selenium can lead to a blue shift in the absorption spectrum and the range of this shift can vary from preparation to preparation. Thus, it is deduced that the bandgap of Se increases from 1.7 eV in bulk to 3.3 eV in the nano-range.[31] The least toxic form of selenium is elemental Se, and hence its nano-form has attracted significant attention. Interestingly, functionalized SeNPs exhibit less cytotoxicity than their other forms such as selenate, selenite, selenoproteins, and inorganic selenium.[32,33] In clinical trials, instead of conventional selenium sources, elemental nano-sized selenium can be a better alternative. Fig. 2 demonstrates the decrease of cytotoxicity as the selenium nanoparticle size increases.[34] SeNPs are highly biologically active,[35] anti-hydroxyl radicals,[36] and chemo-preventive,[32,37] have a detoxifying effect on heavy metal exposure,[38] and prevent DNA oxidation.[39]

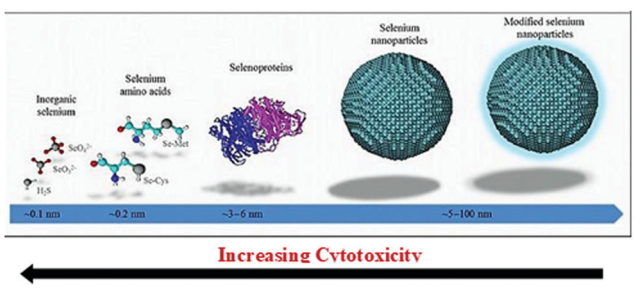

Fig. 2 Extent of cytotoxicity from various sources of selenium with respect to their size. Reproduced from ref. 34 with permission from Science Elsevier, copyright 2017.

It has been suggested by various researchers that impetus to conduct research on SeNPs is greatly desired owing to their tremendous applications in the biomedical field due to their excellent antibacterial activity, sometimes even more effective than Ag NPs.[40–42] SeNPs have been synthesized in various forms such as nanowires, nanorods, and nanotubes through various methods such as sonochemical,[43] refluxing, microwave,[44] hydrothermal,[45] gamma irradiation,[46] pulsed laser ablation,[13,47,48] and physical evaporation approaches.[49–51] The precursors mostly used in these methods are sodium selenite, sodium selenate, sodium selenosulphate, selenous acid and selenium oxide. Use of these precursors is often preferred because selenium in selenite and selenate forms has a hazardous effect even at extremely low concentrations and gets accumulated in the bio-system. In recent times Khanna *et al.* have demonstrated exclusive use of 1,2,3-selenadiazole as a source of selenium for a variety of semiconductor NP ink/quantum dots including selenium nanoparticles.[2,52–55] Converting them to biologically and technologically important SeNPs can help in revitalizing the environment and protect from contamination of Se compounds. Various reviews on the biological applications of selenium nanoparticles and their compounds[56] have been published in recent years while focusing on their biological synthesis methods.[57] This review emphasizes the different synthesis methods of SeNPs and their advantages and disadvantages over each other. The authors also present a detailed discussion of various biological applications of SeNPs such as anti-cancerous, antioxidative, antidiabetic, antiparasitic, antimicrobial, antibacterial, antifungal and chemopreventive agents.

2. Synthesis methods

The synthesis of SeNPs by various methods has been reported. These methods can be broadly divided into two categories, namely biological and chemical reduction. Biological reduction methods include reduction of various organic/inorganic compounds of selenium *via* biological agents such as bacteria or plant extracts and their conversion to non-toxic and beneficial SeNPs. Chemical reduction uses chemical reducing agents. This method can further be classified depending upon the energy source used or the apparatus employed for the reaction. Researchers have reported mainly hydrothermal, microwave, and sonochemical methods in this category. This broad classification is presented in Fig. 3 and then these methods are further discussed in sub-sections.

2.1. Chemical reduction method

Among the vast varieties of synthesis methods reported, reduction of Se salts is the most common and simplest method to synthesize SeNPs.[58] The sources can be natural compounds from plants or microorganisms[59,60] or reagents/chemicals having the ability to cause reduction in the oxidation state such as ascorbic acid.[61] However, the nanoparticles (NPs) synthesized from natural compounds are found to be less toxic than those

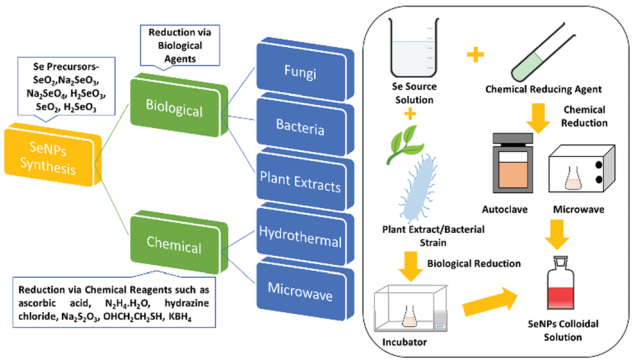

Fig. 3 A systematic representation of various synthesis methods of selenium nanoparticles.

prepared by employing chemicals.[62] In this section, synthesis *via* the chemical method is discussed and synthesis from natural compounds, *i.e.*, biogenic reduction, will be discussed in a later section. Chemical reduction uses chemical compounds that reduce the element, its salt or compounds and the size is controlled by use of surfactants or growth terminating reagents such as polyvinylchloride (PVP), folic acid, *etc.*[63] to obtain a stable colloidal solution of SeNPs desired for various applications. Taking SeO_2 as the precursor, El-ghazaly *et al.*[64] synthesized spherical SeNPs about 13 nm in size where PVP served as the stabilising agent and KBH_4 as the reducing agent in ice-cold solution. The appearance of orange colour indicated the formation of α-Se. The particle shape and size was <10 nm in diameter based on transmission electron microscopy (TEM) analysis. Gao *et al.*[36] reported the use of protein molecules to stabilise hollow SeNPs formed *via* reduction of sodium selenite with mercaptoethanol. The reaction was carried out at a low temperature (<10 °C) and continued for almost 3 days. Particles with an average diameter of nearly 30 nm and a shell thickness of 4 nm were identified and the characteristic binding energy of 55.3 eV corresponding to Se(3d) from the X-ray photoelectron spectroscopy (XPS) spectrum confirmed Se in the zero-valent state.

In another study, Tran *et al.*[65] reduced sodium selenite by ascorbic acid using polyvinyl alcohol (PVA) as the stabilising agent, resulting in an average particle size of 70 nm as observed from dynamic light scattering (DLS) measurements. The absorption was observed in the wavelength range 250 to 450 nm, and the non-appearance of a sharp peak was attributed to the non-metallic nature of Se. The formation of elemental selenium was also confirmed by a characteristic XPS peak at 54.2 eV for Se (3d). Khalid *et al.*[66] repeated the same experiment for PVA capped SeNPs to study their application in cellular imaging. They observed an XPS peak at almost the same value as reported by Tran *et al.*[65] A similar UV-Vis absorption band was observed, and the PL showed an emission at 580 nm. By using the same chemical sources and reagents along with chitosan as an additional stabilising agent, Boroumand *et al.*[67] obtained spherical NPs of sizes 136 and 195 nm, respectively, where the UV-Vis spectra showed absorption peaks at 264 and 310 nm. Similarly, by changing the stabilising agent to polysorbate 20, Vahdati *et al.*[20] obtained a characteristic UV absorption peak at 265 nm consistent with a previous report but with a much smaller particle size in the range of 35–45 nm in comparison to that obtained by using PVA or chitosan. Likewise, Shah *et al.*[68] also used PVA as the stabilizer to obtain SeNPs of 50–100 nm size. The authors for the first time reported that sodium selenosulphate responded to the acrylonitrile monomer, forming SeNPs. By replacing acrylonitrile with acetonitrile, the authors could not isolate Se nanoparticles. This suggests that the nitrile group was not directly involved in the reaction. Using hyperbranched polysaccharide as the stabiliser in the reaction of selenious acid with ascorbic acid in water led to formation of highly stable (>1 month) SeNPs with an average size of about 24 nm which was calculated through DSC.[69] Lin *et al.*[70] used a very mild reducing agent, *i.e.*, dilute SO_2 solution, and selenious acid as the selenium source. Selenous acid being a strong oxidising agent gets easily reduced by SO_2. Sodium dodecyl sulfate (SDS) was used as the stabilizer and the reaction temperature was kept at 80 °C. The variation in particle size with time was studied by TEM. The particle size varied from 30 nm to 200 nm in a time span of 30 s to 4 minutes. The article by Yu *et al.*[71] highlighted the use of sodium thiosulfate as the reducing agent. Reaction of selenium dioxide with sodium thiosulfate in the presence of SDS for about 4 h in ambient conditions yielded monodisperse SeNPs of about 70 nm size as estimated from the TEM images. Huang *et al.*[72] studied the effect of the size of SeNPs on their inhibiting action towards methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* (MSSA and MRSA). For this, they synthesized spherical SeNPs of size ranging from 43 to 205 nm by varying the ratio of SeO_2, the reducing agent sodium thiosulphate and the capping agent PVA. From the antibacterial and cytotoxicity studies, they observed the highest efficacy for 81 nm sized particles. The synthesized particles were found to be spherical and mono-disperse from the scanning electron microscopy (SEM) images.[72] The SeNPs synthesized using the chemical reduction method by the use of polysaccharides as stabilizing/reducing agents was critically reviewed by Shi *et al.*[73]

2.1.1. Microwave synthesis. The microwave method has now become one of the general chemical methods used for materials synthesis. The method is rapid, effortless, inexpensive, clean, provides the end product in high yield and is often termed as a green synthesis route. Over conventional methods where heating takes place *via* conduction, microwave heating is more efficient as heating through microwave radiation is more uniform as the radiation interaction is directly with the molecules. These advantages led researchers to exploit this method for the synthesis of SeNPs as well. However, the literature available on the utilization of microwave energy for preparation of SeNPs is very scarce. One of us previously reported the synthesis of both red and black SeNPs from cycloocteno-1,2,3-selenadiazole by decomposition *via* microwave energy. 1,2,3-Selenadiazole was taken in diphenyl ether with oleic acid as the surfactant. In 10–12 minutes the formation of amorphous red Se particles was confirmed by an UV-absorption band at 400 nm, and when the reaction proceeded further for a few

more minutes, the band shifted to 490 nm and black Se was formed. The corresponding PL peaks were observed at 430 and 510 nm with broad emission profiles. The red Se showed a trigonal structure as deduced from the XRD measurements where the peaks are observed at 2θ values of 23.92°, 30.11°, 41.64°, 44.16°, 45.89°, 52.31°, 56.31°, 56.55° and 62.07°. For the black monoclinic Se, the peaks were observed at 2θ values of 21.80°, 24.80°, 33.19°, 43.51°, 46.79° and 62.70°. Hence, by simply varying the reaction time, various polymorphic forms of Se can be achieved.[2] In another report, $SeCl_4$ was taken as the source, reduced using hydrazine, where the polymer SDS was used as the surfactant, and exposed to microwave irradiation for 4–5 minutes at 750 W to obtain black SeNPs. Several researchers have used microwave irradiation to synthesize SeNPs with narrow size distribution.[74] Mellinas *et al.*[75] for the first time reported the use of *Theobroma cacao* L. bean shells (CBS) as the reducing and stabilising agent for synthesis of SeNPs. The authors have designed a model using a central composite design technique to optimize the reaction conditions. The data for 23 different samples were fed which included parameters such as time, power, amount of precursor, *i.e.*, Na_2SeO_3, Z-potential and crystallite size. Based on this model, the optimal reaction conditions were obtained as 15.6 min, 788.6 W, 0.14 g of Na_2SeO_3 and 50 mL CBS extract solution which yielded particles of ~ 42 nm diameter. The TEM images revealed uniformly distributed spherical particles of 1–3 nm diameter which were found to be stable for 2 months. This attempt opens up a new way in the synthesis of SeNPs *via* microwave and also highlights the technological applications of SeNPs in food and medicine. Panahi-Kalamuei *et al.*[31] reported the synthesis of SeNPs using chemical compounds such as sodium dodecyl sulfate (SDS), polyethylene glycol (PEG 600) and cetyltrimethylammonium bromide (CTAB). $SeCl_4$ was used as the starting material which on dissolving in water produces selenious acid which was reduced using hydrazine hydrate. The reduction potential of Se^{4+}/Se is 0.74 eV and that of $N_2H_4{\cdot}H_2O/N_2$ is −1.16 eV. Hence, the electrode potential is 1.9 eV. Therefore, they chose hydrazine hydrate as the reducing agent and microwaved the mixture for 4 min at 750 W to obtain 5–25 nm particles using SDS. They mentioned that when surfactants like CTAB and PEG are used bigger sized and agglomerated particles will be formed. According to them, this was because Se^{4+} ions present in the reaction media are more stabilised by the anionic surfactant. A similar trend was observed on increasing/decreasing the reaction time/wattage.

2.1.2. Hydrothermal method. The hydrothermal method is not widely popular for the synthesis of biologically compatible SeNPs as reflected from the scarcity of literature. However, the available reports showed that very small sized particles, *i.e.*, 10–20 nm, can be achieved by this method. Shin *et al.*[76] reported the use of cellulose nanocrystals for the first time in reduction of Na_2SeO_3 to obtain SeNPs having size in the range of 10–20 nm. The method is very convenient and eco-friendly. Another example of environment-friendly synthesis is the synthesis reported by Abbasian *et al.*[77] where they used coffee bean extract to reduce Na_2SeO_3 to Se. The reaction completed in

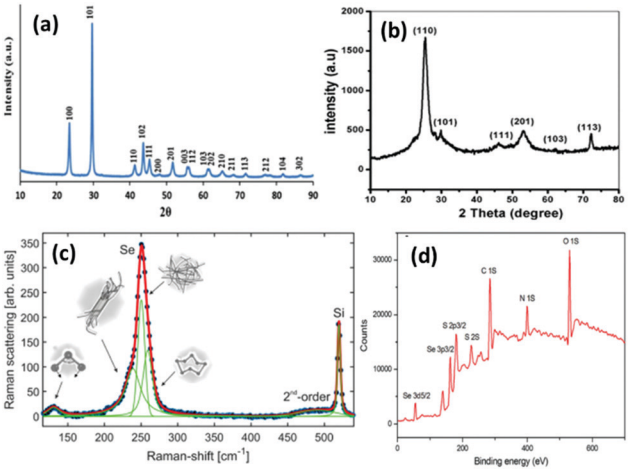

Fig. 4 (a) XRD pattern of SeNPs synthesized *via* the hydrothermal method. Reproduced from ref. 78 with permission from Science Elsevier, copyright 2013, (b) XRD pattern of SeNPs synthesized using drumstick extract. Reproduced from ref. 105 with permission from John Wiley and Sons, copyright 2019, (c) Raman spectra of Se representing the presence of various phases at different energies. Reproduced from ref. 48 with permission from Springer Nature, Copyright 2019. (d) XPS spectrum of L-cysteine capped SeNPs. Reproduced from ref. 109 with permission from RSC Publications, copyright 2017.

15 minutes and at a medium temperature. Spherical nanoparticles of ~15 nm average size were synthesized by reduction of Na_2SeO_3 *via* hydrazine chloride. The XRD peaks (Fig. 4b) at 2θ values of 23°, 28°, 42°, 46°° and 52° confirmed the formation of black Se in the tri-dimensional phase.[78] Glucose and Na_2SeO_3 were sealed in an autoclave and reacted in an ethylene glycol and water mixture at 85 °C for 45 minutes. From this reaction, Chen *et al.*[79] obtained t-Se spherical nanoparticles of a 320 nm average size which were further converted into nanorods on prolonged reaction.

2.2. Biogenic reduction

Green synthesis of metal NPs have gained the attention of researchers in the last two decades. Despite the various advantages of SeNPs over organic and inorganic selenium compounds, the main problem is their poor cellular intake. Therefore, it is desirable to synthesize SeNPs *via* a biological route to offer improved biocompatibility and stability. The previous methods mentioned above require chemical reducing and stabilising agents which may be toxic and can hinder their utilization in biological systems. Generally, it is believed that biological agents from plant extracts and microorganisms represent a superior option in contrast to chemical methods to satisfy the increasing demand for low-cost and non-hazardous preparation methods. It has been reported that biological extracts act as bio-reducing agents, as well as stabilizers for nanoparticles. There is a tremendous amount of literature available on the biosynthesis of SeNPs.[80–87] Biological agent mediated synthesis is easy as this does not require special apparatus and conditions. These biological reagents include bacteria, fungi, algae, protein molecules and plant extracts. For

instance, several researchers have reported the synthesis of SeNPs using fenugreek extract,[88] *Cassia auriculata* extract,[89] *E. officinalis* fruit extract,[90] microbial polymers,[91] *Bacillus* sp. B2,[92] *Saccharomyces cerevisiae* var. boulardii yeast cells,[93] *Penicillium chrysogenum*,[94] *Penicillium expansum*,[95] *Vitis vinifera* aq.,[96] *Withania somnifera* extract,[97] *Azadirachta indica*,[98] *Aloe vera* leaf extract,[99] *Burkholderia fungorum*,[100] *Diospyros montana* leaf extract,[101] lemon leaf extract,[102] or bacteria grown from Mueller–Hinton broth[103] as reducing agents with incubation of the precursor mixture for a day or two. However, the use of plant extracts is even more cost effective than using bacteria or fungi as bacterial culture and isolation requires techniques, experience, and special equipment. With this method, high-quality SeNPs can be produced without requiring specific equipment, with less or no product wastage, and without the need of a large amount of solvent. Hence, such methods are considered as single-step, inexpensive and eco-friendly. Plant extracts contain terpenes, flavonoids, tannins, coumarins, cinnamic acid, phenolic acid, vitamins, sterols, polysaccharides, enzymes, proteins, *etc.* which can act both as reducing and as stabilizing agents. Recently, a few review articles brought out the importance of plant-based SeNPs, the simplicity in the synthesis and the feasibility for biological applications.[57,104] Moreover, preparation of SeNPs using medicinal plants may enhance their beneficial properties. These biological catalysts are vital environmentally as they reduce the toxic oxyanions present in the environment into non-toxic elemental selenium. Fig. 4b shows the XRD pattern of SeNPs synthesized using drumstick extract showing peaks at 2θ values of 25.38°, 29.98°, 46.1°, 53.00°, 62.38°, and 72.00° due to [100], [101], [111], [201], [103], and [113] planes, respectively, showing the crystalline nature of Se.[105] However, the XRD diffraction peaks for red Se prepared from Muller–Hinton broth were obtained at 23.78°, 29.79°, and 43.88° indexed to the face centred cubic (fcc) planes [100], [101], and [102], respectively, and UV absorption was observed at 263 nm.[103] The most intense peak for the hexagonal phase of SeNPs appears at 29.73°.[106] The characteristic Raman peak for elemental Se is observed at 254 cm^{-1}. However, a slight shift may be observed depending upon the polymorphic forms of Se. Fig. 4c shows the Raman spectra of SeNPs synthesized *via* the laser ablation method which shows a mixture of various phases.[48] The authors interpreted that the peak at the lowest frequency of 131 cm^{-1} corresponds to bending vibrations. The Se–Se stretching in crystalline Se chains appears at 237 cm^{-1} and 250 cm^{-1}. The peak at 259 cm^{-1} was reported to be due to the vibration modes of in the Se_8 crown structure. In general, depending upon the intensity of a particular peak, one can estimate the type of Se formed. Piacenza *et al.*[107] suggested the use of biologically synthesized SeNPs in bio-imaging. They synthesized SeNPs from yeast extract which exhibited a strong photoluminescence emission in the blue-red region of the visible spectrum and a luminescence lifetime comparable to those of mostly used fluorophores. Afzal *et al.*[108] reported the use of various cyanobacterial strains for the biogenic synthesis of SeNPs and studied their antioxidant properties. Out of the many strains used, *Arthrospira indica* SOSA-4 was suggested to be the best strain as it yielded SeNPs of 11.8 nm size and improved the antioxidant activity. When heated for a few minutes, reaction of L-cystine with selenious acid yielded cystine capped SeNPs whose size was determined by the DLS technique and valency was confirmed by the XPS spectra. The appearance of peaks at 55.5 eV and 161.5 eV for Se $3d_{5/2}$ and Se $3P_{3/2}$, respectively, affirms Se in the zero-valent state. The XPS spectrum is shown in Fig. 4d.[109]

In another report, Ramamurthy *et al.*[88] prepared 100–150 nm SeNPs by both chemical and biogenic methods. They observed that the size obtained from the biogenic method was slightly bigger than that achieved by the chemical method, yet the biogenic method proved to be more efficient mainly because biological strains are a combination of various reducing and stabilising agents. For the synthesis of SeNPs, researchers have mostly reported the use of biogenic/biotic reduction. The various biological agents used along with the precursor and reaction conditions are summarized in Table 1.

3. Biomedical applications

The biomedical applications of SeNPs have attracted global interest of many researchers due to their importance at cellular and tissue levels. It is well known that excessive production of toxic reactive oxygen species (ROS) can be triggered by various abiotic stresses, thus causing several diseases, due to damaged essential nutrients such as carbohydrates, proteins, and lipids.[110] The continuous rise in diseases like cancer, diabetes, and bacterial infections is threatening the worldwide healthcare system. Currently, treatment of cancer needs various kinds of therapies such as chemotherapy, radiotherapy, or a combination of both to reduce the global death rate.[111,112] The adverse effects of such therapies generally are of great concern.[113] It has been documented that Se supplements alongside regular anticancer treatments upgraded the productivity of chemotherapeutic medications, declining results and enhancing the generic state of the patients.[114–116] The new clinical preliminaries have assessed the well-being and efficiency of selenium, both in viability and toxicity of normal anticancer treatments.[117] Numerous *in vivo* and *in vitro* studies at the supranutritional level have exhibited an anticancerous impact by selenium.[118,119] Davis *et al.*[120] reported that the frequency of liver malignancy can be decreased by 35% on consuming supplements of selenite salt. A few studies revealed that, by taking 200 μg of selenium each day, as Se yeasts, the risk of colorectal, lung, and prostate cancers has decreased.[121] Similarly, Se supplements also reduce the stomach malignancy risk.[122] It has been reported that a lower dosage of selenoprotein (SelP) can increase the risk of cancer in prostate, throat, kidney, colon, and lungs.[123] Selenium rich Brassica and Allium plants lessen the risk of colon malignant growth.[121] Despite having such advantages these organic and inorganic sources of selenium exert higher toxicity and possess lower biocompatibility. To overcome these issues, SeNPs came to the limelight.

Table 1 Summary of the reactions carried out by various researchers for synthesizing SeNPs using different biological sources

S. no.	Se precursor	Biological agent/extract origin	Reaction conditions	Morphology and size of particles	Applications	Ref.
1	SeO_2	*Bacillus licheniformis*	Incubated at 37 °C for 48 h	Spherical with a diameter of 10–50 nm, λ_{abs} = 263 nm, colourless to orange-red (red Se)	Antimicrobial against foodborne pathogens	103
2	SeO_2	*Bacillus licheniformis*	Incubated at 37 °C for 24 h	Spherical with a diameter of 50–80 nm, λ_{abs} = 560 nm	Chemopreventive against lung carcinoma	124
3	Na_2SeO_3	*Azadirachta indica*	Incubated for 5 min and 10 min	λ_{abs} = 560 nm, size ∼153 nm λ_{abs} = 580, 670 nm, size ∼287 nm	Antibacterial against Gram positive and Gram negative bacteria	98
4	SeO_2	*Trigonella foenum-graecum* leaf extract	Stirring at room temperature for 2–8 h	D = 20 nm, nanospheres with a 5–12 nm diameter, λ_{abs} = 355 nm	Anticancer Degradation of sunset yellow FCF	125
5	Na_2SeO_3	*Terminalia Arjuna* leaf extract	Incubated at 30 °C for 72 h	Size = 10-80 nm, λ_{abs} = 390 nm, dark red, λ_{em} = 595 nm	Effect against As(III) toxicity	126
6	H_2SeO_4	L-Cystine	Heating at 105 °C for 1 h	Nanospheres ∼60 nm, red Se	Interaction with human serum albumin	109
7	H_2SeO_3	*Trigonella foenum-graecum* L. leaf extract	Incubated at RT for 24 h	Absorption band = 200–400 nm, red Se, 50–150 nm oval particles	Breast cancer	88
8	Na_2SeO_3	Glutathione (GSH)	Instant formation of SeNPs	Nanospheres of 40–100 nm size	Prevention of PVC related medical infections	127 and 128
9	Na_2SeO_3	Glutathione (GSH)	Instant formation of SeNPs in basic media	Hemispherical, size = 80–200 nm	Cytotoxicity of SeNP coated PVC in rat dermal fibroblasts	6
10	$Na_2SeO_3 \cdot 5H_2O$, capped with PVP	*Pseudomonas alcaliphila* (bacteria)	Incubated for 48 h	λ_{abs} = 280 nm, Raman = 254 cm^{-1} (m-Se), nanospheres of 40–100 nm size	The role of PVP explained in text	129
11	H_2SeO_3	*Vitis vinifera* extract	Refluxed together for 15 min in water	Nanospheres of 3–18 nm size	—	130
12	Na_2SeO_3	Ethanol extract of Bee propolis from *Apis mellifera* colonies along with ascorbic acid	Stirred at RT for 24 h	Brown to orange colour change λ_{abs} = 265 nm 52–118 nm diameter	Antioxidant, antimicrobial, antibacterial, antifungal	131
13	Na_2SeO_3	*Allium sativum* extract	Incubated for 72 h until color change	7–45 nm, stable up to 2 months Dark pink colour of solution, λ_{abs} = 400 nm	Antioxidant	132
14	SeO_2	*Lactobacillus brevis*	Incubated at 37 °C for 72 h	—	Anticancer (studies on mice with breast cancer)	133 and 134
15	Na_2SeO_3	Various cyanobacterial strains	Incubated at 32 °C for 2–5 days	λ_{abs} = 259–274 nm, red spherical NPs with sizes in the range of 11–60 nm depending upon the strain	Antioxidant	108
16	Na_2SeO_3	*Moringa oleifera* (drumstick) leaf extracts	Incubated at RT for 24 h	λ_{abs} = 299, 400 nm, λ_{em} = 599 nm, bandgap = 2.3 eV Mixture of nanospheres and nanorods Average size = 18.85 nm (calculated by Scherrer's equation) and 23–35 nm from TEM	Degradation of sunset yellow dye Anticancer studies on human colon, breast and hepatic cancers	105
17	$NaHSeO_3$	*Crispum* (parsley) leaf extracts	Kept overnight at room temperature	Orange-red Se λ_{abs} = 270 nm Spherical with a maximum number of particles with a size around 400 nm (DLS) Zeta potential = −14.2 mV	—	135
18	Na_2SeO_3	Rhizobacterium *Azospirillum brasilense* Sp7	Incubated at 32 °C for 24 h	Nanospheres of 50–100 nm diameter coated with a thin layer of protein	—	136
19	Na_2SeO_3	L-Cystine and peptone from soybean	Stirring for 10 h at 25 °C	36.2 nm (from XRD) 20–50 nm (TEM)	Protection against irradiation used nephropathy	106
20	H_2SeO_3	*Diospyros montana* leaf extract	Incubated at RT for 24 h	4–16 nm from TEM and DLS	Antibacterial activity against Gram (+), Gram (−) bacteria and fungi, anticancer activity against human breast cancer	101
21	Na_2SeO_3	Mushroom polysaccharide protein complex – stabilising agent, ascorbic acid – reducing agent	Kept at RT for 12 h with stirring	100 to 600 nm in size depending upon concentration of the stabilising agent	Anticancer activity against human breast cancer cells	137

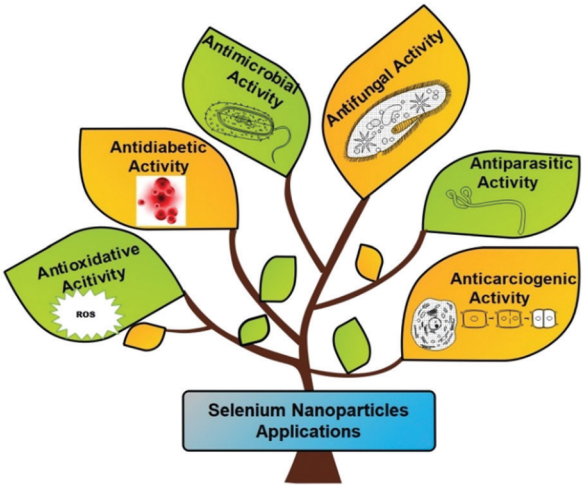

Fig. 5 Pictorial representation of various applications of selenium nanoparticles.

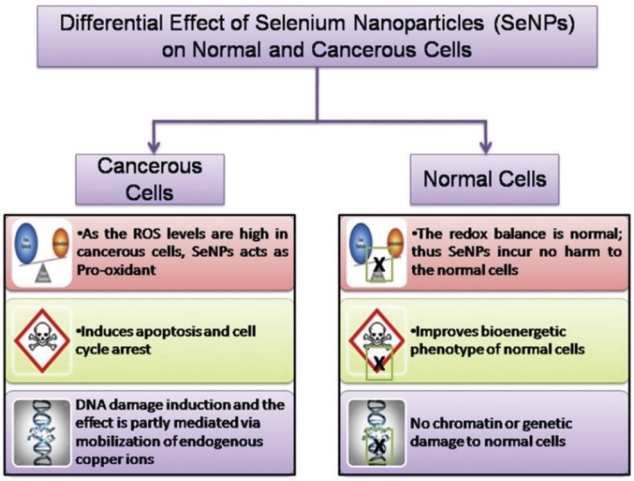

Fig. 6 A schematic of the effect of SeNPs on cancerous and normal cells. Reproduced from ref. 146 (A. Khurana, S. Tekula, M. A. Saifi, P. Venkatesh and C. Godugu, *Biomed. Pharmacother.*, 2019, 111, 802–812), copyright authors 2019, open access Science Elsevier.

Nano-selenium in the form of nano-medicine offers excellent properties such as antimicrobial, anticancer, antidiabetic, antiparasitic, and antioxidant as shown in Fig. 5. The antioxidative properties of nano-selenium minimize the impact of ROS and free radicals. The higher efficiency of SeNPs displays augmented medicinal effects as antibiotic, antidiabetic, cytotoxic, and chemoprotective medicines in comparison to the traditional therapeutic medicines.[138] They can also be used as therapeutic and theranostic agents.[139] It is noteworthy that various studies on SeNPs evidenced reduced toxicity and characteristics of interfacing biomaterials with tissues and cells. SeNPs are biologically active and naturally accessible and take part in numerous oxidoreductive cycles. They also show many regulative outcomes to help the appropriate functioning of plants and living bodies and numerous medical advantages.[34,140,141] Researchers have shown that SeNPs can be utilized as a cancer preventive agent by controlling the cell damage caused by free radicals, in anticancer therapies, and as antimicrobial agents. These can also be used as an ingredient in nano-biosensor fabrication. The action mechanism of SeNPs can be defined in two ways: (a) disrupting the integrity of the cell membrane through ROS generation and (b) alteration of the DNA sequence of microorganisms by damaging the cell wall and binding to the cell membrane to inhibit the growth of microorganisms. The cycles associated with SeNP preparation can be utilized in wastewater treatment and bioremediation. They can play a significant role in the treatment of heavy metals by combining with them to suppress their poisonous impact.[56] Based on the abovementioned advantages the next section discusses the various applications of SeNPs in detail.

3.1. Anti-carcinogenic activity

Nowadays, selenium nanoparticles are widely being investigated for their anti-cancer activity against breast, lung, kidney, and osteosarcoma cancers based on *in vivo* and *in vitro* experiments.[88,124,134,142,143] However, due to selenium toxicity and bioavailability elemental selenium and naturally sourced selenium (selenocysteine and selenomethionine) cannot be used in cancer therapies.[144] Nano-selenium has advantages over other natural sources of selenium because of its size, porosity, and bio-dispersion. Thus, *Polyporus umbellatus* polysaccharide (PUP) capped SeNPs have been utilized to detect the *in vitro* anti-proliferation effect with the MTT assay. Particularly, PUP-SeNPs inhibit the cell growth of four types of human cancer: (a) MDA-MB-23 cells causing breast cancer in humans, (b) HepG2 cells responsible for human liver cancer, (c) HeLa cells known for human cervical cancer, and (d) HT 29 for colon cancer. It is shown by researchers that, by using nano-selenium of the above nature, no toxicity to normal human cells such as liver cells (LO2), embryonic kidney cells (293T), and mouse embryonic fibroblast cells (NIH3T3) was observed.[145] A schematic of the effect of SeNPs on cancerous and normal cells is shown in Fig. 6.[146]

It has been demonstrated by numerous analyses that incorporation of low Se leads to various hazardous diseases. Se acts as a chemopreventive agent when utilized at optimal doses.[147,148] Selenium has therefore been proposed as a disease therapy agent in combination with chemotherapy and radiation.[117] The most extreme anticarcinogenic effect of Se has been reported when it is administered at the beginning phase of the disease.[149,150] The risk of cancer in humans can increase due to the presence of arsenic (As) in drinking water. However, it has been reported that the generation of As(III)-activated ROS can be minimized by use of *Terminalia arjuna* (TA) leaf extract encapsulated SeNPs, which fortifies As(III)-induced cell death and DNA catastrophe.[102,151] Metastatic breast cancer in a mouse model has been reported to be treated by oral administration of *Lactobacillus brevis* with SeNPs, which increases interferon generation and delayed hypersensitivity for triggering the immune response.[134] Therefore, it has been reported by many researchers that if SeNPs are conjugated with

organic moieties and drugs, they can inhibit accumulation of Se nanoparticles, thereby enhancing the anticancer activity and minimizing the antibiotics' toxic effect.[88,143,152–155] The nanoconjugates of SeNPs and doxorubicin show enhanced cytotoxic effect against cancer cells by assisting antibiotic cellular uptake. In a study of lactate dehydrogenase activity and cell viability, Yang *et al.*[143] found that doxorubicin alone was responsible for destroying 20% of cancer cells, whereas more than 50% of cancer cells were destroyed by conjugation of SeNPs and doxorubicin. As an anticancer drug responsible for oxidative stress and DNA cross-linking, cisplatin leads to nephrotoxicity and spermatotoxicity. Interestingly, nephrotoxicity can be reduced using 11-mercapto-1-undecanol functionalized SeNPs by preventing ROS-mediated apoptosis. The antioxidative properties of SeNPs in combination with cisplatin enhance the sperm quality and spermatogenesis.[153,154] During breast cancer treatment, anastrozole is used to inhibit the growth of aromatase which leads to side effects such as bone fracture and osteoporosis. These can be prevented by conjugating anastrozole with SeNPs.[155,156] Similarly, SeNPs prepared using highly branched β-(1–3)-D-glucan obtained from fruiting plants of *Auricularia auricula-judae* (AF1-Se) showed strong suppression against human breast adenocarcinoma cancer cell lines such as MCF-7, MDA-MB-468, and MDAMB-231.[157] SeNPs decorated using various polysaccharides extracted from *Pleurotus tuberregium* (PTR), *Ganoderma lucidum* (GL), *Coriolus versicolor* (CV), and *Polyporus rhinoceros* (PR) showed the highest activity for the gastric cancer cell line AGS.[158] Induction of cell apoptosis is the key mechanism that plays an important role in the antitumor activities of SeNPs and polysaccharide conjugates. Apoptosis, which is also known as programed cell death, can be described by certain governing properties such as nuclear chromatin condensation, cytoplasm shrinkage, development of apoptotic parts, and membrane dysfunction.[159] The cellular growth of human lung cancer cell line A549 can be inhibited by utilizing the complex of *Arabinogalactans* (LAG) and SeNPs.[160] The human breast cancer can be treated by PUP coated SeNPs through stimulating mitochondria mediated and death receptor mediated apoptotic pathways. The anti-cancer activity of these complexes was regulated by the Bax/Bcl-2 ratio, endorsing cytochrome-*c* release, enhanced caspase-9, -8, and -3 activities and poly(ADP-ribose) polymerase cleavage.[161] Therefore, the higher toxicity of SeNPs for cancer cells can be synergistically utilized with anticancer drugs for cancer treatment.

3.2. Antioxidant activity

ROS and reactive nitrogen species (RNS) free radicals are generally generated in the human body during several physicochemical and biochemical reactions. The higher amounts of intermediate complexes such as superoxide and hydrogen peroxide produced during these reactions are responsible for cellular damage, leading to generation of lethal diseases. Therefore, antioxidative compounds are utilized to suppress the creation as well as scavenging of these free radicals.[162,163] The surface of Se nanoparticles decorated with various organic

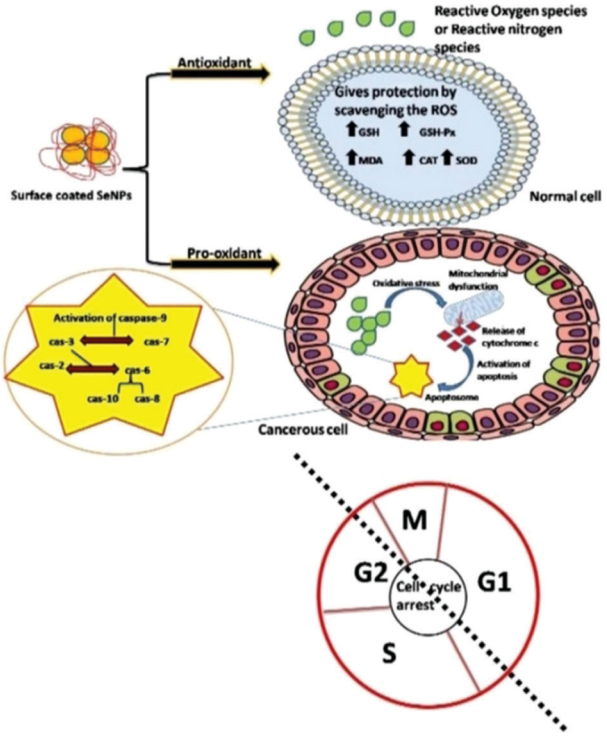

Fig. 7 A systematic representation of the action mechanism by surface decorated Se NPs on various cells as an antioxidant and a pro-oxidant. Reproduced from ref. 164 with permission from Science Elsevier, copyright 2020.

molecules and plant extracts act as both antioxidants and pro-oxidants on different cells of the human body and their action mechanism is shown in Fig. 7.[164] Battin *et al.*[165] reported that selenium nanoparticles can play an important role in minimizing the free radical concentration to prevent the oxidative damage of DNA in both *in vivo* and *in vitro* experimental conditions. It has also been documented that selenoprotein is a key source of selenium and produces vital antioxidants such as deiodinase, thioredoxin reductase, and glutathione peroxidase.[166] In an investigation, Zhang *et al.*[167] showed that sodium selenium inhibited the growth of *Candida utilis* by improving the excretion and biosynthesis of glutathione. Similarly, chitosan functionalized SeNPs showed enhanced glutathione peroxidase and anticipated lipofuscin development in mice.[168] Additionally, $ABTS^{\circ}+$ and superoxide anion radical can be scavenged by utilizing SeNPs in combination with *Cordyceps sinensis exopolysaccharide*.[145] The plant-based synthesis of selenium nanoparticles demonstrated antioxidative activity through ABTS and DPPH assays.[169] Further, the Kong group[170] presented the enhanced antioxidative activity of *gum-arabic* functionalized SeNPs (GA-SeNPs) for scavenging hydroxyl radicals and the DPPH assay test. In an investigation, selenium nanoparticles acted as a hepatoprotective component against acetaminophen accelerated hepatotoxicity by refining liver capacity and restraining oxidative stress in rats. In another study Kokila *et al.*[101] demonstrated the conceivable antioxidative properties of SeNPs. It is known from the literature that the

shape and size of nanoparticles can play a key role in such studies. For example, hollow spherical selenium nanoparticles have shown antioxidative properties.[32,36,37] Thus, plant based SeNPs show better prevention against ROS mediated oxidative stress induced diseases.

3.3. Antidiabetic activity

The high amount of glucose in our body due to the absence of enough insulin creation or inadequate usage of insulin leads to chronic diseases like diabetes. The insulin chemical is responsible for maintaining the blood sugar level. Diabetes negatively impacts people of all age groups. Several researchers have reported the use of selenium nanoparticles in the treatment of diabetes because of its effective controlling ability to regulate the blood sugar level.[171] The long-term effects of diabetes can damage large and small blood vessels, causing a problem in the functioning of various human organs. Diabetes leads to the generation of various diseases in the heart, legs, brain, eyes, kidneys, skin, digestive system, oral health, and immune system as shown in Fig. 8. Deng *et al.*[172] reported that Se nanoparticles loaded with insulin (INS-SeNPs) can be delivered orally to treat diabetes in mice. In their study the researchers stated that the insulin was released in the blood in a controllable manner and showed excellent stability in digestive foods. The Liu group[173] examined the enhanced antidiabetic activity of *Catathelesma ventricosum polysaccharides* (CVPs) coated Se nanoparticles in *streptozocin* (STZ) induced diabetic mice. Similarly, the effect of SeNPs in combination with insulin was investigated by Quraishy *et al.*[174] to enhance the activity of hyperglycemia and hyperlipidemia in STZ induced diabetes in mice. At a concentration of 2.0 mg kg^{-1} body weight, chitosan stabilized SeNPs resulted in improved antidiabetic activity.[175] Furthermore, phytomedicines are proven candidates to combat diabetes in an effective way.[176] Therefore, Deng *et al.*[177] demonstrated that extracts of mulberry leaf and *Pueraria lobata* (MPE)

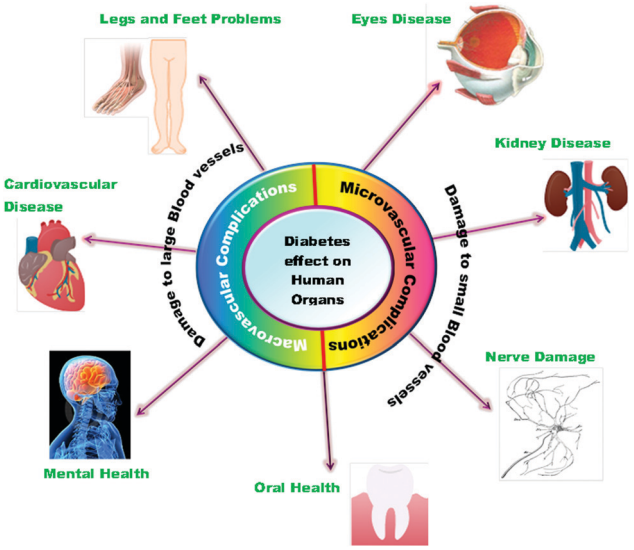

Fig. 8 Effect of diabetes on various human organs.

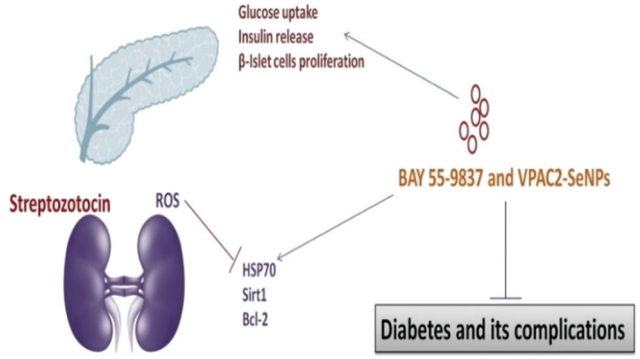

Fig. 9 The effect of SeNPs on diabetic cells. Reproduced from ref. 146 (A. Khurana, S. Tekula, M. A. Saifi, P. Venkatesh and C. Godugu, *Biomed. Pharmacother.*, 2019, **111**, 802–812), copyright authors 2019, open access Science Elsevier.

(phytomedicines) coated SeNPs exerting a hypoglycemic effect can cure diabetes mellitus. The plasma associated selenium demonstrated a positive effect on prevalent and incident diabetes by redox regulation and signaling of insulin pathways.[178] Therefore, selenium nanoparticles functionalized with various moieties are expected to play a crucial role in treating different types of diabetes. A schematic of the effect of SeNPs on various diabetic cells is shown in Fig. 9.[146]

3.4. Antimicrobial activity

Living beings are susceptible to microbial infections leading to numerous diseases causing great health concerns. Nowadays, most of the pathogenic organisms have become drug-resistant because of the constant utilization of a wide range of antibiotics. Particularly, multidrug-resistant microorganisms and fungi are profoundly becoming irresistible as they have procured protection from practically all the accessible antimicrobial drugs.[179–181] Therefore, anti-infection agents are developed for the treatment of these irresistible diseases. There are a variety of metal nanoparticles as well as metal oxides and their combinations which have been documented as potential antimicrobial agents. SeNPs have also found tremendous scope in biomedical applications as an antimicrobial agent to protect implanted clinical gadgets from bacteria. Tran *et al.*[41] incorporated SeNPs by an *in situ* method into regular polymers such as polyvinyl chloride, polyurethane, and silicon, which are generally used in biomedical devices. They observed that the antibacterial performance was directly linked with the concentration of selenium as the coating material in combination with different polymers. Their findings stated that nano-selenium coated polymers essentially can hinder *Staphylococcus aureus* (*S. aureus*) growth, in contrast to uncoated polymers. Additionally, they discovered that SeNP-covered PVC shows more prominent antibacterial effects compared to commercially available Ag-covered PVC.[41] Generally, biofilm development on the surfaces of clinical gadgets by microbes is difficult to treat. Thus, SeNPs act as a suppressing agent for biofilm formation.[34,182–184] Wang *et al.*[42] reported biogenic SeNPs utilizing *Bacillus licheniformis* JS2 to suppress bacterial

(*S. aureus*) adherence, biofilm development, and microcolony formation to various polymer surfaces. These outcomes have possible incentive for application as antibacterial covering prostheses against *S. aureus* and other clinical gadgets against nosocomial infections.[183] Shakibaie *et al.*[26] studied various biofilm forming microbes such as *S. aureus*, *Proteus mirabilis*, (*P. mirabilis*), and *Pseudomonas aeruginosa* (*P. aeruginosa*) to check the viability of biogenic SeNPs-*Bacillus* sp. *MSh-1*, having spherical morphology with the dimension range of 80–220 nm. For comparison purposes they incubated the biofilm formation assay with both SeNPs and SeO_2 with microbes. In both the cases, they observed no significant decrease in the biofilm formation; however, due to the lower toxicity of SeNPs they were preferred over SeO_2. It was believed that SeNPs show antibacterial activity due to oxidative stress.[185] Huang *et al.*[186] reported a new inorganic antibacterial agent based on *quercetin* (Qu) and *acetylcholine* (Ach) functionalized SeNPs (Qu-Ach@SeNPs), which demonstrated improved antimicrobial activity against multidrug-resistant superbugs (MDRs) in contrast to individual Qu@SeNPs and Ach@SeNPs. They observed that when Qu-Ach@SeNPs adhered to the bacterial cell surface, causing disruption of the cytoplasmic membrane, the growth of bacterial cell methicillin resistant *S. aureus* (MRSA) was inhibited and the DNA structure was damaged by antibacterial action as shown in Fig. 10.[186]

In a separate study researchers[40] also found that an *in vitro* study involving SeNPs emphatically suppressed the growth of *S. aureus* (60 times higher) at different doses such as 7.8, 15.5, and 31 μg mL^{-1} for time periods of 3, 4, and 5 h, respectively. However, this study was found unsuitable in microbiology in terms of an effective antimicrobial agent. Therefore, to overcome these issues Mittal *et al.*[187] combined selenium and silver nanoparticles to enhance the antimicrobial activity. Here, Ag-SeNPs having a size range of 30–35 nm were synthesized utilizing bioactive gallic acid and *quercetin* (QC). The antimicrobial activity of the composite of Qu-gallic acid@Ag-SeNPs was found to be superior to both silver nitrate and sodium selenite against *Escherichia coli* (*E. coli*) and *Bacillus subtilis* (*B. subtilis*) on agar plates. They also found comparable results of the nanocomposite with an antimicrobial agent, chloramphenicol, for an equivalent dose of 50 μg mL^{-1}. Here, the authors described the antimicrobial mechanism in two ways: in the first assumption, the nanoparticles adhere to the bacterial cell wall, where silver NPs are released and destroy the bacterial cells; in the second assumption, the interconnectivity of AgNPs with DNA and bacterial protein and more activity for sulfur and phosphorus compounds leads to destruction of these compounds. Menon *et al.*[188] reported biosynthesized SeNPs from *Z. officinale* with spherical morphology and a 100–150 nm size range. They examined the antimicrobial activity of the SeNPs against five microbial species such as *E. coli*, *Klebsiella* sp., *Pseudomonas* sp., *S. aureus*, and *Proteus* sp. The *Proteus* sp. bacterial growth was effectively inhibited by SeNPs at a concentration of 250 μg mL^{-1}. Generally, SeNPs have size and concentration dependent effects against various microorganisms.[189] Further, selenium and tellurium nanoparticles exhibit antimicrobial activity and destruction of biofilm formation. These nanoparticles were effective on inhibiting the growth of *E. coli* JM109, *Pseudomonas aeruginosa* PAO1, and *S. aureus* ATCC 25923.[190] Consequently, SeNPs can be utilized as an effective antimicrobial agent in pharmaceutical applications.

3.5. Antifungal activity

SeNPs acquire antifungal properties for various biological applications. To name a few, SeNPs can be used for the treatment of fungal infections in immunity compromised patients, improvement in probiotic concentration, and fabrication of antifungal and antibacterial cloths for protecting skin from *S. aureus* and *Tinea pedis* infections[191] as shown in Fig. 11. To prove this, Yip *et al.*[192] demonstrated that nano-Se modified with biogenic *polysaccharide*–protein (PSP) complexes collected from *Pleurotus tuber*-regium deposited on a fabric was effective in inhibiting the growth of *S. aureus* and *Trichophyton rubrum* bacteria. Similarly, Shakibaie *et al.*[193] examined the antifungal activity of *Bacillus* sp. Msh-1 functionalized SeNPs against *Aspergillus fumigatus* (pulmonary infection) and *Candida albicans* (skin infection). Shahverdi *et al.*[24] reported SeNPs prepared from *Klebsiella pneumoniae* to treat antifungal infections from *Malassezia sympodialis*, *Malassezia furfur*, and *Aspergillus terreus* in the concentration range from 10 to 260 μg mL^{-1}. Particularly, SeNPs can provide antifungal activity in patients having less immunity against nystatin-immune *Candida* sp.[194]

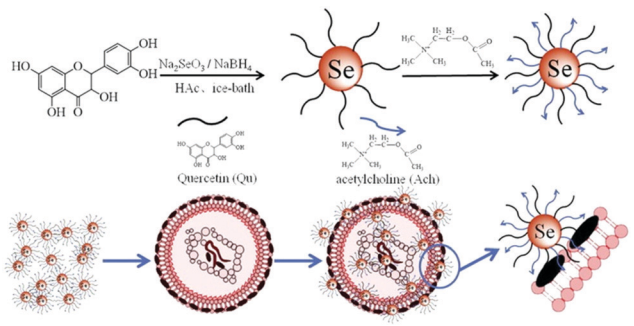

Fig. 10 A schematic representation of the synthesis of Qu-Ach SeNPs and their antibacterial action. Reproduced from ref. 186 with permission from Science Elsevier, copyright 2016.

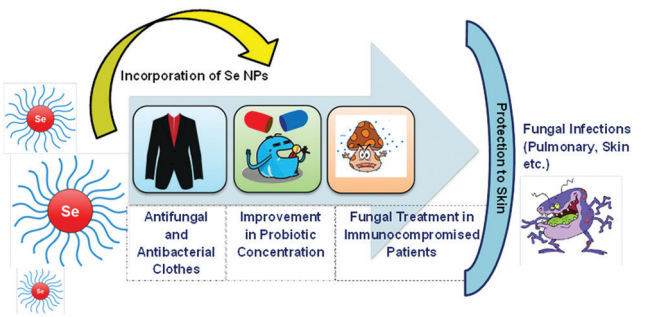

Fig. 11 A schematic of the utilization of SeNPs against various fungal infections.

and a more constructive therapy to encounter intrusive aspergillosis in comparison to the amphotericin B drug.[193] However, conflicting results have been obtained by the Kazempour group on SeNPs prepared from *Klebsiella pneumoniae.* They found that SeNPs lack in treating the post-antifungal effect of *Aspergillus niger* (*A. niger*) and *Candida albicans* (*C. albicans*) and a lower concentration of Se stimulated the growth of *A. niger.* It was assumed that the reason behind this mechanism is 'the physiological impact of selenium on specific proteins in *A. niger*. The outcomes may have direct ramifications on dermatitis caused by *A. niger* or *C. albicans*. These pathogenic microorganisms can regrow on the skin by exposing to SeNPs' environment. Generally, the post-antifungal effect (PAE) is a vital pharmacodynamic boundary which helps in setting up measurement regimes by demonstrating inhibition of antimicrobe development after exposing microorganisms to antimicrobial agents for a short period of time.[195–197]

3.6. Antiparasitic activity

In the past few years, different research groups have made aggressive efforts on exploring the antiparasitic properties of selenium nanoparticles.[25,198,199] Various types of parasitic diseases and their effects on human organs are shown in Fig. 12. By *in vivo* and *in vitro* studies, it was found that biosynthesized SeNPs from *Bacillus* sp. Msh-1 can be used in the treatment of Leishmania major parasites such as *Promastigote* and *Amastigote*.[25] Similarly, *in vitro* experiments of leishmanicidal activity to combat *Leishmania tropica* (*L. tropica*)[200] and *Leishmania infantum* (*L. infantum*)[199] have been reported by use of *Bacillus* sp. Msh-1 functionalized SeNPs. The gel electrophoresis method has been reported for *in vitro* investigation of selenium nanoparticles to understand the time-dependent decrease in *Promastigote* multiplication due to the presence of DNA fragmentation.[201] Biosynthesized SeNPs with a size range of 80–220 nm showed a strong scolicidal activity against parasitic infections (*Cystic echinococcus*) through an *in vitro* study.[202] A comparable time-dependent cytotoxic outcome was also illustrated against intracellular amastigotes. A study on male mice (BALB/c) infected with *Leishmania major* showed a reduced progression in lesion growth by ejaculation of SeNPs. Soflaei *et al.*[199] reported the antileishmanial properties of SeNPs in both *Promastigotes* and *Amastigotes* of *L. infantum* in contrast to SeO_2. The study demonstrated that SeNPs showed improved performance and less cytotoxicity than SeO_2 in a time and dose dependent antileishmanial activity. In another study, Mahmoudvand *et al.*[200] reported that SeNPs with a particular size range were effective in inhibiting the resistance of *Meglumine antimoniate* (MA) and MA-sensitive *L. tropica in vitro*. Essentially, these outcomes indicated suppression of promastigote depending on the dose, decreased intramacrophage amastigote feasibility in the two strains, and outstanding impact on prophylaxis treatment. Additionally, SeNPs exhibited improved antileishmanicidal activity in conjugation with MA, in contrast to SeNPs or MA alone.[138]

Hence, it is concluded that biosynthesized SeNPs with a particular particle size range shows higher resistant against Leishmania parasitic diseases.

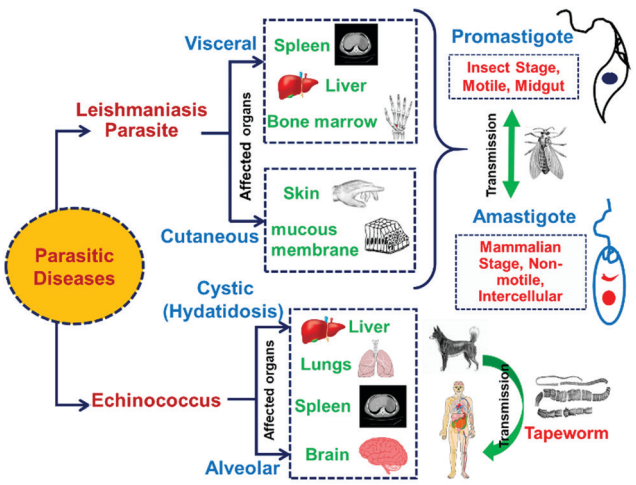

Fig. 12 Types of parasitic diseases that can be treated by SeNPs.

3.7. Other biological applications

Besides the antibacterial properties, SeNPs have also been utilized as wound dressing materials. Biswas *et al.*[203] confirmed the antibacterial properties of permeable chitosan/polyvinyl alcohol (PVA) (CS) *in situ* mediated Se nanorods compared to Ag nanoparticles (CS–Ag). Both the nanoparticles CS–Se and CS–Ag exhibited antibacterial activity against Gram-negative (*E. coli*), Gram-positive (*S. aureus*), and methicillin-resistant *S. aureus* (MRSA). The slow release of Ag and Se nanoparticles was dependent on the delivery medium utilized during treatment. From the study it was found that CS–Se scaffolds are less cytotoxic toward mammalian cells when compared with the CS–Ag system. Similarly, Ramya *et al.*[204] explored the *in vivo* impact of biosynthesized Se nanoparticles stabilized with *Streptomyces minutiscleroticus* M10A62 (spherical size) on Swiss albino mice for wound treatment. The obtained results demonstrated that a high dose of SeNPs (10%) ointment effectively and quickly healed the wound.

Selenium has been additionally found to have a chemoprotective effect against chemotherapy-prompted toxicity. Bhattacharjee *et al.*[205] examined Swiss albino mice for treating cyclophosphamide (CP)-prompted hepatotoxicity and genotoxicity by utilizing SeNPs. In the mice, SeNPs switched or potentially enhanced the effects of CP-instigated toxicity: rebuilding of cell reinforcement protein activity, decrease in reactive oxygen species, glutathione levels, and chromosomal variations in bone marrow, and DNA damage.[205] Further, in another study they found that SeNPs also possess chemosensitizing and chemoprotective activities. After injecting SeNP adjuvant with cyclophosphamide into Ehrlich's ascites carcinoma (EAC) containing Swiss albino mice, the following changes were observed: a critical decrease in practical tumor cell count, packed cell and tumor volume, while an increase in tumor-bearing hosts' survivability.[206] Gao *et al.*[207] reported SeNPs as an effective chemotherapy protective agent against

chemotherapy-prompted toxicity of irinotecan by both *in vivo* and *in vitro* studies.

In another study, it was found that the red-allotrope of selenium nanoparticles (rSeNPs) show higher cytotoxicity towards head and neck squamous cell carcinoma (HNSCC) than human dermal fibroblast (HDF) cells, which resulted in cell proliferation.[208] Additionally, SeNPs can be used as a potential candidate in chemoradiotherapy and radiation sensitizer. Generally, to treat cancer cells external radiation therapy has been utilized broadly. However, these unpredictable radiations can damage adjacent healthy cells. To overcome this unavoidable impact, chemo-radiotherapy can be utilized with a radioactive seed to deliver enhanced, efficient and precise radiation. Based on this concept, Bhattacharjee *et al.*[205] performed a combined *in vivo* and *in vitro* experiment by utilizing folic acid capped SeNPs (FA-SeNPs) in conjugation with radioactive ^{125}I seeds to impart enhanced anticancer activity. In comparison with individual treatment, the combination of (FA-SeNPs) and ^{125}I seeds demonstrated a better *in vivo* antitumor effect and lower cytotoxicity in MCF-7 infected mice. Yu *et al.*[209] reported that Se nanoparticles in combination with radiation reduces the damage to nearby tissues and enhances the carcinogenic cell affectability to the harmful impacts of illumination on MCF-7 breast cancer cells by *in vitro* studies. Karami *et al.*[106] reported the radioprotective effects of SeNPs and sodium selenite on gamma radiation (0, 2, and 8 Gy) incited nephropathy in mice for 14 days. They concurrently treated the mice by administrating SeNPs (spherical and 20–50 nm in size) or sodium selenite (0.1 mg kg^{-1}). After 48 hour exposure they found that SeNPs were more viable than sodium selenite on controlling the factors responsible for nephropathy.

4. Conclusion and future prospects

Selenium is an essential micronutrient required for proper functioning of biological and metabolic mechanism within the human body. Deficiency of selenium leads to the generation of several harmful disorders such as cancer, neurological, muscular, immune, *etc.* Generally, selenium can be depicted within a very narrow concentration range due to its deficiency, physiological effect, and toxic doses. At optimal doses Se acts as an antioxidant, whereas at higher doses it shows pro-oxidant activity. To overcome this issue, a precisely controlled dosage of Se is generally suggested. Selenium has various health advantages because of its bioavailability in the form of selenoproteins as well as lower molecular weight. Various selenoproteins (Se1P, Se1F, Se1S, Se1M), thioredoxin reductases, and glutathione peroxidases show redox activity and control redox reactions in cells. However, concerns related to selenium toxicity lead researchers to focus on nano-selenium. The present review emphasized the various methods used for the synthesis of selenium nanoparticles mainly focused on biogenic methods and their biological applications. Biogenic methods have more advantages over chemical reduction methods due to their higher biocompatibility, bioactivity, and lower cytotoxicity. Biological synthesis is economical, eco-friendly and safe unlike chemical reduction techniques requiring hazardous chemicals, high temperatures and acidic pH. Use of plant extracts, however, is more favourable in comparison to the bacterial path as it eliminates the tedious procedures and cost for maintaining the cell cultures.

SeNPs have various biological applications due to their excellent properties. SeNPs play a key role in various biological applications due to their association with various moieties such as selenoproteins, selenocysteine, selenomethionine, *etc.* Several studies showed that SeNPs are excellent in combating fatal diseases like cancer, diabetes, Alzheimer's, drug-induced toxicity, *etc.* However, nanoparticle induced toxicity is still a major concern for researchers. The authors concluded from the literature that mostly SeNPs ranging from 50 to 200 nm were effective for their use as a therapeutic agent in cancer treatment and antioxidant and antimicrobial applications.

The near future potential of selenium nanoparticles can be considered in pharmaceutical applications and nutritional supplements. Biogenic SeNPs can be explored for their use as anti-TB and anti-viral agents, drug delivery systems, and as catalysts. More precise clinical trials are required for checking the viability of SeNPs on human health. Extensive research is required to develop less toxic and low cost synthesis methods and to understand the role of nano-selenium in cancer therapy, chemotherapy, and radiation therapy to modulate their efficiency and cytotoxicity. Particularly, the development of new nanoparticle delivery systems can provide substantial dietary and therapeutic potential by offering transport of selenium in organs which can modify the physiochemical properties of the nanoparticles, and higher stability within the gastrointestinal tract by permitting precise release of selenium.

Author contributions

All the authors contributed equally.

Conflicts of interest

There are no conflicts to declare.

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