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Potentialities of selenium nanoparticles in biomedical science

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Nanotechnology is defined as the branch of science dealing with extremely small-sized particles with a size in the range of 1–100 nm, which are termed nanoparticles. Due to the extremely small size of nanoparticles, they display unique electronic and optical properties, which differentiate them from their bulk form. Thus, due to the unique properties of nanoparticles, they play a crucial role in a variety of fields, including the biomedical, environmental, agricultural, and industrial fields. Selenium belongs to Group 16 of the periodic table with an atomic number of 34 and its nanoparticles have been highlighted as a potential material to alleviate several problems due to the formation of biofilms, production of ROS, low redox activity, etc. These nanoparticles can be synthesized through chemical, physical and biological methods. Since existing reviews mainly concentrated on the individual applications of selenium nanoparticles such as in diagnosis and therapeutics, the present review mainly highlights the potential activity of selenium nanoparticles in the biomedical domain, making them a potential theragnostic agent. Specifically, this review will present detailed information on the bioimaging and therapeutic activity, together with the role of selenium nanoparticles in the current scenario of the ongoing pandemic (SARS-CoV-2). It will also focus on procedures for their synthesis and properties that make them potential candidates for applications in various domains. Finally, we provide a detailed future outlook.

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1. Introduction

Nanotechnology has emerged as the biggest boon to the field of science and technology in last few decades and has shown rapid growth, which has dramatically transformed materials science, biomedical, environmental, agricultural, and industrial domains.^{1–5} Several types of nanomaterials have been discovered, which are commonly used in various biomedical applications, namely, CNTs (carbon nanotubes), metals (Cu, Se, etc.), metal oxides (cerium oxide (CeO_2), magnesium oxide (MgO), etc.), fullerenes, quantum dots (CdSe and CdTe), dendrimer-bound materials, and polymeric materials.⁶ Moreover, metal nanoparticles such as silver (Ag), gold (Au), cerium (Ce), iron (Fe), and selenium (Se) have achieved a distinctive position in the area of nanotechnology due to their enormous potential in the delivery of drugs, proteins, genes, and siRNA and are also potential candidates as chemotherapeutic agents, anti-inflammatory agents, etc. Among them, selenium nanoparticles are the most studied as selenium is a semi-solid metal, which was first discovered in 1817 by Jöns Jacob Berzelius.⁷ The word selenium marks its origin from the Greek word ‘Selene’, indicating the moon, it has an atomic number of 34 and is an element of Group 6 of the periodic table. Selenium generally appears red in colour in powder form, black in vitreous form and metallic grey in crystalline form, resembling tellurium and sulphur, where selenium was discovered as a by-product during the synthesis of sulphuric acid.⁸

Selenium is one of the essential elements in the human body, which is required in low concentrations, and is a compulsory dietary basic component of 25 human selenoproteins and enzymes having selenocysteine.⁹ However, selenium in the environment is present in various oxidation states (2[–], 0, 4⁺,



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and 6⁺) such as the elemental state (Se^0), in the form of selenates (SeO_4^{2-}), selenides (Se^{2-}), and selenites (SeO_3^{2-}) and can easily switch from one oxygen state to another. Many factors play an important role in these transformations such as pH, redox potential, humidity, and oxygen concentration.^{10,11} Thus, the higher oxidation state of these elements is found to be dominant. Moreover, free-state selenium exists in five different allotropic forms, among which the three are crystalline and the others are amorphous. Owing to the high toxicity caused by selenite (Se^{4+}), selenite is reduced to elemental selenium (Se^0) by biogeochemical cycles.¹² Selenium nanoparticles have gained increasing popularity due to their unique properties such as advanced semi-conductivity, and catalytic, photo-electrical, and photo-conducting activity, demonstrating their potential as candidates for electronic and optical applications.^{13,14} Furthermore, due to the low cytotoxicity exhibited by selenium nanoparticles compared to selenium compounds, they possesses many therapeutic and diagnostic roles, making them potential elements for clinical/biomedical applications.^{15–19}

Moreover, selenium nanoparticles are more efficient as a cofactor for both thioredoxin reductases and glutathione peroxidases than inorganic and organic selenium compounds.^{9,20–22} Free radicals are generated in a very low amount during normal metabolism reactions, which carry an electron in their outermost shell. Furthermore, free radicals are generally formed inside the cell, including hydrogen radicals and superoxide (O^{2-}).²³ The normal metabolism of oxygen produces a by-product called ROS, which plays a major role in inflammation, and consequently, normal cells are affected, which further leads to the disruption of the cell membrane, proteins, and DNA



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and causes pathogenicity, ultimately leading to apoptosis. Various methods can be employed to synthesize selenium nanoparticles, namely physical (laser ablation, ultra-violet (UV) radiation, and hydrothermal techniques), chemical, and biological methods.^{24–26} Biological methods utilize biological organisms such as fungi, yeast, plant, and bacteria, and thus are eco-friendly and non-toxic methods for the synthesis of nanomaterials,^{27–32} and the synthesized nanomaterial is more stable due to the use of natural stabilizers.³³ In contrast, chemical methods mediated by precipitation, acid decomposition, etc. are unsafe for biomedical applications since they utilize extreme temperature, expensive methodologies, acidic pH, and harsh chemicals, which can cause toxicity to normal cells and hindering biomedical processes.²⁴ The modification of selenium with compounds such as chitosan (Cs) enhances its size and biomedical application. Fig. 1 presents the various forms of selenium structures, which can be modified by Cs.³⁴

Earlier reviews of selenium nanoparticles^{35–38} only highlighted their individual aspects, such as properties/synthesis/applications. However, the present review presents (Fig. 2) the improved, up-to-date, and detailed progress and advances in the biomedical applications of selenium nanoparticles by elaborating the theragnostic (diagnostic and therapeutic) facets of these nanoparticles. In addition to their biomedical applications, this review also briefly highlights the potential diagnostic and therapeutic utility of selenium nanoparticles in the current scenario of the ongoing pandemic (Novel Corona-Virus Pandemic). The use of selenium nanoparticles in the biomedical field has gained increasing popularity in the past few years and is still evolving quickly. Besides the biomedical aspects of selenium nanoparticles, this review also features the properties (physicochemical and biological) and methods for the synthesis of selenium nanoparticles. Therefore, this review compiles up-to-date details about the development, current status, advances, and prospects of selenium nanoparticles in the biomedical domain. Hence, this review is unique, presenting the complete biomedical aspects of selenium nanoparticles and their properties, synthesis, prospects, and utility in the management of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2).

2. Properties

There are several factors and reaction parameters, namely synthetic method, chemical or starting material, type of additive or surfactant, pH, temperature, nature of the solvent, reaction time, and media, that decide the properties (physical, chemical, and optical) and morphology of a nanomaterial. Nanomaterials are characterized by employing numerous techniques such as scanning and transmission electron microscopy, energy dispersive spectroscopy, X-ray photoelectron spectroscopy, X-ray diffraction, selected area electron diffraction, and low-energy electron diffraction. This review presents a brief overview of the various physical, chemical, optical and biological properties of selenium nanomaterials, which will help researchers study their various applications in different domains.

2.1. Physico-chemical properties

The atomic number and weight of selenium are 34 and 78.96, respectively.³⁹ Furthermore, this element exhibits six stable isotopes, i.e., ⁷⁴Se, ⁷⁶Se, ⁷⁷Se, ⁷⁸Se, ⁸⁰Se, and ⁸²Se, with a 4s₂ and 4p₄ outer electronic configuration. Moreover, the melting point of selenium is lower than 220 °C, and its crystallization occurs at 200 °C.^{40,41} Due to the presence of complex polymeric structures, the mobility of the atoms of selenium is reduced, which leads to the slow arrangement of selenium atoms onto the hexagonal array, and therefore it is difficult to crystallize selenium near its melting point. The most thermodynamically stable crystal structure of selenium (c-Se) has an atomic radius of 1.17 Å,⁴² which is known as grey metallic selenium. The structure of c-Se consists of a helical chain arranged in a hexagonal array and is observed as a distorted cubic primitive lattice in which each atom has two nearest proximate of the same chain and four nearest proximate found in adjacent chains.⁴³ Swanson, Gilfrich, and Ugrinic revealed that its hexagonal cell dimensions are $a = b = 4.3662 \text{ \AA}$ and $c = 4.9536 \text{ \AA}$, together with the chiral space group of $P3_121$ or $P3_221$ (enantiomorph of $P3_121$).^{44,45} Hexagonal selenium has a density of 4.82 g cm^{-3} , boiling point of 685 °C, and work function of 5.9 eV.⁴² Further, the Se₈-rings and polymeric chains of

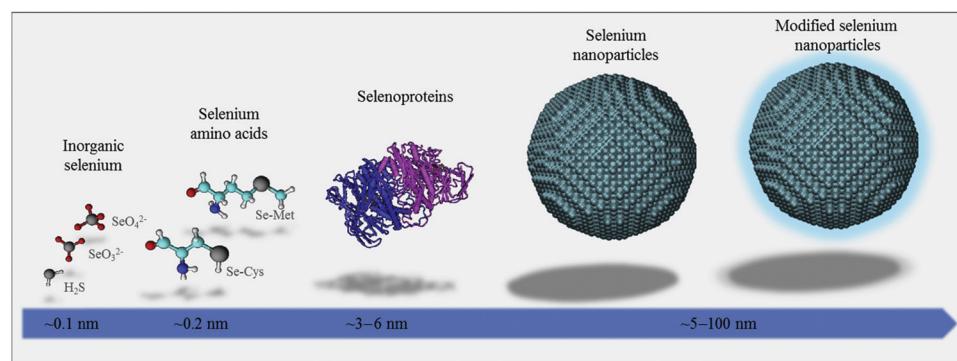


Fig. 1 Comparison of the different sizes of various selenium forms and selenium nanoparticles, which could be modified by various polymers such as chitosan (reproduced from S. Skalickova, et al., *Nutrition*, Elsevier, 2017 (ref. 34)).

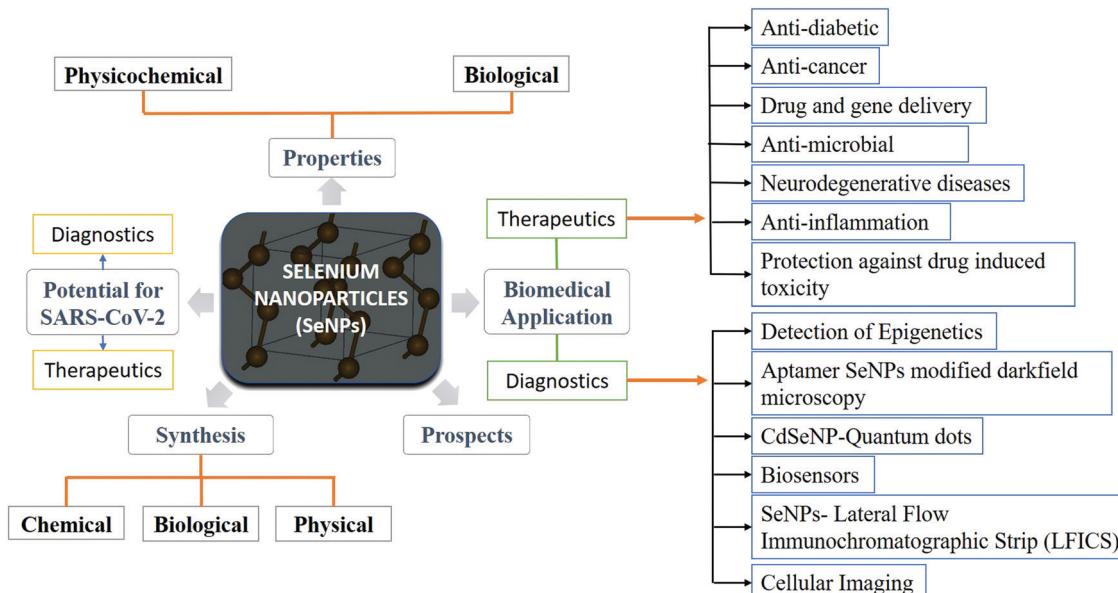


Fig. 2 Illustrations of emphasized details in this review.

Se-atoms form amorphous selenium (a-Se), in which the polymeric chain can be easily dissolved in CS_2 solution.^{46,47} The glass transformation temperature of a-Se is observed at 48–50 °C, and its accurate composition mainly depends on the substrate temperature, deposition rate, etc., where many of the early works showed that an evaporated film consisted of Se_8 -rings when the substrate was kept at room temperature. However, when the substrate was kept at 70 °C, the film consisted of polymeric chains.^{48–51}

2.1.1. Electrical properties. The outstanding high resistivity of selenium in the range of 10^{12} to $10^{14} \Omega \text{ cm}$ makes it best suited for application in detectors, considering that they produce ultra-low dark currents together with low noise signals. The existence of dangling bonds and non-radiative transitions allows selenium to acquire photo-acoustic signals at 800 nm. The absence of a proper periodic arrangement in selenium leads to a higher bandgap for a-Se (1.99 eV) compared to c-Se (1.85 eV), but c-Se has lower concentrations of selenium compared to a-Se, which endows c-Se with less non-radiative recombination loss together with a smooth charge. Therefore, due to its high resistivity, a-Se has high potential for detection applications, whereas c-Se is much more suitable for the production of solar cells.^{52–54}

2.1.2. Optical properties. The doping density, defect density, and band structures decide the difference between the optical and electrical properties of selenium. Its optical properties are highly dependent on its size, shape, surface, characteristics, etc., which are fascinating and essential. When the bulk material is reduced to the nano-range, it shows enhanced energy level spacing and the development of surface plasmon resonance (SPR), resulting in surface charge redistribution and precision in phase-coherent oscillations.^{55,56} The optical properties of selenium are studied using the absorbance from its fluorescence spectrum, and a wide range of applications such as biosensing, imaging, photocatalysis, photo-electrochemistry is based on

these properties.^{57–60} A difference in the saturation magnetization, electrical conductivity, and band gaps of nanomaterials causes variations in their properties (optical, magnetic, and electrical). These variations allow nanomaterials to be considered for the construction of optoelectronic and opto-magnetic devices.

The linear and non-linear optical properties of selenium have been widely explored together with its alloys with Te, Si, etc.^{61–63} Due to the lack of free conduction electrons in selenium, exciton resonance or transition occurs when selenium nanoparticles are exposed to light irradiation. Functionalization of selenium nanoparticles can transform their bandgap and find prospective applications in optoelectronic devices. One experiment tried to explain the effect of the concentration of the selenium precursor and demonstrated that the radius of selenium nanoparticles affects their optical absorption spectrum.^{64–67} Selenium nanoparticles when dispersed in host-viscous polymer solutions followed by evaporation of the solvent, resulted in selenium nanoparticles with a size of 43 Å, and furthermore, studies to determine their optical properties were carried out employing UV-visible spectroscopy and a monochromator. The results showed that the prepared selenium nanoparticles displayed a bandgap of 2.6 eV.⁶⁸ Optical properties are greatly affected by size, and thus the optical properties of chemogenic selenium nanoparticles were observed using a spectrophotometer. In this study, a broad absorption band was observed in the range of 300–500 nm and 300–550 nm for 50 nm and 100 nm-sized selenium nanoparticles, respectively, and the same was also observed for biogenic and chemogenic selenium nanoparticles.^{69–78} The maximum exciton resonance peak was observed at around 300–340 nm and 520 nm for 50 nm and 100 nm-sized selenium nanoparticles, respectively, due to the presence of biomolecules such as proteins and amino-acids, which absorb light and cause variations.^{79–81}

Further, in the photoluminescence study, using a fluorescence spectrophotometer, it was observed that selenium nanoparticles with a size of 50 nm and 100 nm gave intense peaks at around 300–400 nm and 300–500 nm, respectively.⁸² Hence, these experiments clearly showed the dependence of the optical and luminescence properties of selenium nanoparticles on their size, and it can be concluded that better optical and luminescence properties are achieved when the nanoparticles are smaller in size. Moreover, many properties can be modified and advanced by minimizing the size of nanoparticles, which can be further used for several applications such as sensors, bioimaging, and solar cells.

2.1.3. Catalytic activity. Selenium nanoparticles show a direct bandgap and act as a semiconductor, which helps them acquire unique chemical resistance to oxidation and hydrolysis. Furthermore, as their size decreases, their catalytic property is enhanced, and therefore, selenium nanoparticles are highly studied for their catalytic activity and applications. Moreover, the electronic properties and bandgaps of selenium can be modified by doping with several elements. Further, selenium nanoparticles are found to be nontoxic and can be potentially used for the elimination of organic and toxic water pollutants (environmental application), where it has been observed that Se(0) potentially captures mercury vapour.⁸³ In a study conducted for the elimination of copper by adsorption on Se(0) nanoparticles, it aimed initially to study the potential of ascorbic acid and its effect on the copper in the presence of selenium nanoparticles. Subsequently, using kinetic equations and adsorption isotherms to set up the adsorption criteria, the adsorption of copper by selenium nanoparticles was demonstrated and adsorption artifacts were identified. Finally, an examination of the adsorption methods was done, and the results of these studies indicated that with the help of a suitable and accurate reducer, selenium nanoparticles could potentially remove copper from aqueous solution, and hence have potential in environmental applications.⁸⁴ In addition, selenium, when properly mixed with ruthenium (Ru), can enhance the electrocatalytic oxygen reduction reaction (ORR) by enhancing the functions of selenium as an oxygen adsorption site and electron bridge.⁸⁵ Further, when doped with selenium, bismuth sulfides potentially degrade methylene blue under the influence of visible-light irradiation ($\lambda = 400$ nm), and hence it can be concluded that doping with bismuth sulfides improves the photocatalytic activity of selenium.⁸⁶ Therefore, this suggests that selenium-doped materials show enhanced and advanced potential in various domains.

The distinctive catalytic behaviour of selenium nanoparticles was demonstrated by Yang *et al.* by studying the decolorization of Congo red in the presence of UV light. It was reported that with an increase in the size of the selenium nanoparticles, the dye decolorization decreased.⁸⁷ It is well known that functionalized nanoparticles show enhanced properties, which was also proven in a recently conducted experiment, in which trypan blue was degraded through photocatalytic reaction using zinc-oxide/selenium nanoparticles. Moreover, selenium nanoparticles can effectively inhibit

calcium oxalate (CaC_2O_4) at the industrial level, but this characteristic of selenium nanoparticles was found to be more potential in the medicinal field since they inhibited calcium oxalate (CaC_2O_4) urinary stones. In addition, selenium nanoparticles also inhibited the growth of *Staphylococcus aureus* via their catalytic activity, hence making them potential inhibitors of biofilms.⁸⁸

Selenium exhibits protective action against cardiovascular diseases, and it is hypothesized that the selenium-containing antioxidant enzyme glutathione peroxidase 4 (GPx4) exhibits potential to prevent the oxidative modification of lipids and reduce platelet aggregation, which lead to a decrease in the build-up of low-density lipoprotein in the artery wall, causing atherosclerosis and furthering result in a lower risk of heart attack/stroke.⁸⁹ Moreover, the catalytic activity of selenium nanoparticles was also observed in nanobiosensors when selenium nanoparticles were deposited on a glassy carbon electrode that immobilized horseradish peroxidase (HRP) on the selenium nanoparticle layer. It was observed that the modified selenium nanoparticles improved the electrocatalytic activity towards hydrogen peroxide (H_2O_2).^{90,91} This review briefly discusses commendable catalytic potential of selenium nanoparticles and focuses on the enhanced characteristics caused their modification. The biocompatible nature of selenium nanoparticles helps this nanomaterial act as an excellent biosensing platform to directly understand the electrochemistry and electrocatalysis mechanisms of heme-containing proteins/enzymes.

2.2. Biological properties

Selenium is considered a potential micronutrient that is used widely in therapeutics and diagnostics applications. At present, there are 25 seleno-enzymes, which contain residues of selenocystines (SeCys) in their active sites and play an important role as antioxidants (GPx). They are also found to play a role in the transportation of selenium as selenoprotein P, which functions to maintain thyroid hormone production (iodothyronine deiodinase) and the intracellular redox status (thioredoxin reductase). To investigate the biomedical activity of selenium, its biological properties should be discussed. Hence, this review highlights key biological features of selenium nanoparticles, which help them play a potential role in the biomedical sphere.

2.2.1. GPx-like activity of selenium compounds. The antioxidant mechanism includes increasing the expression of metal-binding activities and GPx-like radical scavenging. The endogenous metabolic processes produce reactive nitrogen and oxygen species (RNS and ROS), which are free radical species and highly unstable as their outermost shell is occupied with an unpaired electron. These free radicals attain stability by eliminating the electrons from other compounds, producing many reactive species by a chain reaction cascade. The excess production of reactive species from endogenous and exogenous sources can lead to redox imbalance and high oxidative stress in the cell, which damage lipids, proteins and DNA, further causing dysfunction of vascular smooth muscle cells, monocytes, and endothelial cells and resulting in cardiovascular,

Parkinson's and Alzheimer's diseases.⁹² GPx actively detoxifies various types of peroxides such as H₂O₂, fatty acid hydroperoxides, and phospholipid hydroperoxide, but the hydroperoxy groups of thymine actively detoxify GPx. Many compounds such as diaryl diselenide, monoselenides, and cyclic selenenyl amides show mimetic GPx and Ebselen's activity, being the best investigated to date,⁹³ and these compounds mainly catalyse the reduction of hydroperoxides in the presence of thiol. Although the GPx mimetic activity mechanism is still unclear, besides this, in an alternative pathway, it has been suggested that the catalytic cycle of GPx includes selenylsulfide, selenol, and selenenic acid as intermediates. Another study showed that with the help of non-biological thiol, synthetic monoselenides oxidize hydrogen peroxide to selenoxide initially, and finally to hydroxyl perhydroxy selenane (R-(HOO)-Se-(OH)-R), which oxidized the thiol and showed that selenoxide and selenenic acid are highly oxidized compound.⁹⁴

2.2.2. Radical scavenging activities of selenium compounds. Selenium and its compounds such as monoselenides, selenomethionine (SeMet), methylselenocysteine (MeSeCys), diselenide selenocysteine (CysSeSeCys), glutathione selenylsulfide (GSSeH), and selenodiglutathione (GSSeSG) show radical scavenging properties and reduce oxidants. Due to the inefficiency of the selanyl radical (RSe) to oxidize protein, its generation can potentially exhibit spreading of radical damage.⁹⁵ It was observed in peroxy radical-induced hemolysis that diselenide (CysSeSeCys) and monoselenides (SeMet and MeSeCys) exhibited scavenging activity for peroxy radicals together with GPx-like activity.⁹⁶ Moreover, SeMet and CysSeSeCys protect plasmid DNA from peroxy nitrite-induced single-strand breaks through the reduction of peroxy nitrite-initiated oxidation and nitration reactions.^{97,98} Free tyrosol radicals and tyrosol radicals present in protein are damaged by CysSeSeCys and GSSeH, which prevent further oxidation in cells and damage the protein structure.⁹⁹ The breakage of plasmid DNA and protein carbonylation and gamma-radiation-induced lipid peroxidation are inhibited by SeMet, MeSeCys, and CysSeSeCys *in vitro*.¹⁰⁰ It has been observed that selenolate MeSe exhibits *in vivo* radical scavenging activity, which can be associated with angiogenesis by the reduction in ROS levels in hypoxic tumor cells by methylseleninic acid (MeSeA) and further by MeSeCys, and most probably inhibiting hypoxia-inducible factor-1a (HIF-1a), which eventually inhibits tumor xenograft growth.¹⁰¹

2.2.3. Metal binding. Metals have been applied for the therapy and diagnosis of many diseases such as cancer, cardiovascular, and neurodegenerative diseases. The toxicity of metals highly depends on their capability to generate oxidative stress.¹⁰² Although metals such as copper and iron highly prevent misregulation, this can cause side effects to the cell by the generation of ROS through Fenton reactions.¹⁰³ Besides, selenium can prevent oxidative damage *in vitro* by directly binding with metal ions, which reduces metal-mediated oxidative damage through various methods such as GPx-like activity, direct interaction with free metals, cooperation with DNA, and radical scavenging in solution. Electronic absorption spectroscopy was used to test the oxidative damage on DNA caused by

DNA binding with metals. The addition of selenium compounds to a solution of DNA and metal ions resulted in a significant reduction in oxidative DNA damage, which led to the conclusion that the free metal ion binding, not the DNA-bound ions, is the major reason for the reduction in oxidative damage. It was also reported that the selenium metal species generated the same amount of ROS as free metals in solution with H₂O₂. Therefore, it was proposed that selenium metal species may exhibit protection activity towards DNA, preventing it from oxidative damage by binding at the ROS generation sites, causing less damage, or preventing excess H₂O₂ from reaching the sensitive areas of DNA molecules. However, this theory still needs to be tested and verified.

Furthermore, the different results obtained in a study on Cu(II) showed that selenium dioxide and selenite exhibited greater potential to prevent oxidative damage to a lesser extent compared to Cr(III) and Fe(II). However, only the selenium-Cu(II) species produced less ROS than the free metals. The potential of selenium *in vitro* to prevent oxidative damage by binding to metal ions depends mainly on two factors, the selenium compound species and the free metal ion. Therefore, there are probably numerous mechanisms through which selenium compounds can diminish the oxidative damage mediated by metals, namely GPx-like activity, by associating with DNA, radical scavenging in solution, and direct interaction with free metals.¹⁰⁴

2.2.4. Pro-oxidant properties. Selenium nanoparticles are the most widely studied among the inorganic nanoparticles and have been proven to be a potential material for fighting drug resistance, carrier for the delivery of gene and drugs, etc. It has been suggested that the accumulation of nanoparticles in malignant cells results in the formation of ROS, which leads to cytotoxicity. Malignant cells contain an acidic pH, which exhibit a redox imbalance that helps selenium nanoparticles to enter *via* receptor-mediated endocytosis and exhibit pro-oxidant effects by free radical generation at one side, disrupting the mitochondrial membrane. The disruption of the mitochondrial membrane causes the leakage of mitochondrial proteins, leading to endoplasmic reticulum (ER) stress and initiation of apoptosis by activation of MAPK/Erk (mitogen-activated protein kinases/extracellular signal-regulated kinases), Wnt (wingless-related integration site)/β-catenin, NFκB (nuclear factor kappa-light-chain-enhancer of activated B cells), PI3K/Akt/mTOR (phosphatidylinositol 3-kinases/protein kinase B/mammalian target of rapamycin) and other apoptotic pathways. Selenium nanoparticles regulate these pathways and are important in oncogenic signaling, leading to cellular propagation, which will hinder the growth-promoting signals and decrease the angiogenic signalling in tumor cells, helping reduce their growth and proliferation. The pro-oxidant mechanism of selenium nanoparticles includes their reduction by the Trx/TrxR/GSH/GR/GRx (thioredoxins/thioredoxin reductases/glutathione/glucocorticoid receptor/glutaredoxins) pathway, and eventually by the utilization of NADPH⁺H⁺, resulting in the production of the selenide (Se⁻) anion, which further forms free radicals (O²⁻), and ultimately generate reactive oxygen species (ROS).¹⁰⁵

2.2.4.1. ROS production. Intramolecular disulfide bonds, selenium trisulfide, and a selenylsulfide bond (S-Se) are formed when the vital thiol groups of cysteine and proteins react with selenium, which produces reduced GSH residues.¹⁰⁶ Further, this leads to the inactivation of signaling molecules through the oxidization of redox-cysteine residues found in the catalytic domain of the active enzymatic site. The binding affinity of transcription factors (activator protein-1 and NF-κB) to target DNA sites is affected by selenium-induced oxidation.^{107–109} Other redox-sensitive enzymes, such as protein kinase C, JNK, Na⁺-K⁺-dependent ATPase, caspase-3, Cdk2, human squalene monooxygenase, glucocorticoid receptors, prostaglandin D synthase, and mitochondrial proteins are affected by the thiol oxidation by selenium as they are redox-dependent signal molecules.^{108,110–119} Hence, it is observed that many of the signal transduction pathways controlling apoptosis and cell survival are disturbed by selenium-induced thiol modification.

Reactive oxygen species (ROS) are defined as chemically reactive molecules, and Fig. 3 illustrates the generation of ROS. Besides, all aerobic organisms produce various ROS such as hydroxyl radicals, nitric oxide derivatives, superoxide anions, and hydrogen peroxides through different pathways. The superoxide anion (O_2^-) is generated intracellularly *via* the transfer of electrons leaked from several reactions such as mitochondrial electron transport chain and NADPH cytochrome P450 reductase to oxygen in the endoplasmic reticulum. Moreover, it is also released from the enzymatic actions of certain enzymes such as cyclooxygenase, NADPH oxidase, lipoxygenase, flavoenzymes, and uncoupled nitric oxide synthase.¹²⁰ Besides these methods, the superoxide anion can also be endogenously produced by selenium compounds such as diselenides, selenocysteine, selenite, and selenium dioxide, and thiols such as reduced GSH/L-cysteine.^{121–123} In addition, the superoxide anions quickly transform into hydrogen peroxide (H_2O_2) through superoxidase dismutase followed by Fenton reactions in which with the help of Fe^{2+} , H_2O_2 is converted to the hydroxyl radical, which is highly reactive.

More reactive species (NO_2 and HO) are formed *via* the reaction of hydroxyl radicals with nitrogen oxide (NO) through an $ONOO^-$ intermediate. Selenium exhibits the capability to affect the cellular redox status negatively, which leads to a reduction in status decline in cells, impaired protein functions, and reducing cellular damage, and can be utilized for various types of therapeutic applications such as cancer cell apoptosis, anti-inflammation, and antimicrobial activity when taken up at a low molar concentration. Selenium causes programmed cell death, which changes the cellular morphology, such as blebbing of the membrane, nuclear breakdown, condensation of chromatin, and formation of apoptotic bodies, which are voluntarily eliminated through phagocytosis. Further, this results in the activation of cysteine-aspartic-specific protease, also known as caspases, which then is initiated by the process of internucleosomal DNA fragmentation and mitochondrial-dependent/independent apoptosis.¹²⁴ The selenium-induced apoptotic process affects DNA fragmentation and has been observed in various human cancer cell lines, including colonic carcinoma (HT29 and SW480), hepatic carcinoma (HepG2), glioma (A172 and T98G), and leukemia (HL-60), together with the murine monocytic RAW264.7 cell line.^{125–129} Selenite is considered the best redox-active compound for the generation of ROS among the selenium compounds. However, selenium nanoparticles have been proven to be a potential therapeutic compound to initiate redox cycling with oxygen to synthesize ROS. A single-step reduction of selenium to the selenium anion is required using pathways of Se reduction such as Grx- and Trx-coupled GSH systems, which are found to be overexpressed in cancer cells. Also, the low toxicity of selenium nanoparticles has made them gain more attention.

The mitochondria are the site of aerobic respiration, ATP generation, and responsible for mitochondrial respiration of the cell and highly sensitive to oxidative stress.¹³⁰ Thus, accurate photodynamic therapy (PDT) agents are provided to the mitochondria, which can effectively improve the therapy as oxidative sensitivity of mitochondria can lead to interference in the cellular energy supply. Selenium-induced apoptosis in cancer

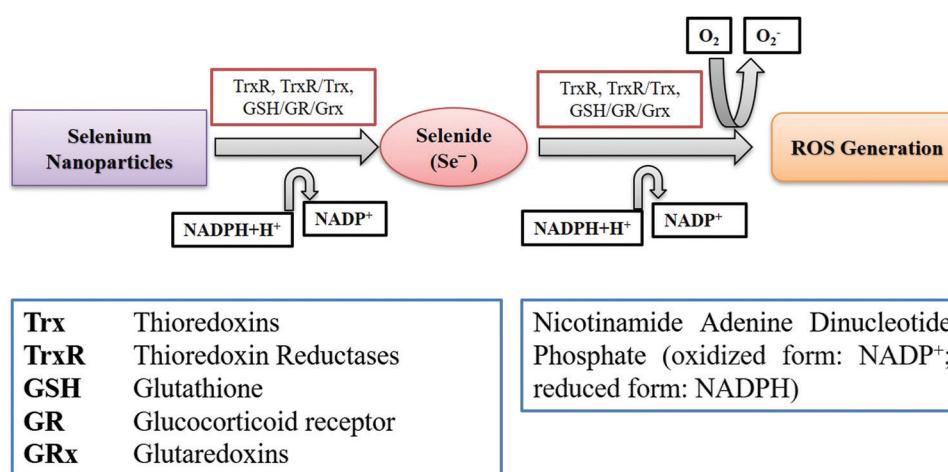


Fig. 3 Generation of ROS through selenium nanoparticles.

cells also affects the mitochondria and mitochondrial-mediated apoptotic pathways, including oxidative damage to the thiol group of mitochondrial protein, release of cytochrome *c*, and disruption of the mitochondrial membrane potential, which activate caspases.^{131,132} Moreover, human serum albumin (HSA)-coated selenium nanoparticles decorated with triphenylphosphine (TPP), which is a well-documented functional organic moiety having notable mitochondria-targeting properties,¹³³ were developed, exhibiting monodispersity and long-term stability for storage. The successful increase in the colocalization of the selenium nanoparticles in the mitochondria was observed, leading to an increase in ROS production, and thus, efficiently damaging the mitochondria, leading to cell apoptosis and low cytotoxicity. Hence, this proves that selenium nanoparticles are a potential therapeutic agent.¹³⁴ Furthermore, the endocytosis of selenium nanoparticles produced a large amount of mitochondrial ROS and ATP depletion, which cause damage to the mitochondria and also increase the level of TNF (tumor necrosis factor) and IRF1 (interferon regulatory factor 1), which was observed by qPCR.¹³⁵ In another study, the accumulation of selenium in peritoneal cancer cells was observed using decorated selenium nanoparticles with sialic acid, transferrin, folate, or other agents possesses the capacity for targeting cancer cells.^{136–142}

3. Synthesis

Due to the colloidal nature of selenium nanoparticles, their preparation is difficult and complicated, restricting their commercialization. Besides, monodispersed selenium nanomaterials can be prepared with a pre-defined size and perfectly synthesized *via* synthetic (chemical) routes. For the synthesis of nanomaterials, there are mainly three preparation techniques (Fig. 4), and this review briefly describes each synthesis pathway by highlighting the characteristics and morphologies of the prepared selenium nanoparticles.

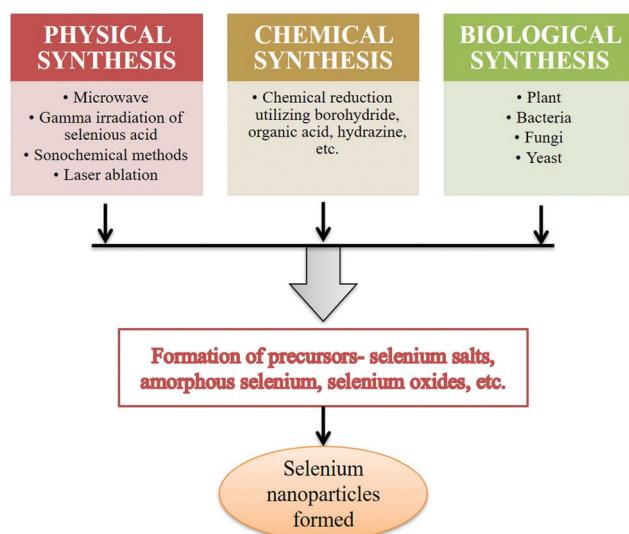


Fig. 4 Various methods for the synthesis of selenium nanoparticles through the formation of precursors.

3.1. Chemical synthesis

The chemical synthesis of nanoparticles is a route in which chemicals are utilized in a controlled environment for initiating the synthesis reaction. Selenium nanoparticles of a pre-defined size can be easily synthesized by utilizing this route, as well defined by many scientific investigations in the synthesis of selenium nanoparticle *via* this route. One example is the synthesis of selenium nanoparticles with a size of 76–150 nm *via* the addition of a polyvinyl alcohol stabilizer to the aqueous medium and the selenium precursor ‘sodium selenosulfate,’ which is a simple ionic liquid-induced wet chemistry method. The yielded nanoparticles were of the desired size range.¹⁴³ Moreover, the pulsed laser ablation method can also be applied to synthesize selenium nanoparticles with a size of around 532 nm,¹⁴⁴ whereas spherical-shaped selenium nanoparticles can be synthesized utilizing sol–gel compounds with varying concentrations. These synthesized nanoparticles exhibit great anti-oxidation activity.¹⁴⁵ Another technique to synthesize spherical selenium nanoparticles is using selenium tetrachloride with distilled water employing a facile microwave method, and the obtained nanoparticles will have a size in the range of ~200–800 nm, which can be used in the fabrication of solar cells.¹⁴⁶ Among the chemical synthesis routes, the hydrothermal route is considered a simple and easy method to prepare trigonal selenium nanorods with an average diameter of 400 nm.¹⁴⁷ Trigonal selenium nanowires with a size ranging from ~10–800 nm with lateral dimensions can be synthesized using a solution-phase approach, and gamma irradiation at room temperature can be employed to easily synthesize hexagonal amorphous selenium nanoparticles with a size of ~70 nm.¹⁴⁸ However, according to the requirement in the biomedical field, chemically synthesized nanoparticles are not suitable, thus restricting the use of selenium nanoparticles. This is because the chemical synthesis route utilizes harsh chemicals for the synthesis of nanoparticles, where even small traces of these chemicals in human cells/tissues/body can lead to systemic toxicity, which restricts their biomedical applications. However, currently, selenium nanoparticles synthesized *via* the green route are attracting increasing attention in the biomedical field for therapeutic and diagnostic applications.

3.2. Biological synthesis

Owing to the complexity caused by chemical synthesis methods, researchers have started adopting green synthesis methods to reduce expenses, complexity, *etc.* Thus, green synthesis has attracted research interest for the synthesis of several nanoparticles. The constant contact of biological entities and inorganic materials has been observed since the beginning of life on this planet. Due to the steady interaction between metal and cells, living cells have an efficient mineral deposit, which plays a crucial function in cells. Currently, the property and chemistry of green-synthesized nanoparticles have attracted attention from researchers to find the interaction between biological and inorganic molecules. Several types of enzymes, fungi, microorganisms, and plant extracts have been utilized to

synthesize selenium nanoparticles of different morphologies and sizes. Thus, this review emphasizes the green synthesis method, especially employing microorganisms, enzymes, and plants.

3.2.1. Plants. Plant extract-mediated nanoparticles are generally preferable as the selenium nanoparticles are synthesized in a single-step process in the presence of bioactive plant extracts such as flavonoids, alkaloids, phenols, and saponins. These bioactive plant extracts ease the biosynthesis of selenium nanoparticles in a single-step and act as herbal capping and reducing stabilizing agents,^{149,150} which results in higher yield compared to chemical synthesis.^{151,152} Plant parts such as buds, leaves, and flowers can be employed for the production of selenium nanoparticles.

An aqueous extract of *Allium sativum* was used to produce spherical selenium nanoparticles, which were crystalline and exhibited pH stability; therefore, proving their potential in a wide array of biological applications.¹⁵³ Another approach was the use of *Aloe vera* to synthesize stable selenium nanoparticles.^{154,155} With the help of *Asteriscus graveolens* extract, spherical selenium nanoparticles with a size of 20.06 nm were synthesized, which showed properties as potent carriers for anticancer drug for targeted delivery.¹⁵⁶ Furthermore, the use of flower extracts of *Catharanthus roseus* and *Peltophorum pterocarpum* for the green synthesis of small-size biocompatible hollow selenium nanoparticles proved to be an alternative route to the physical and chemical synthesis methods,¹⁵⁷ and the synthesis of selenium nanoparticles was also performed using *Clausena dentata*.¹⁵⁸ In addition, selenium nanoparticles with a crystalline size of 65 nm were biologically synthesized using *Diospyros Montana*, in which phytoconstituents such as flavonoids and phenols act as reducing agents and nanoparticle stabilizers.¹⁵⁹ The fruit extract of *Embllica officinalis* was used to synthesize amorphous, stable, negatively charged (-24.4 mV) selenium nanoparticles with a size of 15–40 nm and interesting potential biological applications such as antimicrobial, anti-oxidant, and biocompatibility together with dose-dependent free radical scavenging activity.¹⁶⁰ Additionally, the extract of green tea together with sodium selenite (Na_2SeO_3) as a reducing agent and *Lycium barbarum* polysaccharides (LBP) as a surface capping agent produced spherical functionalized selenium nanoparticles with a size of 83–160 nm, which were beneficial for various biological activities such as high antioxidant activity, consisting DPPH and ABTS free radical scavenging.¹⁶¹ Besides, *Acalypha indica* was used to synthesize size-controlled selenium nanoparticles via an eco-friendly and cost-effective method for producing different-sized particles,¹⁶² and stable selenium nanoparticles with a size in the range of 100–500 nm were also synthesized from the extracts of ginger.¹⁶³ Hence, based on the above discussion, it can be concluded that by utilizing different plant extracts, various types of selenium nanoparticles can be synthesized with desired sizes and for various applications in the clinical/biomedical, environmental, agricultural, and industrial fields and the green route for the synthesis of selenium nanoparticles can open new avenues for researchers in the materials chemistry domain.

3.2.2. Microbial synthesis. From the start of life, living organisms and inorganic materials have been continuously connected. Due to this rhythmic communication, life is still maintained on this planet. Currently, scientists are focused on the relationship between inorganic molecules and biological entities. Studies and research have revealed that several microorganisms exhibit potential to produce inorganic nanoparticles either through intracellular or extracellular routes. This segment of the review describes the production of selenium nanoparticles via microbial synthesis by mainly focusing on bacterial-, fungal-, and yeast-mediated synthesis.

3.2.2.1. Bacteria. For the microbial synthesis of metal nanoparticles, prokaryotic organisms have been the most explored and studied among the microorganisms due to their easy manipulation. One of the earliest studies on an obligately anaerobic, Gram-negative, bacterium SES-3 strain (a selenate respiring bacterium) showed that their growth mechanism involves the coupling of oxidation from lactate to acetate plus CO_2 in association with the reduction of selenate to selenite or nitrate to ammonium and can also reduce selenite to elemental selenium (Se^0). Therefore, SES-3 exhibits potential to reduce selenate to Se^0 completely. However, further investigation showed that SES-3 could reduce selenate to Se^0 , but selenite cannot be reduced to Se^0 due to the inhibition caused by sulfite, selenate, and nitrate.¹⁶⁴ Stable, uniform nanospheres with a size of 3000 nm were synthesized via selenium respiring bacteria, including *Bacillus selenitireducens*, *Selenihalanaerobacter shriftii*, and *Sulfurospirillum barnesii*.^{165,166} Further, in the facultative anaerobic bacteria, it was observed that under oxygen-free conditions, Se(vi) was reduced to selenium nanoparticles, which were regulated by oxygen transcriptional factors,¹⁶⁷ and the diversity of selenate-respiring aquatic bacteria derived from the aquatic sediments, which were collected from different areas, showed the potential to utilize selenate as a terminal electron acceptor in the production of elemental selenium by converting selenite.¹⁶⁸

It was observed that varying concentrations of sodium selenite (Na_2SeO_3) and the concentration of biomass largely influenced the size of the selenium nanospheres, for example, a low initial biomass concentration of *Shewanella* sp. produced selenium nanoparticles with a size in the range of 1–20 nm after 2 h incubation and higher concentrations of this bacteria produced selenium nanoparticles with a size in the range of 51–60 nm after 24–72 h incubation.¹⁶⁹ A study observed that *Pseudomonas alcaliphila* possessed the capability to synthesize monoclinic selenium nanoparticles with a size in the range of 50–500 nm at 28 °C and ambient pressure. Further, they efficiently transformed the nanospheres to nanorods in a reaction time of 24 h.¹⁷⁰ *Veillonella* is a Gram-negative, anaerobic cocci-shaped bacteria that can reduce selenium oxyanions to synthesize nanospheres from Se^0 , which are subsequently reduced biologically to form reactive selenide and produce chalcogenide precipitates with a size in the nanoscale range such as zinc selenide. Zinc selenide is prepared via a precipitation method by utilizing suitable metal cations, and this chalcogenide

precipitate on the nanoscale exhibits extraordinary optical and semiconducting properties. Moreover, the selenite reduction occurs through hydrogen, which acts as an electron donor within the cell, and the reduction rates can be enhanced *via* the addition of a redox mediator (anthraquinone disulfonic acid). Hence, this process exhibits potential to synthesize nanocrystals based on chalcogenides, which can be utilized in optoelectronic devices and biological labeling as precursors for more environmentally friendly synthesis than that used in traditional organometallic synthesis.¹⁷¹ In addition to the abovementioned bacterial synthesis routes, Se⁰ can be synthesized from probiotic yogurt bacteria such as *Lactobacillus* sp., *Bifidobacteria* sp., and *Streptococcus thermophilus* by utilizing sodium hydrogen selenite (NaHSeO₃) salt as the source of selenium, and further, it was confirmed that lactic acid bacteria could integrate selenium into intracellular proteins as seleno-cystine (SeCys), which is reportedly the predominant form of selenium found in the lactobacillus species.^{172,173} Therefore, from the above studies, it can be assumed that selenium respiring bacteria and many other bacterial strains show great potential to be utilized as an agent for the microbial synthesis of selenium nanoparticles, and these synthesized nanoparticles can be further utilized in various domains for a variety of applications.

3.2.2.3. Fungi. Fungi show high tolerance and metal accumulation activity, and they are considered the most viable platform for the generation of metallic nanoparticles.¹⁷⁴ It has been found that most fungi are sensitive to selenium, and therefore selenium compounds show antifungal properties. Further, a study well established that when the fungal bodies are incubated with a higher concentration of selenium, it leads to cellular damage and the initiation of detoxifying mechanisms in fungal cells, and it was suggested that fungi collected from areas with high selenium accumulation were more tolerant to selenium compared to that collected from non-accumulated selenium areas. This phenomenon was observed in *Rhizosphere* fungi such as *Alternaria seleniphilia*, and some other fungi groups such as *Curvularia*, *Cladosporium*, and *Alternaria*.^{175,176} Moreover, Se⁰ was synthesized on the mycelium by different taxonomic groups of fungi such as *Chaetomium globosum*, *Trichoderma viride*, *Pleurotus ostreatus*, and *Aspergillus niger*. Further, *Alternaria alternata* could synthesize uniform and stable selenium nanoparticles.¹⁷⁷ Hence, fungi-synthesized selenium nanoparticles have beneficial applications in the biomedical field, and there is also an urgent need for researchers working in this area to focus on this synthesis route for the preparation of metal and metal oxide nanoparticles, as this method is efficient, high yielding, and cost-effective.

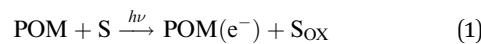
3.2.2.4. Yeast. Unlike fungi, yeast shows high capability to bioaccumulate many trace elements such as selenium during its cell growth phase.¹⁷⁸ Further, it was observed that *Saccharomyces cerevisiae* synthesized selenium nanoparticles in a selenium-rich medium under various fermentation conditions such as temperature, time of fermentation, initial pH value, and shaking speed. The experiment showed that the ideal

conditions for organic and total selenium incorporation in yeast cells was the addition of 25 µg mL⁻¹ sodium selenite for 9 h of incubation at 28 °C and initial pH of 5.8 together with 48 h fermentation time.¹⁷⁹ Owing to the low selenium toxicity in yeast, selenium nanoparticles can play a potential role in the food and pharmaceutical industries. However, to date, the synthesis of selenium nanoparticles through this route has not been explored in-depth, and scarce literature is available regarding the mode of mechanism for the synthesis of selenium or metal/metal oxide nanoparticles through yeast-mediated green synthesis. However, a few reports have shown that the synthesized material through this route has various applications in various domains. Hence, there is an urgent need for researchers working in the nanobiotechnology and materials science domain to investigate the yeast-mediated green synthesis of metal (selenium, cerium, etc.) and metal oxide (cerium oxide, magnesium oxide, etc.) nanoparticles.

3.3. Physical synthesis

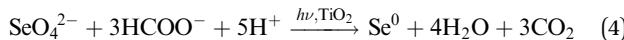
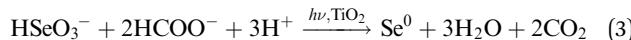
A variety of techniques are available to synthesize nanoparticles and their different types such as powders, tubes, rods, and thin films, and to synthesize the desired type of nanomaterial, new methods are being developed or sometimes the existing methods are modified. The method to be used mainly depends on the type of nanomaterial to be produced. One of the methods is the physical method based on top-down and bottom-up approaches, but the different types of physical synthesis routes are mainly based on the bottom-up approach for synthesizing nano-sized materials. The first step involves the evaporation of the material and the second step involves rapidly controlled condensation to synthesize the required particle size. Hence, the three main physical synthesis routes are discussed in more detail in the sub-sections below for the synthesis of selenium nanoparticles.

3.3.1. Photocatalytic synthesis. Photocatalytic synthesis is considered a crucial approach to synthesize selenium nanoparticles of the desired size at room temperature. The photocatalytic process exhibits one of the most important characteristics, where it transforms the inorganic waste created during reactions into safe by-products. Further, polyoxometalate (POM) anions can be used to synthesize selenium nanoparticles *via* the photocatalytic process since POM exhibits unique redox properties, as shown in chemical reactions (1) and (2). The presence of several oxygen-bridged clusters of metal supports the release of electrons in different stages without requiring disintegration,^{180–188} as revealed in the chemical reaction below.



It was observed that under irradiation conditions and pH regulation, the POM anions functioned as potential oxidants for Na₂SeO₃ salt. Another experiment was performed, in which Se(IV) and Se(VI) ions were reduced in the presence of a

photocatalyst (TiO_2 powder) for the synthesis of selenium nanoparticles *via* the photocatalytic technique.



The above reactions (3) and (4) show that TiO_2 acts as a photocatalyst that can easily convert metal salts into their elemental state, which can be easily recovered.¹⁸⁸ Therefore, it can be utilized to manage environmental pollution, and the only setback of this method is that it forms heterogeneous particles in this individual reaction. However, several strategies can be employed to overcome this setback, such as controlling the size by changing the reaction conditions.^{189,190} One of the reactions reduced selenious acid (H_2SeO_3) *via* the UV irradiation of tungsten-silicate acid solution ($\text{H}_4\text{SiW}_{12}\text{O}_{40}$, Tryptone Soya Agar (TSA)), which synthesized size-controlled selenium nanoparticles. The catalytic activities of the material were also studied for the decolorization of Congo red dye in the presence of UV light. Due to the small size of the nanoparticles, they exhibited high catalytic activity.^{191,192} Thus, the particle size is considered a crucial parameter for upgrading highly potential selenium-supported catalysts for the decolorization of dyes.

3.3.2. Vapor deposition technique. The chemical vapor deposition (CVD) synthesis route can be employed to synthesize pure selenium nanoparticles and their equivalent nanocomposites with a preferred morphology. The CVD technique involves the production of a thin film deposit on the surface of a substrate by utilizing volatile precursors.^{193,194} The development of selenium nanowires from bulk powder in an argon gas atmosphere was performed by varying the temperature, which produced selenium nanowires of various diameters.¹⁹³ Hence, the temperature and the nature of the catalyst (copper, iron, nickel, and silicon) exhibited a major effect on the nucleation rate of the nanowires and further produced highly porous selenium. Copper nanocomposites with hybrid ink were developed *via* a non-vacuum

deposition process. The prepared composites showed efficient solar energy conversion efficiency, which can be further utilized for solar cell applications.¹⁹⁴

4. Biomedical applications

Selenium nanoparticles have potential applications in various domains such as the environment, biomedical, and agricultural fields, as shown in Fig. 5, due to their small size and existence as several allotropic forms. Moreover, selenium is also present in the human body and is an essential micronutrient needed in the diet. Fig. 6 shows the requirement of selenium in different body parts. Further, this review specifically discusses the biomedical applications of selenium nanoparticles by highlighting their therapeutic and diagnostic properties in detail.

4.1. Therapeutic application

Therapeutics is the branch of medicine that deals with the treatment/cure of various diseases. This review covers the detailed study of the various therapeutic roles of selenium nanoparticles such as antimicrobial activity, anti-cancer activity, delivery of drugs and genes in the following sub-sections.

4.1.1. Antimicrobial activity. Nanotechnology is a field that has been widely explored and holds potential in the biomedical field due to the high-surface-to-volume ratios and nanosize of nanoparticles, which allow more active sites for interaction and functionalization with biological systems such as cells, tissues, and bioactive molecules. The size of nanoparticle allows the absorption of many drugs and can be used in cancer treatment, inhibiting microorganisms, *etc.*⁸⁸ Moreover, selenium nanoparticles exhibit antioxidant properties and scavenge ROS radicals, and therefore, can be used as a natural antioxidant agent. In addition, they are also known to inhibit algal growth *in vitro*, and thus nanoparticles of metals and metal oxides are considered a new generation of anti-microbial agents, which have been highly explored, and the antimicrobial applications

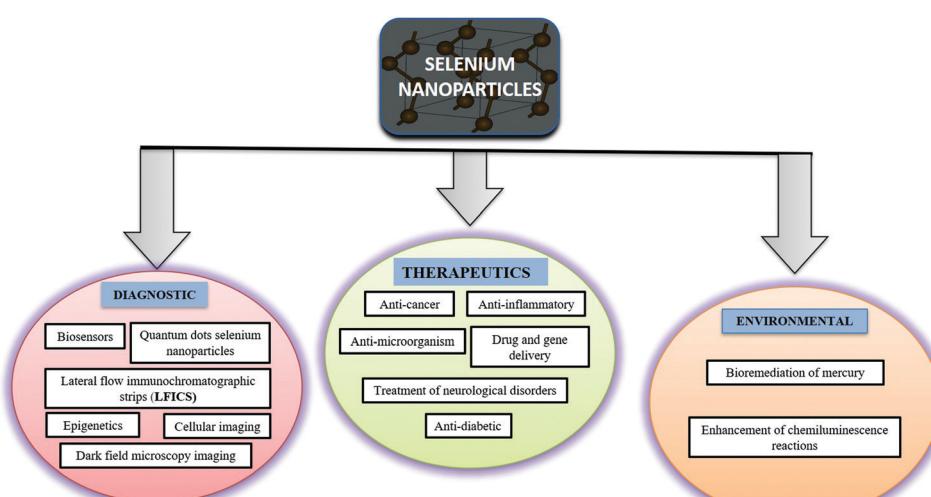


Fig. 5 Potential applications of selenium nanoparticles for biomedical (therapeutics and diagnostics) and environmental domains.

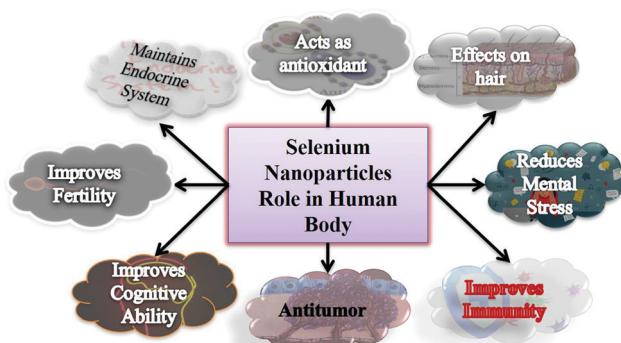


Fig. 6 The potential use of selenium nanoparticles in the human body.

of selenium nanoparticles are elaborated in the following subsections.^{195–199}

4.1.1.1. Antibacterial. Antibiotic-resistant bacteria are generally considered to be inhibited by nanoparticles as nearly all antibiotic resistance mechanisms show a limited effect on nanoparticles as in the case of silver nanoparticles,²⁰⁰ gold nanoparticles,²⁰¹ selenium nanoparticles,²⁰² palladium nanoparticles,²⁰³ copper oxide nanoparticles,²⁰⁴ and many more.^{205–207} Selenium is a trace element found in the human body as an essential compound in 25 selenoenzymes and reductase, and hence, it displays lower toxicity compared to silver nanoparticles.^{208,209} A nanotoxicological study was performed to study the toxicity level of selenium nanoparticles in bacterial cells, which also compared the toxicity levels of selenium nanoparticles and silver nanoparticles loaded on Cs polyvinyl alcohol scaffolds. The results obtained demonstrated that the selenium nanoparticle-embedded scaffolds exhibited more cytocompatibility than the silver nanoparticles, but both showed good antibacterial properties.²¹⁰ It has also been reported that the electrostatic attraction caused between the negatively charged bacterial cell membrane and positively charged nanoparticles plays a crucial role in deciding the antimicrobial efficiency of nanoparticles. Therefore, negatively charged selenium nanoparticles efficiently inhibit the growth of Gram-positive bacteria,^{203,211–213} and due to this, positively charged nanoparticles are more investigated than negatively charged ones.^{214,215} Furthermore, selenium nanoparticles can be surface modified with a positive charge for efficient anti-microbial activities. The influence of selenium nanoparticles on microorganisms is still unknown. However, studies have suggested that varying concentration of sodium selenite (Na_2SeO_3) salt affects the growth of bacteria as many survive in low concentrations of Na_2SeO_3 , producing a high concentration of Se^0 , which leads to the generation of ROS and causes damage to the bacterial genetic material by producing hydrogen selenide (H_2Se) when reacted with oxygen. Further, ROS production leads to an increase in toxicity in microbial cells. Unlike other compounds, selenium compounds such as sodium selenate (Na_2SeO_4) and sodium selenide (Na_2Se) cause inhibitory effects on the plasmid DNA of *E. coli*, and further, it was also shown that selenium dioxide (SeO_2), similar to Na_2SeO_3 , can damage bacterial plasmid DNA

under H_2O_2 stress conditions.²¹⁶ Similarly, antibacterial activities against many bacteria were studied using organo-selenium compounds such as 2,4,6-tri-*para*-methoxyphenylselenopyrilum-chloride perhydroselenoxyanthenone, and the results obtained from these studies exhibited their extraordinary anti-bacterial activity.^{217,218} Moreover, when incubated with lysozyme in the form of a monohybrid system, selenium nanoparticles showed effective inhibition properties against *Escherichia coli* and *Staphylococcus aureus*.²¹⁹ Similarly, methicillin-resistant *Staphylococcus aureus* (MRSA) was potentially inhibited by synthesizing a synergistic nanocomposite surface conjugating quercetin (Qu) and acetyl-choline (Ach) selenium nanoparticles (Qu-Ach@SeNPs), which directly attached to the bacterial cell wall and caused irreversible damage to the membrane.²²⁰

Furthermore, to observe the anti-bacterial property of selenium nanoparticles, they were stabilized by the positively charged spider silk protein eADF4(k16), to provide a net surface positive charge, and these nanoparticles exhibited increased bactericidal efficacy against Gram-negative bacteria (*E. coli*).²²¹ It is well known that the size of nanoparticles highly defines their anti-bacterial properties; therefore, selenium nanoparticles with a size of 81 nm and a concentration of $10 \mu\text{g mL}^{-1}$ showed the highest inhibition in the growth of methicillin-sensitive *Staphylococcus aureus* (MSSA) and methicillin-resistant *Staphylococcus aureus* (MRSA) by depleting the amount of internal ATP, which promotes ROS generation and further leads to the disruption of membrane proteins, and these nanoparticles were also found to be non-toxic towards mammalian cells.²²²

4.1.1.2. Anti-fungal. The increase in anti-fungal resistance in pathogenic fungi has changed the investigation and development of new antibiotics and antimicrobial formulations. Currently, the antifungal properties of many compounds (inorganic and organic) against pathogenic fungi are being tested.²²³ Selenium nanoparticles exhibit low toxicity and good antioxidant activities, which have attracted interest from many researchers for the development of anti-microbial drugs.^{224,225} Selenium sulfide has been highly used as an anti-fungal agent and is commonly used in antidandruff shampoos.²²⁶ *Candida albicans* are opportunistic pathogenic yeast and are commonly found in the gastrointestinal, oral cavity, and urogenital tracts, which cause mild to severe infections, and they mainly infect people with low immunity or who are using antibiotics for a long period.²²⁷ *C. albicans* overgrowth is mainly caused by an imbalance in the microbiota, which causes their infection to spread, and the lactic acid bacteria are Gram-positive bacteria that make up the intestinal gut microflora and are important probiotics as they can improve the intestinal microbial balance and also inhibit the inhabitation of pathogenic micro-organisms.²²⁸ Further investigations on the antimicrobial properties of lactic acid bacteria showed that selenium nanoparticle-enriched *Lactobacillus* spp. when co-cultured with *C. albicans*, inhibited their colony growth in the culture, therefore exhibiting anti-fungal properties against *C. albicans*. It has been assumed that *Lactobacillus* releases potent exometabolites, which inhibit colonies of *C. albicans*²²⁹ and can be possible anti-*Candida* probiotic

formulations for future use. Further, to overcome drug-resistant pathogens, novel nanotechnological techniques have been developed, and it has been reported that silver nanoparticles and selenium nanoparticles have great potential to inhibit *C. albicans* biofilm formation. An experiment on the role of selenium nanoparticles role in *C. albicans* biofilm inhibition also concluded that the physical parameters such as crystallinity and size of the selenium nanoparticles are the major parameters affecting the viability of the *C. albicans* biofilm.^{230–232}

In addition to the above-reported information, the infections caused by *Candida* can either be superficial, which only infects the skin or mucous membranes, or can be invasive, which are life-threatening. Selenium nanoparticles have great potential to prevent *Candida* infection by accumulating themselves as organic compounds in the cell wall of yeast through chemisorption in an extensive amount, and further mixing of selenium with cell proteins leads to the displacement of sulfur from amino acids containing sulfur, namely methionine (Met) and cysteine (Cys). Besides, selenium is absorbed in the cytosol through transporters such as sulfate permeases (SulP1 and SulP2), and the toxic activities of inorganic selenium such as ROS generation that lead to DNA breakage, protein misfolding, and dysfunction of enzymes in yeast are involves the reaction of selenites with thiol-containing compounds.^{233,234} Besides cancer research,^{235,236} chemically synthesized Cs-decorated selenium nanoparticles possess extraordinary anti-fungal properties, and Cs, which is used as a capping and stabilizing agent in the synthesis of selenium nanoparticles, is a polysaccharide derivative of chitin, which is a biocompatible, biodegradable, bio-adhesive, positively charged polymer with low cytotoxicity.^{237,238} The study concluded that the Cs–selenium nanoparticles exhibited effective anti-fungal properties against *C. albicans*.²³⁹ Furthermore, the selenium nanoparticles prepared using *Klebsiella pneumonia* exhibited anti-fungal properties, as shown by the germination of *Aspergillus* sp., namely *Aspergillus terreus*, *Aspergillus fumigatus*, and *Malassezia furfur*, and the anti-fungal activity of 50 and 100 ppm of myco-synthesized selenium nanoparticles was very effective in inhibiting mycelial growth of *Colletotrichum capsici* and *Alternaria solani*.²⁴⁰

4.1.2. Anti-diabetic. Glucose is taken up from the diet and can be controlled by insulin, which is secreted by the pancreas. However, when the pancreas cannot secrete insulin properly, this leads to the generation of a metabolic disorder in which the blood glucose level is significantly higher than normal, which is known as diabetes mellitus. Endothelial dysfunction leads to an increase in the oxidative state, which causes the onset and progression of diabetes. According to insulin secretion, diabetes is classified into two major types, *i.e.*, type-I and type-II diabetes. In the former, less insulin is secreted in the body, which can be due to auto-immunity, genetic disorders, viral infection, or acute poisoning, leading to organ failure. The latter is commonly occurring and is generally caused by an improper diet and lack of exercise, which results in insulin resistance. An increase in the glucose level in the blood can also lead to several problems such as damage to the liver, eye, kidneys, and heart.²⁴¹

According to the literature, it can be concluded that there is a relation between the selenium concentration in the blood and diabetes,^{242–244} considering that a patient suffering from diabetes has a high concentration of selenium compared to a non-diabetic person.^{245,246} The body of the diabetes mellitus patient requires more antioxidation species to decrease the oxidative and inflammatory response, and selenium exhibits dynamic anti-oxidant and anti-inflammatory properties. Therefore, selenium acts as a vigorous anti-oxidant and modulator. Furthermore, the size of an element plays an important role in defining its biomedical use. Therefore, selenium nanoparticles are more preferred for diabetes care, and thus, type-I and type-II diabetes mellitus can be easily treated with the help of selenium nanoparticles because they can prevent hypoglycemic activity by decreasing oxidative damage and sensitizing insulin, which can be used as an anti-hypoglycaemic agent.²⁴⁷ A study on the effect of the hypoglycaemic effect of selenium nanoparticles in streptozotocin (STZ)-induced diabetic rats with type-I diabetes model was conducted, and the results showed that the selenium nanoparticles increased hyperglycemia and hyperlipidemia in the diabetic model probably by inducing insulin-mimetic activity, which also prevented histological injury in the hepatic and renal tissues of rats.²⁴⁸ Similarly, *Catathelasma ventricosum* polysaccharide-fabricated selenium nanoparticles (CVP-SeNPs) were introduced in the same model, and the result of this study suggested that these nanoparticles exhibited potential anti-diabetic activity compared to selenium nanoparticles alone. In another study, Cs-stabilized selenium nanoparticles (CsS-SeNPs) were synthesized, which were administered in a rat model in a dose-dependent manner of 2.0 mg kg^{-1} to check their anti-diabetes effect, and the results showed a very potential anti-diabetic effect.²⁴⁹ Further studies on STZ-induced rats were performed to check the anti-diabetic activity of selenium nanoparticles, and in one of the experiments, the STZ-induced rats were orally fed with selenium nanoparticles in the form of liposomes for 21 days. It was observed that the liposomal selenium nanoparticles showed potential anti-diabetic activity by increasing the secretion of insulin, which preserves the integrity of the pancreatic cells by preventing inflammation, decreasing the level of glucose, and oxidative stress, thus enhancing the antioxidant defense system.²⁵⁰ Moreover, the selenium nanoparticles were modified with peptide-conjugated chitosan known as SCD, consisting of the 32-amino acid-derived PACAP-derived peptide DBAYL (pituitary adenylate catalase activating peptide), which is a neuroendocrine peptide that plays a crucial role in the metabolism of carbohydrates and lipids. It further activates VPAC-2 to mediate glucose-dependent insulin secretion and decreases the blood glucose levels, and the novel SCD showed improved effects in improving insulin sensitivity, hyperglycemia, and lipid profiles. Moreover, it also restricted hypoglycemia, and compared to clinical drugs such as Ex-4, which needed to be injected twice per day, SCD was found potential to be long-lasting in a single dose.²⁵¹ Hence, based on the above evidence, it is obvious that selenium nanoparticles exhibit great anti-diabetic potential independently and when combined with

other agents such as BAY 55–9837 and VPAC-2 for combating hyperglycemia. The mechanism of their anti-diabetic activity is demonstrated in the schematic illustration in Fig. 7.¹⁰⁵

4.1.3. Anti-cancer. The uncontrolled division of cells and their spread to surrounding tissue leads to cancer or malignancy of cells, and annually, around 8.2 million deaths are due to different types of cancer, which is one of the major causes of death globally. Deaths caused by cancer globally will continue to increase, where it has estimated that by 2030 it will reach around 13.1 million, which is about a 70% increase. Further, almost over 200 types of cancer are known to date, consisting of six types of biological features, including angiogenesis, proliferative signalling, resistance to cell death, evasion of growth suppression, invasion and metastasis, and replicative immortality.²⁵² Moreover, the increase in civilization and enhancement of cosmopolitan status have created an alarming change in the environment, which has been a major factor responsible for the transformation in the ecological climate.²⁵³ Magnetic resonance imaging (MRI), bio-sensing, chemotherapy, gene therapy, computed tomography (CT), and immunotherapy are the different types of diagnostic methods applied for the early diagnosis of cancer.^{254,255} With bionanotechnology, new innovative methods have been created for molecular diagnosis/imaging and drug delivery using genes and proteins for cancer treatment. Currently, the combination of immunology and nanotechnology for treatment has resulted in the development of nano-immune-chemotherapy with immune target specificity as a treatment of cancer. It has been observed that selenium was alone found to be essential for cancer-protection action against prostate, lung, breast, and colon cancers.^{256,257} Because the ROS level is high in cancer cells, selenium nanoparticles act as pro-oxidants, resulting in apoptosis and cell cycle arrest (Fig. 8).¹⁰⁵ The low toxicity, simple preparation methods, *in vivo* degradability, convenient administration route, high bioavailability, and antioxidant activity of selenium nanoparticles make them significant for application as nanomedicines and can also be used as nanocarriers.^{258–260} Selenium nanoparticles have been reported to be efficient anti-cancer agents as they arrest the cell cycle at the S-phase through induction by eIF-3 protein complex deregulation, and hence stop

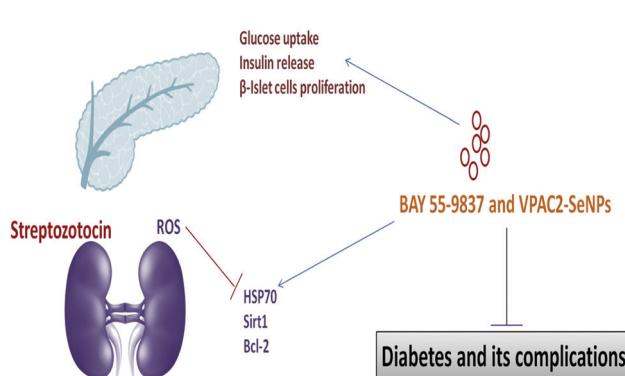


Fig. 7 The anti-diabetic activity of single and combined selenium nanoparticles for combating hyperglycemia (reproduced from A. Khurana et al., *Biomed. Pharmacother.*, Elsevier, 2019 (ref. 105)).

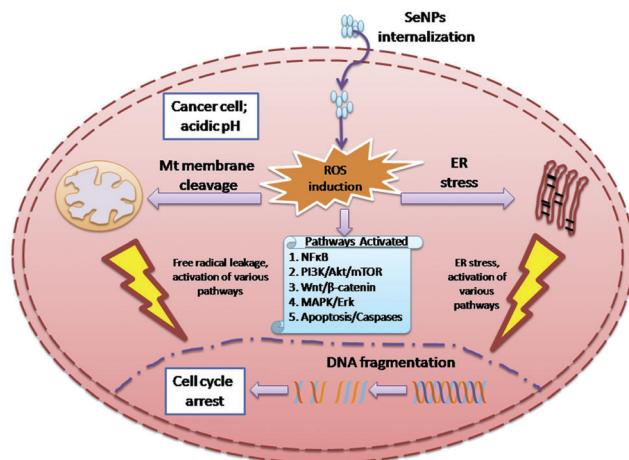


Fig. 8 Common mode of mechanism data for selenium nanoparticles' anticancer activity (reproduced from A. Khurana et al., *Biomed. Pharmacother.*, Elsevier, 2019 (ref. 105)).

the growth of cancer cells.²⁶¹ One of the latest studies on the anti-cancer activity of selenium nanoparticles showed that they alter the biomechanical properties (Young's modulus, adhesion force) of the cell membrane of the cancer cells.²⁶² Besides their unique anti-cancer potential, selenium nanoparticles exhibit better selectivity between normal and cancer cells than the same concentrations of $\text{Se}^{+}\text{(iv)}$.²⁶³ These nanoparticles are precisely internalized in cancer cells through endocytosis, which initiates the apoptotic signal transduction pathway, leading to cancer cell death.^{264,265} Selenium nanoparticles provide a large surface area due to their small size and are therefore desirable, which allows them to scavenge free radicals and passively target tumor cells for efficient internalization.^{266,267} Moreover, selenium nanoparticles are obtained through inorganic selenium *via* chemical/green synthesis and can be utilized as therapeutic agents, where these synthesized nanoparticles exhibit various mechanisms such as the modification of thiol compounds and chromatin binding overproduction of potential mitochondrial membranes. Besides, the interaction of selenium nanoparticles with intracellular proteins and cysteine-containing enzymes (glutathione peroxidase and superoxide dismutase) accumulates ROS inside cancer cells, which leads to the destruction of only cancer cells, and thus they do not harm normal cells.²⁶⁸

Selenium nanoparticles exhibit higher toxicity to cancer cells than normal cells due to increased mitochondrial respiration, leading to increased metabolic activities. Further, nanoformulation has enhanced the permeability and retention of drug accumulation at the tumor site, which was initially reduced by the difference in tumor porosity, and for active targeting, different moieties and active molecules (antibodies, peptides, aptamers, etc.) should be attached to the specific receptors of the tumor cells. The excess generation of free radicals increases oxidative stress and elevates the development of cell carcinogens, and thus, a lower selenium level is observed in the body of cancer patients. Although selenium compounds suitable as an anti-cancer agent are still conflicting due to the concentration-dependent activity at the target site, low-moderate dosages can stimulate growth,

whereas higher levels are toxic. Selenium nanoparticles balance the selenium release by decreasing the selenium distribution in normal tissues and increasing it in the tumorous tissues, and thus provide appropriate conditions for the administration of the correct selenium coating medicine in which low-to-moderate concentrations serve for body balance, and a high concentration is used for a therapeutic role. Further, selenium nanoparticles trigger glutathione S-transferase (GST), which shows a chemoprotective effect and leads to ROS production, inhibiting the maturation of cancer cells in the peritoneal cavity. Considering that ROS alters the activities of glutathione and thioredoxin, the intraperitoneal administration of selenium nanoparticles is suitable.^{269–272}

When human breast carcinoma (MDA-MB-231) and human cervical carcinoma (HeLa cells) were treated with selenium nanoparticles to study their anti-proliferative properties *in vitro*, it was observed that the growth was inhibited in both cell lines in a dose-dependent manner.²⁷³ Furthermore, the selenium nanoparticles synthesized from carboxylic acid showed effective anti-cancer properties by inducing cell apoptosis in the cancerous cells and can be utilized for cost-effective and advanced cancer therapy.²⁷⁴ Moreover, a comparative analysis of selenium nanoparticles on the growth suppression of various types of carcinoma cells, namely breast cancer MCF-7 cells, androgen-independent prostate cancer DU-145 cells, human lung cancer A549 cells, and androgen-dependent LNCaP cells, was performed. According to this study, it was reported that through caspase-mediated apoptosis, the cell viability of selenium nanoparticles treated LNCaP cells decreased. It was also observed that the selenium nanoparticles decreased the regulation of the Er protein, which is responsible for stopping prostate cancer propagation.²⁷⁵

Further, the spread of tumors is mainly caused by the proliferation of the cancerous cells in blood vessels, which is considered the major step for the growth of cancerous cells.^{276–279} Functionalized selenium nanoparticles exhibit the property of inhibiting tumor growth, and the use of biomolecules as vehicles for the fabrication of nanomaterials is widely investigated nowadays. Surface-modified selenium nanoparticles by amino acids are biocompatible and safe materials, and for decorating selenium nanoparticles, different types of amino acids (valine, aspartic acid, and lysine) were used, and then anticancer activity was investigated. The results of this study suggested that the lysine-decorated selenium nanoparticles exhibited better anti-cancer activity compared to the valine and aspartic acid-decorated selenium nanoparticles. It was also reported that the upstream signaling of caspase activation and mitochondrial dysfunction were caused due to the overproduction of ROS in the cancer cells, and further, the obtained results concluded that the amino-acid decorated selenium nanoparticles (SeNP@AAs) are potential chemoprotective and chemotherapeutic agents for cancer care.²⁸⁰ In another study, selenium nanoparticles combined with ruthenium (Ru) exhibited inhibitory effects on angiogenesis in human umbilical vascular endothelial cells (HUVEC), but they also caused cytotoxic side-effects. The further enhancement by

thiol-conjugation between Ru and selenium (Ru-MUA@Selenium) increased the inhibitory effect and was also able to target cancer cells *in vivo*.^{281,282}

Moreover, to enhance the antitumor activity of selenium nanoparticles, human serum albumin was coated on mesoporous selenium nanoparticles, which were designed to deliver DOX (doxorubicin). The interaction between SPARC (secreted protein and rich in cysteine) and the nanoparticles in MCF-7 cells boosted the cellular uptake, and the mesoporous selenium nanoparticles showed GSH-dependent drug release and decreased the side effects of DOX. They also enhanced the tumor-targeting effects. In addition, novel selenium-substituted hydroxyapatite nanoparticles (SeHAN) were synthesized by a group of researchers and tested on a human hepatocellular carcinoma nude mouse model, and the results of this study demonstrated that these synthesized selenium nanoparticles exhibited low toxicity. Further, they provided a survival advantage, and the blood biochemical studies revealed that the SeHAN nanoparticles exhibited low toxicity on the kidney and liver functions and have potentiality as a future anti-cancer agent.²⁸³ Further, lactic acid bacteria (LAB) can reduce selenium ions to Se0 nanoparticles and deposit them in the intracellular spaces, and thus when combined with selenium nanoparticles, they exhibited great anti-cancer potential. The combination was orally administered to a highly metastatic breast cancer mouse model, which remarkably increased the natural killer cell cytotoxicity, delayed-type hypersensitive response, and high IFN- γ and IL-17 levels. It also extended the life span and decreased the metastasis of the liver tumor. In addition, it was also reported that both components acted as immunostimulators, enhancing the immune response of the cancer-affected mice. A375 human melanoma cells were treated by inducing mitochondria-mediated apoptosis by selenium nanoparticles fabricated in *U. pinnatifida* polysaccharide solutions, and the cell apoptosis was observed in a dose-dependent process, which was exhibited by DNA fragmentation and translocation of phosphatidylserine. Moreover, hyaluronic acid is a negatively charged polysaccharide, which exhibits excellent biocompatibility and biodegradability, together with low toxic activities when studied *in vitro*. Hyaluronic acid-functionalized selenium nanoparticles (HA-SeNPs) exhibited a potential anti-tumor effect when analyzed in a Heps tumor mouse model. It extremely decreased the tumor mass, and the results also revealed that the HA-SeNPs could control immune-regulating properties, helping them exhibit anti-tumor properties.^{284–286}

4.1.4. Neurodegenerative diseases. Elevated oxidative stress in the brain and neurons causes a high consumption of O₂, polyunsaturated fatty acid, and a decrease in enzymatic anti-oxidant activities, and it is well-known that an elevation in oxidative stress and free radical production in the body leads to the generation of neuro-degenerative diseases,²⁸⁷ namely Parkinson's disease, Alzheimer's disease, Huntington's disease, epilepsy, cerebral ischemia, and traumatic brain injury. In addition, it was also observed that patients suffering from brain diseases such as Alzheimer's disease and Huntington's disease have a deficiency of selenium, leading to neuronal loss and brain dysfunction and detriment.^{288,289}

Elemental and modified selenium nanoparticles show a direct anti-oxidant effect on the brain and neurons as they present as a cofactor in GPx, which helps in scavenging H₂O₂ and efficiently prevents oxidative damage.²⁹⁰ Treatment with selenium can decrease the risk of neurodegenerative diseases, as observed in animal models.^{291–293} Although the exact mechanism of selenium nanoparticles exhibiting neuroprotective activity has not been solved, various mechanisms are being proposed. Moreover, selenium nanoparticles can also be used to diagnose Alzheimer's and Huntington's diseases as the selenium levels are reported to be low in patients. Diagnostic methods for detecting selenium concentration or GPx can be investigated further. Another common cause of death worldwide is ischemic stroke or cerebral stroke, which is caused due to the shortness of blood flow in the brain, and selenium nanoparticles functionalized with monoclonal antibodies (OX26) can play a potential role by protecting from ischemic stroke by targeting different cellular pathways regulating the cellular metabolic state, inflammatory reactions, oxidative defense system, and apoptotic death.

4.1.5. Drug and gene-delivery. The extraordinary physicochemical and biological properties of nanoparticles and their easy bio-availability and low toxicity have offered them potential applications in the pharmaceutical field. They can be easily

synthesized according to the preferred size, shape, controlled release, surface charge, and gene and drug loading capacity. Selenium nanoparticles have been widely studied among the various nanoparticles and are known to possess several applications in the biomedical field. They exhibit distinctive features as nano-carriers such as the reduction of drug volume, restriction of drug exposure to healthy cells and tissues, distribution of the drug in solid colloidal form, improving the solubility of hydrophobic materials for parenteral administration, and amplifying the stability of therapeutic agents, which help them to be used as drug carriers.^{294–296} An experiment was performed to utilize selenium nanoparticles to deliver propylene oxide-modified ruthenium complexes and ethylene oxide copolymer, which are considered inorganic therapeutic drugs utilized in cancer therapy.²⁹⁷ An additional approach to deliver anti-cancer drugs, mainly doxorubicin-cisplatin, was developed by combining transferrin-conjugated selenium nanoparticles. This simplified the uptake of doxorubicin-cisplatin into a mammalian breast cancer cell line (MCF-7), which led to apoptosis in the cancer cells.²⁹⁸ Another approach for targeting tumors and multi-stimuli responsive drug delivery based on selenium vehicles is a nanocomposite synthesized using selenium nanoparticles [selenium particles/porous silica/folic acid/copper sulfide/doxorubicin nanocomposite (Se/SiO₂/FA/CuS/DOX) (Fig. 9)], which can

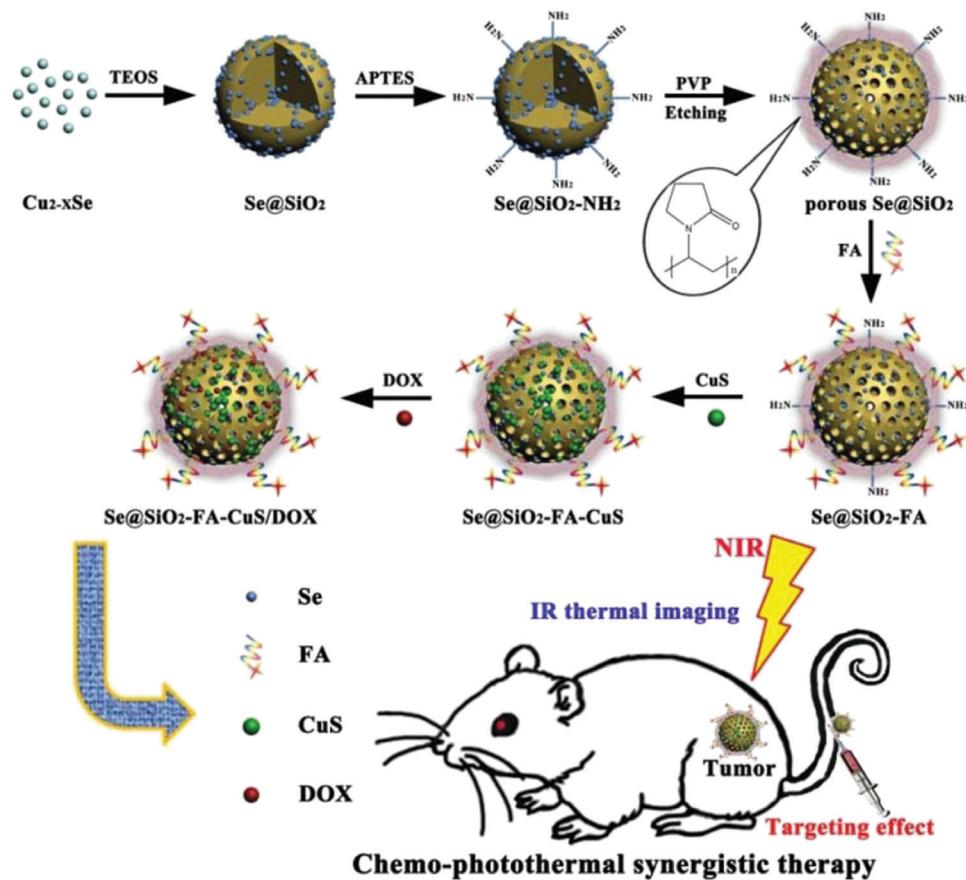


Fig. 9 Schematic illustration of Se/SiO₂/FA/CuS/DOX nanocomposite synthesis and their applications (reproduced from Y. Wang *et al.*, *Nanoscale*, RSC, 2018 (ref. 299)).

be used to combine photothermal therapy (PTT) with chemotherapy of DOX and selenium for cancer treatment. The synthesized Se/SiO₂/FA/CuS/DOX nanocomposite was excellent in targeting ability, and therefore actively accumulated in tumor tissues. Owing to the synergistic effect caused by chemotherapy (Se and DOX) and photothermal therapy, the Se/SiO₂/FA/CuS/DOX nanocomposites could efficiently inhibit the growth of cancer cells both *in vivo* and *in vitro* and could also completely destroy the tumors. Therefore, Se/SiO₂/FA/CuS/DOX nanocomposites exhibit potential as multifunctional nanoplatforms (combining photothermal and chemotherapy) for cancer treatment.²⁹⁹

Moreover, a comparative study was performed to understand the efficiency of irinotecan when delivered individually and when combined with selenium nanoparticles, which revealed that irinotecan combined with selenium nanoparticles exhibited greater toxicity towards the HCT-8 cancer cell line compared to irinotecan delivered alone.³⁰⁰ From other investigations, it has been suggested that the optical properties of selenium nanoparticles play a crucial role in drug delivery at the specific site and time-specific control of payload, which has been observed in both covalently bounded and copulated drugs bonded with selenium nanoparticles.³⁰¹ Moreover, the poly-amidoamine and polyamidoamine-dendrimer modified selenium nanoparticles delivered siRNA and cisplatin to the tumor and did not exhibit toxicity towards normal cells, where the cellular apoptosis occurred through PI3K/Akt/mTOR and MAPK/ERK pathways.³⁰² Besides, polyethylene glycol-functionalized selenium nanoparticles effectively delivered crocin, which effectively inhibited a human lung cancer cell line (A549 506 cells) when studied in a nude mouse model. Crocin-conjugated PEG505 selenium nanoparticles exhibited potential hemocompatibility.³⁰³ Similarly, curcumin-loaded selenium nanoparticles showed anticancer activity against *Ehrlich's ascites* carcinoma in a mouse model through apoptosis, and it also reduced NF-κB signalling and epithelial–mesenchymal transition (EMT), together with improved chemoprotective activity. Furthermore, doxorubicin was carried by mesoporous selenium nanoparticles to targeted breast cancer cells, and the targeting was very specific, and the result of this study demonstrated apoptosis in the breast cancer cells.^{304,305}

At the molecular level, gene therapy presents a flexible base in the inhibition of disease progression and proliferation. However, the effective delivery of siRNA and miRNA in cells is still a challenge in the field of nanotechnology. Li *et al.* delivered siRNA packed inside polyethyleneimine-modified selenium nanoparticles to potentially destroy cancer cells. The selenium nanoparticles successfully delivered the gene by exhibiting remarkable transfection efficiency and generated ROS and apoptosis (*via* p53 and Akt) in the cancer cells. This experiment opened new doors to innovative possibilities that needed to be further explored and researched.³⁰⁶ However, besides this study, no study on the delivery of siRNA has been reported to date.

4.1.6. Anti-inflammatory. Together with many other biological properties, selenium nanoparticles also possess anti-inflammatory properties and researchers are now focusing on

the development of novel strategies to fight inflammation.³⁰⁷ Inflammation is the immune system's response to irritants, germs, foreign objects, *etc.* The NF-κB transcription factor initiates several pro-inflammatory genes in response to cellular stress and is regulated by MAP-K (mitogen-activated protein kinase).³⁰⁸ From past studies, it is evident that selenium nanoparticles exhibit great anti-inflammatory effects, and one example is the anti-inflammatory response of selenium nanoparticles incurred by lipopolysaccharide (LPS)/H₂O₂ (Fig. 10).¹⁰⁵ Besides, a combination of selenium nanoparticles with silymarin was tested on trinitro benzene sulphonic acid (TNBS)-induced colitis in rats to inhibit MAP-kinase. The combination at low concentration inhibited MAP-kinase, NF-κB, and decreased the TNF-α (tumor necrosis factor α) level, whereas pro-inflammatory cytokines (TNF-α and IL-6) and NF-κB signalling were inhibited by another approach using *Ulva lactuca* polysaccharide-modified selenium nanoparticles. The polysaccharide-modified selenium nanoparticles exhibited anti-inflammatory activities by inhibiting the NF-κB pathway and phosphorylation of JNK1/2, p38MAPK1 with the help of inhibitory proteins (Ik-B subunit).³⁰⁹ Also, natural polysaccharides are attracting increasing attention as they are easily available, low toxic, highly biocompatible, and form intramolecular hydrogen bonds, which prevent the accumulation of nanoparticles.

Inflammation mediated by macrophages is a vital cell type that is included in chronic and acute inflammation. Photodynamically active selenium nanoparticles were produced, which were photosensitive and possessed macrophage-targeting bilayers. H₂O₂ depletion in macrophages occurred due to the dual coating of Rose Bengal (photosensitizer) and thiolated chitosan, which can be useful for fluorescence imaging.³¹⁰ Melatonin exhibits direct anti-oxidant activity, which shows immunoregulatory properties, and is therefore highly known to protect liver injury. When melatonin and selenium nanoparticles were combined to form a novel complex, it elevated the anti-oxidant enzyme activity and GPX activity, and reduced the serum AST (aspartate aminotransferase), MDA (malondialdehyde), and

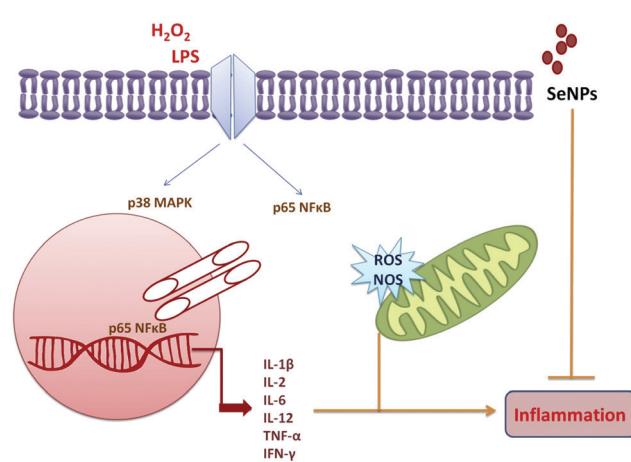


Fig. 10 Mechanism data for the anti-inflammatory effect of selenium nanoparticles in the presence of LPS/H₂O₂ (reproduced from A. Khurana *et al.*, *Biomed. Pharmacother.*, Elsevier, 2019 (ref. 105)).

ALT (alanine aminotransferase) levels, proinflammatory cytokines, and spread of splenocytes and pathological abnormalities of the liver. The reduction in oxidative stress induced by BCG (Bacille Calmette Guerin) was observed in immunological liver injury induced in mice, and therefore, melatonin–selenium nanoparticles showed a protective effect. The effectiveness of oral treatment of selenium nanoparticles was tested on 4T1 breast cancer cells, which showed enhancement of the proinflammatory cytokines such as IL-2, IL-12, Th1, IFN- γ , and TNF- α , and it increased delayed hypersensitivity reaction and immune response, which resulted in a decrease in the tumor volume and increased mice survival rate.³¹¹ Another approach to study anti-inflammatory activity was performed in gum arabic-stabilized selenium nanoparticles (GA-SeNPs).³¹² Further, selenium nanoparticles were surface functionalized by water-soluble derivatives of *Ganoderma lucidum*, which inhibited the range of production of LPS-stimulated nitric oxide (NO) through the suppression of the expression of TNF- α m-RNA.³¹³ Selenium nanoparticles also induced cell necrosis and apoptosis in MCF-7 cells by inhibiting lysozymes and mitochondrial cells.³¹⁴

4.1.7. Selenium nanoparticles protective role in drug-induced toxicity. One of the highly exploited anti-cancer drugs is “cisplatin”, which is used for the treatment of different types of cancers, including testicular cancer, head and neck cancer; however, it produces severe toxic side effects such as nephrotoxicity and genotoxicity by initiating inflammatory pathways, leading to the organ damage by generating oxidative stress. A study reported that the nephrotoxicity in the human kidney caused by HK-2 proximal tubular cells was reduced by 11-mercaptop-1-undecanol (MUN)-decorated selenium nanoparticles. It was also observed that the combined treatment of selenium nanoparticles and MUN exhibited nephroprotective potential by decreasing the activation of caspase-3 together with the inhibition of ROS. Therefore, selenium nanoparticles and the combination exhibited a potential material against the

toxicity of anti-cancer drugs.³¹⁵ Moreover, cisplatin also causes reproductive toxicity, which was decreased by selenium nanoparticles and helped improve sperm characteristics, serum testosterone, and sperm DNA integrity.³¹⁶ Fig. 11 depicts the various types of toxicity caused by different types of drugs on the human body.

Selenium nanoparticles reduce potassium dichromates ($K_2Cr_2O_7$), which initiates the oxidative stress in thyroid glands caused by the chromium induced thyrotoxicity. Selenium nanoparticles also restored superoxide dismutase (SOD), T3, T4, and catalase, together with the GSH levels in treated animals, and they also conserved the cellular structure, hindered cell damage, and stopped extra changes in the thyroid gland.²⁵⁹ In an experiment, selenium nanoparticles efficiently decreased anastrozole-induced osteoporosis and increased bone density when observed in ovariectomized rats. Anastrozole is a drug mainly used for the treatment of breast cancer, but its clinical usage is limited due to bone toxicity. This experiment showed that selenium nanoparticles are a potential treatment for osteoporosis and bone treatment.³¹⁷ These are the numerous reports demonstrating the potential protective role of selenium nanoparticles. However, most of the research did not compare inorganic selenium sources, making it complicated to determine a relation between selenium concentration and the corresponding effect on selenoprotein synthesis.

4.2. Diagnosis

Selenium nanoparticles have a potential role in rapid diagnosis methods due to their incredibly small size. Several diagnosis methods have been discussed in this review, proving the potential of selenium nanoparticles as a diagnostic material.

4.2.1. Biosensors. Biosensors are defined as analytical devices used to detect and analyze signals such as biological, physical, or chemical signals and transform them into measurable signals such as electrochemical and optical signals.

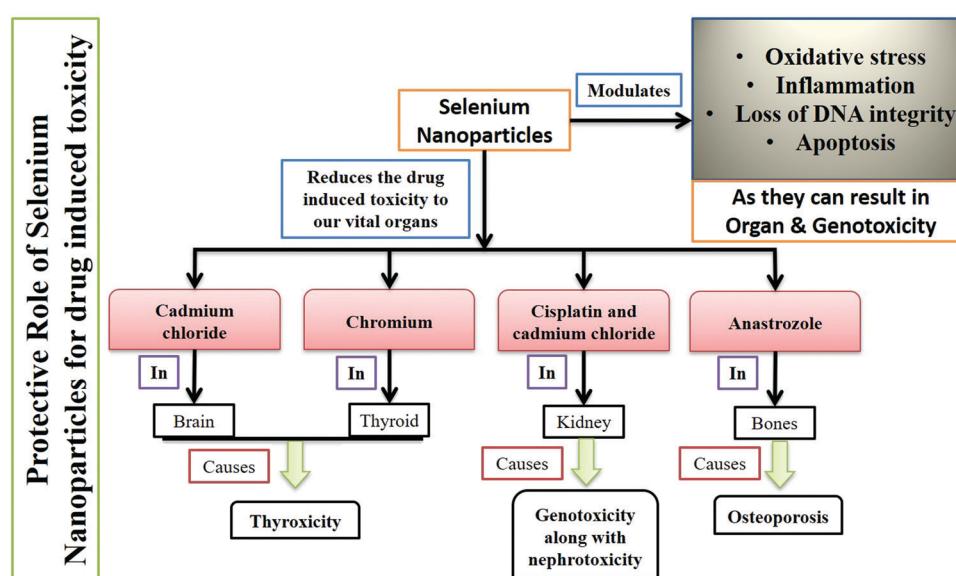


Fig. 11 Protective role of selenium nanoparticle for drug-induced toxicity.

Biosensors consist of sensing elements, transducers, and signal processors. The working mechanism of a biosensor involves the detection of an analyte by a sensing element and is passed on to the transducer to produce a signal, which is further amplified by the signal processor.^{318–321}

Biosensors based on *Bacillus subtilis*-derived selenium nanoparticles were developed to detect H₂O₂ as selenium nanoparticles, which exhibit great adhesive ability to join with H₂O₂ on the surface of the GC (glassy carbon) electrode, showed high sensitivity towards enzymes. High exposure to H₂O₂ leads to side-effects on the central nervous system and is also responsible for acid rain.^{322–324} Thus, the precise detection of H₂O₂ is currently one of the most researched areas. To observe the catalytic properties of selenium nanoparticles, different concentrations of H₂O₂ were used. Further, the increase in the current intensity exhibited better nanoparticle efficiency towards H₂O₂, and the nanoparticle assembled quickly at a very low detection limit in the order of 8×10^{-8} M, and the stabilized catalytic response was studied by visualizing the position of peak current and potential values at a different sweep. Hence, this study showed the biocompatibility of selenium nanoparticles, which can be used as a potential biosensor platform for carrying out electrochemical and electrocatalytic actions of heme-containing proteins/enzymes. The biogenic-derived selenium nanoparticle biosensor exhibited a detection limit of 8×10^{-8} M compared to the chemically synthesized selenium nanoparticles, which exhibited a low detection limit of 9.2×10^{-7} M.^{325–328} Further studies on modified selenium nanoparticle-based H₂O₂ biosensors were performed, in which selenium nanoparticles were modified by amino derivatives, which provided a distinct selectivity and sensitivity to selenium nanoparticles for the estimation of H₂O₂. The biosensing capability of selenium nanoparticles was enhanced by reacting them with cadmium and iron ions.^{329–331}

Well-tuned and functionalized selenium nanoparticles show a potential for application in biosensors and can be used for the diagnosis of various disease, and further, they can also be used to detect pollutants in the environment. Hence, the superiority of selenium nanoparticles and their low price can be used together to create great opportunities for environmental and biomedical domains.³³²

4.2.2. Cellular imaging. The presence of collagen and flavins creates background signals, which are absorbed by fluorescent biomarkers at certain wavelengths such as 300–500 nm. Thus fluorescence can be observed at 400–500 nm³³³ when studied by laser-induced fluorescence, which is a spectroscopic method utilizing the optical emission excited by the absorption of laser light, and therefore, can be used to study cellular processes.³³⁴ In a study, selenium nanoparticles were explored for their stable intrinsic fluorescence characteristics. Selenium nanoparticles with a size of 80 nm were cultured inside fibroblast cells, and wide-field imaging was done for fluorescence tracking. The selenium nanoparticles were mobile with stable fluorescence inside the cells and did not affect the cell viability. Therefore, they can be used for tracking and imaging cells without using a tag.³³⁵ Further, it was also noted

that the polymer-coated selenium nanoparticles were stable for one month and showed more emission counts than the plain selenium nanoparticles. The antibacterial activity of selenium nanoparticles makes them potential antibacterial materials, which exhibit the capability to show stable fluorescence for biomedical imaging and therapeutic applications.³³⁶

4.2.3. Membrane-based lateral flow immunochromatographic strip. Colloidal selenium nanoparticles, also known as colloidal selenium, encompass a class of rust-colored particulates that can be observed by the naked eyes. Like other coloured nanoparticles, these colloidal nanoparticles are also an alternative label for constructing lateral flow immunochromatographic strips (LFICS). Moreover, for the qualitative detection of chronic human gonadotropin (hCG) in urine, colloidal selenium nanoparticles can be used as a label for LFICS.³³⁷ Another approach for semi-quantitative lipoprotein detection in plasma was reported by complicated LFICS using reporter colloidal selenium nanoparticles.³³⁸ Currently, the rapid detection of melamine from colloidal selenium nanoparticle-based LFICS was developed. The melamine source was taken from liquid milk, milk powder, and animal feed, with a limit of detection (LOD) of 150, 1000, and 800 µg kg⁻¹, respectively.³³⁹ These studies were based on the utilization of the colloidal selenium nanoparticle-based LFICS, and no comparison study with LFICS based on other labels was reported. Hence, the researchers can work on the comparative analysis of colloidal selenium nanoparticle-based LFICS with other label-based LFICS, which can further confirm the most suitable LFICS for the detection of analytes.

4.2.4. Darkfield microscopy using aptamer-modified selenium nanoparticles. Darkfield microscopy (DFM) is a distinctive and remarkable imaging platform for single nanoparticles and has been highly utilized in probing chemical reactions,³⁴⁰ quantitation of metal ions, real-time optical sensing at high sensitivity, and *in vivo* imaging at the single-cell level. The unique contrast found between brightly lighted scattering probes and a dark background in DFM has helped overcome genetic disadvantages such as photo-damage and photobleaching, mainly caused by quantum dots and fluorescent molecules used in fluorescence microscopy. Nucleolin (NCL) is recognized as a tumor marker as it is found on the surface of cancer cells and shows selective expression.³⁴¹ It also acts as a receptor for various ligands, such as lipoproteins, cytokines, and the extracellular matrix, bacteria, and viruses. Thus, targeting and imaging the overexpressed NCL in cancer cells can be a potential strategy for cancer diagnosis.

Aptamer-modified selenium nanoparticles were used to diagnose cancer cells [human epidermoid cancer cells (HeP-2)] as a biocompatible light scattering probe in DFM imaging for the very first time. The prepared aptamer-modified selenium nanoparticles were highly stable, biocompatible, and water-soluble. They accurately targeted nucleolin and showed its overexpression. When observed under DFM, they exhibited green scattering light at 5.70 nm. This was reported as the first experiment performed by synthesizing aptamer-modified selenium nanoparticles (Apt-SeNPs) to detect cancer cells (HeP-2 cells). Specifically, the selenium nanoparticles formed Se-N/O

bonds with streptavidin (SA) through adsorption to form streptavidin-functionalized selenium nanoparticles (SA-SeNPs).³⁴² Then, Apt-SeNPs were formed by the high affinity interaction between SA and biotin linked on the surface of selenium nanoparticles (biotinylated aptamers, which specifically target NCL).³⁴³ The surface modifications were observed under FT-IR, protein staining BCA assay, and UV-visible spectroscopy. The biocompatible nature of the selenium nanoparticles, SA-selenium nanoparticles, and Apt-SeNPs prove them useful for bio-imaging. The three prepared modified selenium nanoparticles were then tested as light scattering markers and for the bio-imaging of HeP-2 cells. It was observed that the Apt-SeNPs linked particularly to the membrane of the HeP-2 cells by enhancing the light scattering signals. When observed under DFM, it showed that a reduction in the binding affinity occurs when NCL binds *via* surface binding affinity to Apt-SeNPs, which causes a reduction in the scattering intensity of HeP-2 cells. Hence, a new light scattering nanoprobe made from selenium nanoparticles with light-producing power of 1.34×10^3 s fluorescein molecules was synthesized, which exhibited good stability, biocompatibility, hypo-toxicity, and good scattering features, making it a potential light scattering probe to be used in DFM imaging. Selenium nanoparticles with aptamer conjugation were proven to be a promising material in DFM imaging as they effectively targeted NCL, which is overexpressed in cancer cells.³⁴⁴

4.2.5. Detection of epigenetics using selenium nanoparticles. The study of gene expression heritable changes that do not include the changes to the fundamental sequence of DNA is known as epigenetics, which plays a crucial role in cancer growth. Epigenetic factors such as epimodification of DNA, expression of non-coding RNA (ncRNA), and post-translation modification (PTM) of histone control epigenetic changes.^{345,346} Presently, targeted therapy for epigenetic changes is the ideal type of cancer therapy. The use of selenium and its compounds for human health has been reviewed, and research has proven that selenium and its compounds can effectively control all three epigenetic controls and can affect the epigenome of a cell.³⁴⁷ Organic and inorganic selenium compounds (MSC, MSA, seallylselenocysteine, SeMet, and selenite) potentially restrict DNA methyltransferases and histone deacetylases activities, which are up-regulated in cancer cells. The mechanism by which selenium compounds inhibit the epigenetic factor is a bit peculiar depending on their chemical forms.^{348,349} The inorganic (selenite) and organic (MSA) forms were epigenetically affecting recognized gene sets when tested in human chronic myeloid leukemia K562 cells by genome-wide analysis. It was observed that the genes controlling oxygen and hypoxia were affected by inorganic selenium (selenite), whereas organic selenium (MSA) affected the genes responsible for glucocorticoid receptors and cell adhesion.³⁵⁰ Although the epigenetic effects of selenium nanoparticles and their mode of the mechanism on gene expression are still unknown, in the future, diagnosis utilizing selenium nanoparticles for the detection of epigenetic factors can be widely studied and possibly play a crucial role in the early diagnosis of cancer.

5. Potential role of selenium nanoparticles in the current pandemic

At the beginning of December 2019, several undetermined pneumonia-like cases started to occur in the Wuhan City of Hubei Province. When studied deeply, it was revealed that the causative agent was a new and evolved strain of Coronavirus, which was named COVID-19, but now it is known as Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2).³⁵¹ The outbreak of the ongoing coronavirus, namely, MERS-CoV and SARS-CoV-2, has led to a global pandemic by endangering human life and has seriously challenged the continuously increasing population, public health, and sanitation facilities. The wide spread of this virus at high speed has caused researchers to immediately start working on developing diagnostic methods for this infection, developing suitable vaccines, and therapeutics options originating from nanotechnology. In the case of vaccine development, the production of viral vaccines is quite complicated due to the life-cycle stages of viruses, which have varying replication stages in assorted sub-cellular organelles, quick development of multidrug resistance, etc., making the development of a perfect viral vaccine time-consuming. Over the last few decades, the emergence of new disease-causing agents, mainly viruses such as acute respiratory infections, human immunodeficiency virus, parainfluenza virus, adenovirus, human bocavirus, enterovirus, and human metapneumovirus, together with the re-emergence of some evolved viruses such as the varicella-zoster virus, and influenza virus has been reported as leading causes of death worldwide.^{352–355} During the sudden breakouts of diverse novel pathogenic microorganisms, the most crucial challenge and clinical threat are the lack of immunization and therapy for viral infections. As discussed above, acute respiratory infections are caused by infecting the lower respiratory tract, which is the major cause of the increase in the mortality rate, as the pathogens are transmitted to the host through air-borne transmissions, direct droplets, and aerosols. The easiest portal to travel for many viruses such as the influenza virus, rhinovirus, respiratory syncytial virus, parainfluenza virus, and currently, SARS is through human mucosa. It has been observed that illness in the lower respiratory tract has become the major cause of human mortality and morbidity by observing approximately 3 million deaths annually worldwide.^{356–358} The respiratory virus infection generally causes problems for new-born infants, children, older people, and immunocompromised patients. It has been noted that the acute respiratory illness among children that is mainly caused by the parainfluenza virus and/or respiratory syncytial virus has increased the rate of hospitalization in the pediatric section.^{359–361}

SARS is considered a hazardous form of bronchopneumonia and is caused by SARS-CoV-2, and it primarily targets the human respiratory system. A detailed classification of all the CoV viruses (SARS-CoV, MERS-CoV, and SARS-CoV-2) known is illustrated in Fig. 12.³⁶² According to the WHO, the Middle East respiratory syndrome “(MERS)-CoV” occurred as a universal outbreak in 2012, affecting more than 27 countries. By the end

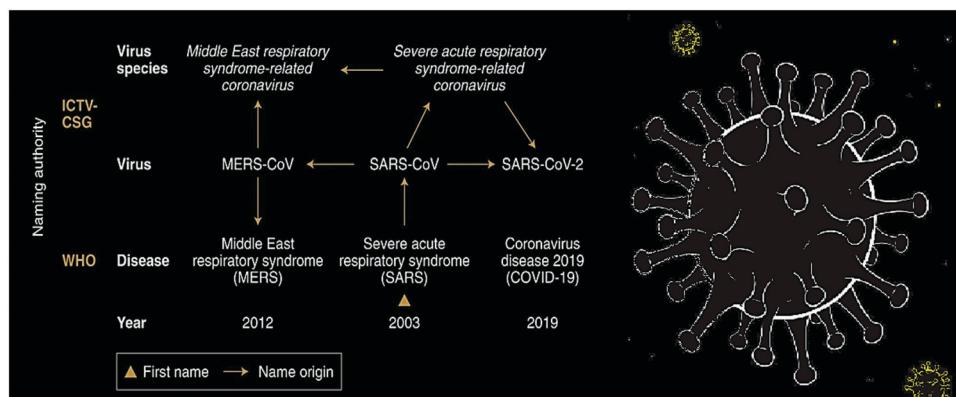


Fig. 12 Classification of SARS-CoV, MERS-CoV, and SARS-CoV-2 (reproduced with permission from M. Nasrollahzadeh, et al., *Nanomaterials*, MDPI, 2020 (ref. 362)).

of 2019, SARS-CoV-2 was detected by researchers, and due to its high infection rate, it was declared a global pandemic. However, it is observed that the infection rate of SARS-CoV-2 is very high, both for older adults and people suffering from morbidities such as cardiovascular/coronary heart illness, hypertension, and diabetes.

The enhancement, upgrading, and applications of atomic or molecular structures at the nano-level from approximately 1–100 nm with variable compositions, shapes, morphologies, sizes, etc. are referred to as nanotechnology.^{363–365} Nanoparticles play an enormous role in biomedical applications such as pharmaceutical application, drug delivery, and anti-cancer and anti-microorganism activity and without exposing healthy tissues/cells. Due to their anti-microorganism property, nanoparticles exhibit enormous potential towards anti-virality by detecting viral illness at an early stage, sensitive imaging, targeted drug delivery, etc. Some commendable examples of nanoparticles being utilized as anti-viral compounds are the delivery of nanovaccines to specific diseased organs/tissues/cells by using engineered nanomaterials and their capability to interact with other biomolecules and inhibit the binding of virus particles with the host cells. Besides their small size, nanomaterials can co-transport antigens, which occur by numerous mechanisms. The proper delivery of the drug to the correct place together with an appropriate concentration in a given period are some properties that are necessary, but it should not cause any off-target effects or any other side-effects.

The distinctive anti-microbial properties of selenium nanoparticles have caused them to gain considerable attention.^{366–368} Selenium is an integral component of many selenoproteins, which regulate several important biological processes such as inhibition of ROS and adjustment of specific enzymes. It is also found as an essential nutritional microelement in the human body and is regulated by cellular redox homeostasis. Selenium deficiency can lead to decreased immunity, resulting in greater sensitivity towards respiratory and virus infections.³⁶⁹ Research has proven that apoptosis initiation is through caspase-3 activation, which is the first step of apoptosis, and therefore is important for the cleavage of several apoptotic caspases and proteins.^{272,370} The activation of caspase is initiated by breaking

two protein fragments and cleaved caspase-3, which is mainly responsible for the proteolytic cleavage of many proteins. The anti-viral activity of selenium nanoparticles has been widely explored for suppressing the viral replication of hepatitis-B.³⁷¹

Furthermore, when selenium nanoparticles were loaded with ribavirin (RBV), they destroyed the H1N1 influenza virus by preventing the apoptosis initiated by H1N1 influenza virus infection through the caspase-3 signalling pathway.³⁷² In another approach, selenium nanoparticles were loaded with oseltamivir or amantadine, which hindered the growth of the influenza virus when tested *in vitro*,^{373,374} and further, selenium nanoparticles were found to decrease the cytopathic effect of the type-1 dengue virus.³⁷⁵ It was also found that selenium nanoparticles strongly initiated a Th-1 cytokine pattern with hepatitis B virus vaccination. Since the spread of coronavirus in the community has been increasing rapidly each day, it is essential to synthesize easy detection methods, where one of the successful methods for the diagnosis of coronavirus is by detecting the antibodies produced by SARS-CoV-2 with the help of lateral flow immunoassay, which has been found to be useful for both symptomatic and asymptomatic patients. A study showed the rapid detection of the SARS-CoV-2 antibody, mainly IgM + IgG, by utilizing selenium nanoparticles, which gave the

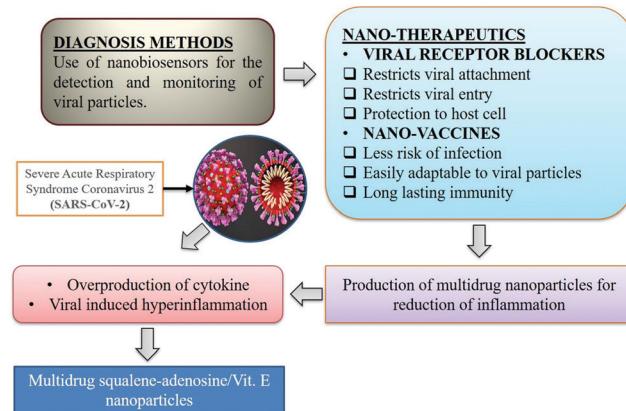


Fig. 13 Biomedical role of selenium nanoparticles with respect to SARS-CoV-2.

result in 10 min and provided the sensitivity and specificity of 94.74% and 95.12%, respectively. The key features exhibited by the developed biosensor based on selenium nanoparticles for SARS-CoV-2 detection were portability, good speed, no use of special devices, and the readout presented in a simple colour change, which can be observed by naked eyes. This kit proved to be suitable for the rapid and real-time detection of the SARS-CoV-2 antibody.³⁷⁶ Therefore, to effectively control and manage the ongoing and future outbreaks, extraordinary breakthrough ideas, smart and intelligent management, and the use of new advanced technologies, utilizing nanotechnology particularly, can be very successful. Fig. 13 shows the potential behaviour of selenium nanoparticles in the diagnosis and therapeutics of viral infections.

6. Conclusion and prospects

Nanotechnology is a new branch of science that mainly deals with very small-sized particles, ranging from 1–100 nm. Nanobiotechnology is a combination of nanotechnology with biology, which produces enhanced eco-friendly and biocompatible products that are beneficial for humankind and the environment. This field has gained limelight from the day it evolved in the biomedical domain.

One of the most explored nanomaterials is selenium nanomaterials, whose atomic number is 34 and is present in the Group 16 of the periodic table. Selenium is a basic element in the body and is an essential nutrient, which should be taken through diet. The human body plays a vital role in many catalytic enzymatic reactions inside the cell involving super-oxide (O^{2+}), hydrogen radicals, lipid perhydroxides, etc.²⁸ Selenium nanomaterials show distinct properties such as optical properties, catalytic behaviour, and radical production, which have made them potential nanomaterials to be used in various domains such as the medical, environmental, and industrial fields. This review focused on the various roles of selenium nanoparticles in the biomedical domain, especially in therapeutics and diagnostics. Besides, modernization is increasing the risk of acquiring many types of lifestyle diseases,³⁷⁷ and the unique redox properties of selenium nanoparticles help them be exploited for the treatment of these diseases such as cancer and Alzheimer's disease. However, a detailed study is still required to fill the gap of knowledge between elemental selenium and selenium nanoparticles to explore their potential in the biomedical domain. Moreover, a prior-art search in different scientific databases such as PubMed and Google Scholar gave few literature studies available related to drug and gene delivery systems based on selenium nanoparticles, and therefore this opens a new avenue for the researchers in the materials science, nanobiotechnology, nanotechnology, and chemistry fields to research this application.

Since the ongoing pandemic has given a big pause in our busy lives, herein, we also highlighted the beneficial and potential role of selenium in combating various types of present and future pandemics, where the potential of selenium

nanoparticles has been proven for SARS-CoV-2 diagnosis. Further, we suggested that researchers should focus on engineering selenium nanoparticles by functionalizing them with synthetic biomaterials (xeno-nucleic acids, peptide nucleic acids, morpholino, etc.)^{378,379} or by forming conjugates with other metal and metal oxide nanoparticles (magnesium, magnesium oxide, cerium, cerium oxide, etc.)^{380,381} and these functionalized selenium nanoparticles will have enhanced potential properties that will offer them more beneficial biomedical applications and can also be used as an anti-viral agents. Besides, the nanoforms of selenium are non-toxic, and when taken orally, have proven benefits to increase immunity, anti-inflammatory reactions in the body. The future of selenium is still left to be explored, as in the case of the agriculture and environmental domains, and data pertaining to the role of selenium nanoparticles is still lacking or in the very infancy phase, which can be further explored and enhanced.

Author contributions

Mr Kshitij R. B. Singh contributed by conceptualization, data curation, investigation, resources, validation, visualization, and writing an original draft. Miss Vanya Nayak contributed by data curation, resources, visualization, and writing original draft. Dr Ajaya Kumar Singh contributed by conceptualization, validation, project administration, supervision, and reviewing & editing the manuscript draft. Ravindra Pratap Singh contributed by conceptualization, validation, project administration, supervision, and reviewing & editing the manuscript draft.

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Conflicts of interest

Author's declare no conflict of interest for this work.

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