UNIVERSIDAD DE INVESTIGACIÓN DE TECNOLOGÍA EXPERIMENTAL YACHAY

Escuela de Ciencias Biológicas e Ingeniería

Biogenic Selenium Nanoparticles in Biomedical Sciences: Properties, Current Trends, Novel Opportunities and Emerging Challenges in Theranostic Nanomedicine of Selenium.

Trabajo de integración curricular presentado como requisito para la obtención del título de Ingeniera Biomédica.

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DEDICATORIA

Dedico este trabajo primeramente a Dios por permitirme culminar con éxito mi carrera universitaria, darme esperanza y fe en los momentos más difíciles. A mis padres Mario Zambonino y Consuelo Soria, que han sido un gran ejemplo de superación y que junto a mi hermano Mario Zambonino, me han apoyado a lo largo de este camino. A mis queridas tías, mis primos, y mis abuelitos Juanita, Nena y Humbertito.

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RESUMEN

En los últimos años, la nanotecnología ha revolucionado las estrategias sanitarias aportando notables avances en el diagnóstico, tratamiento y prevención de enfermedades. Debido a sus propiedades únicas como la biodisponibilidad mejorada y la toxicidad significativamente reducida, las nanopartículas han ganado un gran interés en la investigación del sector biomédico actual. El selenio (Se) es un importante suplemento dietético y un oligoelemento esencial incorporado en selenoproteínas con propiedades moduladoras del crecimiento y mecanismos citotóxicos. Aunque juega un papel vital en muchos procesos biológicos y fisiológicos, el selenio generalmente posee una ventana terapéutica estrecha con un bajo grado de absorción. Por lo tanto, las nanopartículas de selenio (SeNP) se han utilizado ampliamente como una nueva plataforma terapéutica y de diagnóstico con una toxicidad reducida y beneficios excepcionales contra el estrés oxidativo y los trastornos mediados por la inflamación. En la necesidad de desarrollar agentes biomédicos ecológicos, económicos, simples y eficientes que también puedan aliarse con propósitos teranósticos y presentar efectos secundarios insignificantes, se ha prestado especial atención a los SeNP biogénicos. Dado que estudios anteriores no han podido evaluar las posibles aplicaciones biomédicas de los SeNP biogénicos en terapia y diagnosis, la presente revisión analiza en detalle el papel del SeNP biosintetizado como un agente teranóstico innovador para tratamientos personalizados. Además, destaca las propiedades biológicas, físico-químicas, optoelectrónicas y catalíticas únicas de los Se-nanomateriales. Asimismo, aborda la importancia de la nanoescala sobre la actividad farmacológica (farmacocinética y farmacodinamia) y la interacción celular de los SeNPs. Finalmente, se explora el rol de SeNPs en el escenario actual de una pandemia (SARS-CoV-2) y presenta perspectivas a futuro en la nanomedicina traslacional.

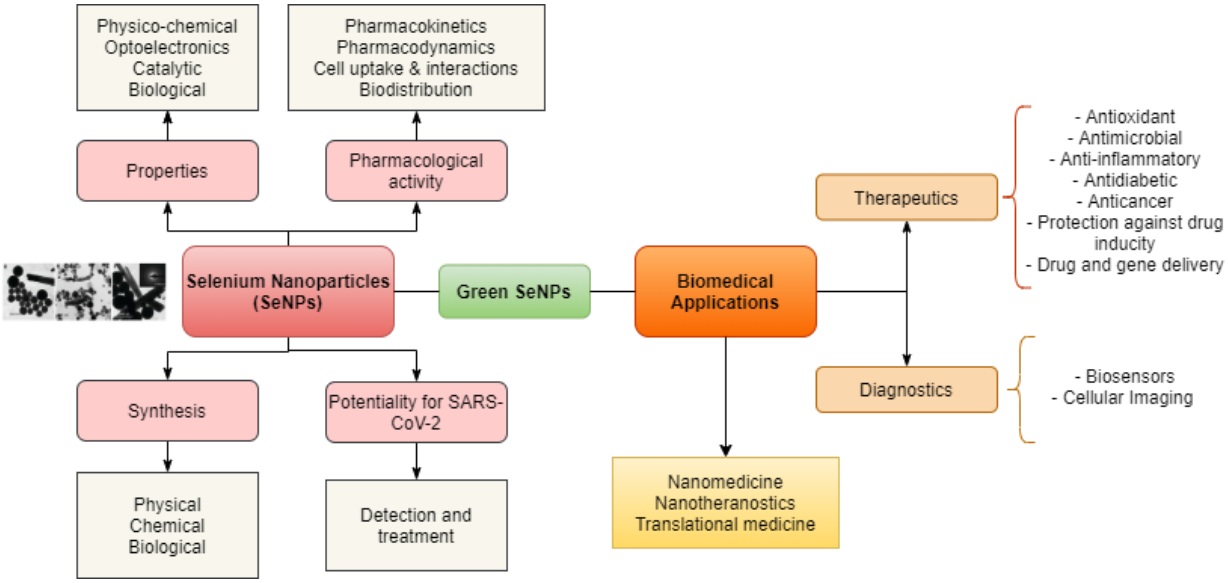
Palabras clave: Nanomedicina; SeNPS; biosíntesis; selenoproteínas, terapéuticas; diagnósticos; teranósticos; aplicaciones biomédicas.

ABSTRACT

In recent years, nanotechnology has revolutionized healthcare strategies by providing remarkable advances in the diagnosis, treatment and prevention of diseases. Owing to their unique properties including enhanced bioavailability, improved targeting, and significantly reduced toxicity, nanoparticles have gained tremendous research interest in the current biomedical sector. Selenium (Se) is an important dietary supplement and an essential trace element incorporated in selenoproteins with growth-modulating properties and cytotoxic mechanisms. Although it plays a vital role in many biological and physiological processes, Se usually possesses a narrow therapeutic window with a low degree of absorption and delicate safety margins. Therefore, selenium nanoparticles (SeNPs) have been broadly used as a novel therapeutic and diagnostic platform with decreased toxicity and exceptional benefits against oxidative stress and inflammation-mediated disorders. In the need of developing eco-friendly, inexpensive, simple and high-throughtput biomedical agents that can also ally theranostic purposes and present negligible side effects, biogenic SeNPs have received special attention. Since previous studies have failed to evaluate the potential biomedical applications of biogenic SeNPs in both therapeutics and diagnostics fields, the present review discusses in detail the role of biosynthesized SeNP as an innovative theranostic agent for personalized nanomedicine-based treatments. In addition, it highlights the unique biological, physico-chemical, optoelectronic and catalytic properties of Se nanomaterials. Furthermore, it addresses the significance of nanosizing on pharmacological activity (pharmacokinetics and pharmacodynamics) and cellular interaction of SeNPs. Finally, this review explores the role of SeNPS in the ongoing scenario of pandemic (SARS-CoV-2) and presents key future prospects in translational nanomedicine.

Keywords: Nanomedicine; SeNPS; biosynthesis; selenoproteins, therapeutics; diagnostics; theranostics; biomedical applications.

GRAPHICAL ABSTRACT



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Chapter I

1. Introduction

Nanotechnology is one of the latest challenging fields of recent research. In a broad sense, it can be defined as an emerging branch of science and engineering for designing tools and devices of 1 to 100 nm in size with specific functions at the cellular, atomic and molecular levels [1–4]. Nanomedicine is a relatively new but fast developing field that can potentially make a major impact to human health through the combination of nanotechnology-based techniques and methods with the biomedical and pharmaceutical sciences [5,6]. Thus, nanotechnology can remarkably assist the therapy, diagnosis, monitoring and control of biological systems for the further development of personalized medicine with tailored and optimized treatments [7–9]. Nanomedicine embraces nanopharmaceuticals, nanoimaging agents, and theranostics [10–13]. The interdisciplinary field of nanotechnology and nanomedicine has propelled to the forefront in investigations from academia, pharmaceutical industry, clinical organizations and several national and international funding and regulatory agencies [14,15].

Nanoparticles (NPs) exhibit unique advantages, such as small size, high surface area, low polydispersity, solubility, safety, surface charge and chemistry, easy modification and multi-functionality [16–19] (Fig. 1). In recent years, NPs have been developed to biologically interact at the molecular and cellular level with a high degree of specificity for diagnosis and treatment of diseases [20–22]. The utilization of NPs is opening new therapeutic opportunities for agents which otherwise cannot be used effectively as traditional drug formulations due to poor bioavailability and drug instability [23]. Especially, metal nanoparticles with their superior intrinsic chemical, biological, and magnetic properties have been designed for several diagnostic [24,25], therapeutic [26–28], health [29] and nutrition [30,31] applications. Most of the nanomaterials hold a great promise for integrating diagnostic and therapeutic applications, such as monitoring the biodistribution and targeted site accumulation, observing and quantifying drug release and longitudinally evaluating the therapeutic efficacy [24,32].

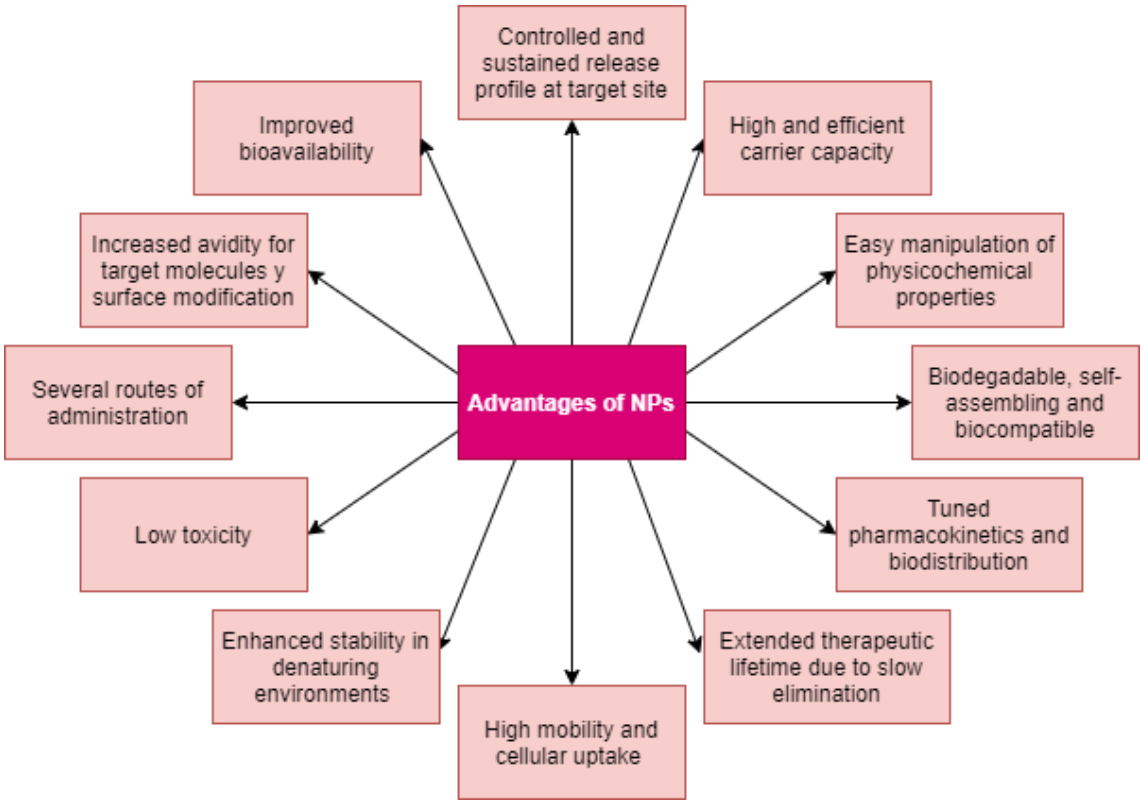

Figure 1. Main advantages of nanoparticles (NPs) in biomedicine.

Special interest has been drawn to SeNPs since selenium is an essential micronutrient for the proper functioning of human and animal body in trace amounts [33]. Selenium (Se) is an important dietary constituent of at least 25 human selenoproteins and enzymes containing selenocysteine [34–36]. The atomic number of Sse is 34 and belongs to the Group-6 in the periodic table. In the environment, Se exists in various oxidation states (2^-, 0, 2^+, 4^+, 6^+) and forms like selenate (Na_2SeO_4), selenite (Na_2SeO_3), selenomethionine (SeMet), selenocysteine (SeCys), and solid state Se (0) [37,38]. The nanoform of Se has attracted a great deal of interest worldwide due to its high degree of absorption, great bioactivity, low toxicity and high efficiency in preventing oxidative damage compared to its organic and inorganic counterparts [39,40]. SeNPs have demonstrated to possess extraordinary anticancer [41–43], antioxidant [44,45], antidiabetes [46,47], antibacterial and antibiofilm properties [48–50], as well as diagnostics applications such as nanosensors, cellular imaging, epigenetics and immunochromatography [51–53]. SeNPs can be fabricated through different physical, chemical, and biological (bacteria, yeast, plants, microalgae) techniques. Nevertheless, biological synthesis remains the widely accepted alternative that has received unrivalled focus in SeNPs [34,54–57]. Green nanotechnology is described as the methods that eliminate or reduce the utilization of lethal or toxic substances resulting in cost-effective and eco-friendly alternatives [58,59]. Further, biogenic SeNPs are highly biocompatible and stable due to natural coatings of biomolecules that prevent aggregation,

avoid extra use of chemical stabilizers, improve the pharmacological activity and protect against physical and chemical degradation [60–63].

The translation of selenium-based nanotechnology to clinical applications requires not only the development of safe, simple, sustainable, and cost-effective methods for the synthesis of SeNPs, but also a thorough understanding of the related physicochemical and biological properties, in vitro and in vivo effects, biodistribution, safety control mechanisms, pharmacokinetics and pharmacodynamics and potential biomedical applications of SeNPs. Despite the advances in the research of biogenic SeNPs to implement a safe-by-design principle to ensure safety for both human health and the environment, there is no review compiling this information. Also, previous researches of SeNPs have only discussed individual aspects such as synthesis, properties and biomedical applications. Therefore, this study attempts to fill this gap by providing a comprehensive and up-to-date review of the theranostics (diagnostic and therapeutic) applications of biosynthesized SeNPs and their potentiality in translation of nanomedicine. Furthermore, the properties, synthesis, and pharmacological activity of SeNPs focused on the molecular mechanism, cellular interaction and role of selenoproteins are presented. In addition, the diagnostic and therapeutic usefulness of SeNPs in the recent scenario of the current pandemic Covid-19 is explored.

2. Methodology

To accomplish this study, a variety of databases such as PubMed, Embase, MEDLINE, and Google Scholar were employed. The focus research was on articles published in the ten last years (2010-2021) to perform an up-dated comprehensive review. The literature search strategy was developed by two ways:

- Manually search in Google Scholar to find specific articles.
- Using two basic Boolean operators (AND/OR) and a combination of keywords including “selenium”, “nanoparticle”, “nanomaterial”, “Nano-selenium”, “Nano-Se”, “nanostructure”, “synthesis”, “biosynthesis”, “green”, “bioreduction”, “biofabrication”, “microorganisms”, “bacteria”, “yeast”, “fungi”, “microalgae”, “plants”, “plant extract”, “cytotoxic”, “bioapplications”, “nanomedicine”, “anticancer”, “antidiabetic”, “antibacterial”, “antibiofilm”, “antiviral”, “” “protection”.

Chapter II

3. Problem statement:

Selenium is a metalloid mineral micronutrient, essential for numerous biological and physiological processes in humans, animals, plants and microorganisms. Nevertheless, its narrow therapeutic window prevents its use to treat and diagnose emergent diseases. Excess amount of selenium is harmful for various organs such as the liver, kidney and heart, whereas selenium deficiency produces serious issues like infertility, muscle problems and weakened immune system. Nanobiotechnology has developed nano-selenium as a potential solution to solve the main problem of the translation of selenium into clinical applications with novel properties such as high biocompatibility and low toxicity. Therefore, it is necessary to understand the safety concerns, biological activity and the therapeutic purposes of SeNPs for preclinical and clinical studies.

4. Objective:

To develop an up-dated and comprehensive review of the research on the main biomedical applications of biosynthesized Se nanoparticles, highlighting the therapeutic and diagnostic effects.

5. Specific Objectives:

- Describe the most relevant properties (physicochemical, catalytic and biological) of selenium and selenium nanostructures.
- Discuss the potential antioxidant and pro-oxidant role of SeNPs.
- Summarize the principal methods used for the synthesis of SeNPs: chemical, physical and biological.
- Discuss the pharmacological activity of SeNPs including the cellular uptake, pharmacokinetics, pharmacodynamics, and biodistribution.
- Comment on the importance of green nanotechnology for SeNPs bioapplications and their clinical translation.
- Analyze the main contributions of biogenic SeNPs as theranostic nanoplatforms in biomedical sciences focusing on therapeutics and diagnostics.
- Examine the key role of SeNPs for the SARS-CoV-2 diagnosis.

Chapter III

6. Selenium and Nanoselenium: General Information

Nanotechnology has been found as an extraordinary platform of technical solutions for complex medical challenges. Nanomedicine involves nanotherapeutics [4], nanopharmaceuticals [64], nanoimaging agents [65,66], and theranostics [28]. Precise nanomedicine offers great physical and biological benefits compared to conventional medicines like enhanced efficacy, improved pharmacokinetics (PK) and safety, reduced toxicity and increased tissue selectivity of drug formulations [5,67]. Particularly, for selenium (Se), the major problem from bench to bedside translation is the narrow window from therapeutic effect to toxicity due to the small margin of dosage error [68]. Selenium is an essential nutrient in the human and animal body for endocrine, reproductive, cardiovascular and immune processes. It also acts as a pleiotropic agent associated with biotherapy and drug delivery for a better immune response and cancer prevention [69].

The inorganic forms of Se are selenite (SeO_3^{2-}), selenate (SeO_4^{2-}), selenide (Se^{2-}) and elemental Se (Se^0); the organic forms are selenomethionine (SeMet), selenocysteine (Se-Cys), and methylselenocysteine (Me-Cys) [68]. Moreover, Se is a principal constituent of some selenoenzymes such as glutathione peroxidases (GPXs), thioredoxin reductases (TXNRDS) and deiodinases (DIO) that are essential for biochemical reactions of biological defense system including the antioxidant activity [70]. Se biogenic compounds can be found in living organisms in methylated species, selenoamino acids, selenoproteins, selenium peptides, selenoenzymes, selenoaminocarboxylix acids and selenium derivatives of pyrimidine, purine, coenzyme A, cholines, steroids, among others [71]. Most of these conformations play an important role in the organism defense against oxidative stress [35]. They have remarkable antioxidant and pro-oxidant effects limited by the dose, life span, chemical form of selenium compound, route of administration and the oxidation state [72,73]. A classification of many Se compounds is presented in Table 1.

Table 1. Classification of Se compounds based on structural features.

Selenium compound	Type
Selenoaminoacids	Selenomethionine (SeMet);
	Methylselenocysteine (MeSeCys)
	Selenocysteine (SeCys)
	Selenocystamine

Se-heterocyclic compounds	1,3-Selenazolin-4-one derivatives
	2-Phenyl-1,2-benzisoselenazol-3(2*H*)-one (ebselen)
	2,5-Bis(5-hydroxymethyl-2-selenienyl)-3-hydroxymethyl-*N*-methylpyrrole (D-501036)
	1,2-[Bis(1,2-benzisoselenazolone-3-(2*H*)-ketone)]ethane (BBSKE)
	2-Cyclohexylselenazolidine-4-(*R*)-carboxylic acid (ChSCA)
	2-Buthylselenazolidine-4-(*R*)-carboxylic acid (BSCA)
Selenocyanates	Isatin analogs
	Diphenylmethylselenocyanate
	1-4-phenylenebis(methylene)selenocyanate (*p*-XSC)
	TMZ-Se
	5-phenylcarbamoylpentyl selenocyanide (SelSA-2)
Selenides	Methylimidoselenocarbamates
	5-Phenylselenyl-methyl-2'-deoxyuridine (PhSe-T)
	5-Methylselenyl-methyl-2'-deoxyuridine (MeSe-T)
	β-selenium amine derivatives
	Se,Se'-1,4-phenylenebis(1,2-ethanediyl) bisisoselenourea (PBISe)
Diselenides	Bis(4-aminophenyl)diselenide
	Bis(5-phenylcarbamoylpentyl) diselenide (SelSA-1)
	Diselenodipropionic acid (DSePA)
	2-Selenium-bridged β-cyclodextrin (2-SeCD)
Se (IV) compounds	Sodium selenite (Na2SeO3)
	Selenous acid
	Methylseleninic acid (MSA)
	Selenium dioxide (SeO2)

However, traditional Se supplements usually possess a low degree of absorption and enhanced toxicity [53]. Then, Se has become a controversial nutrient because high quantities become toxic, provoking death, whereas too small quantities can produce chronic and fatal deficiencies, such as diabetes, thyroid dysfunction, arthrophyma, Keshan disease and cognitive problems [69,74]. The toxicity of Se has been tracked for decades, showing that low levels of Se content produce efficacious anticarcinogenic activity and high levels can generate carcinogenesis, cytotoxicity and genotoxicity (Fig. 2) [75,76]. Indeed, there is some scientific consensus that the high pro-oxidant property of different redox-active forms of selenium compounds is the key actor to combat cancer, demonstrating their high efficacy and selectivity [77]. For example, Se-methylselenocysteine (SMC) and methylseleninic acid (MeSeA) were found to be potential anticarcinogenic selenocompounds with little toxicity and high bioavailability as indicated by the increased glycoprotein selenoprotein P (SEPP) biosynthesis [78]. Cao et al. (2014) reported the remarkable antitumor activity of SMC in pre-clinical trials when combined with four different

cytostatic drugs (cyclophosphamide, cisplatin, oxaliplatin, and irinotecan), offering protection against organ-specific toxicity. Moreover, Selenocystine (SeC), a naturally occurring selenoamino acid, may be a promising anticancer candidate as shown in combination with 5-fluorouracil by enhancing apoptosis in A375 human melanoma [80].

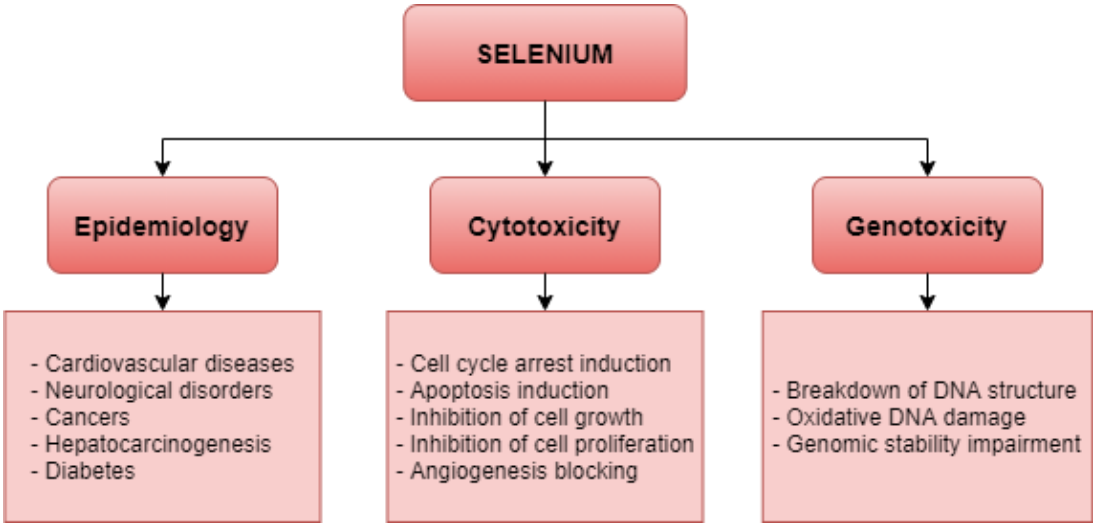

Figure 2. Selenium toxicity in humans and animals: cytotoxicity, genotoxicity, epidemiology.

However, the anticancer activity of Se is not fully demonstrated yet, including the in vivo therapeutic efficacy. The main challenge is the delivery of specific concentrations of redox active selenium directly to the target site (tumor or metastatic cells) to execute the cytotoxic effect [81]. In the need to create innovative systems to upgrade the bioavailability and the controlled release of selenium, much attention has been drawn to nanoscale selenium. Nanoselenium (Nano-Se) has appeared as the answer for the toxicological concerns due to its novel properties including high-specific surface area, high degree of absorption and less toxicity compared to inorganic and organic forms [39,53]. The benefit of Nano-Se is the alternative of utilizing elemental selenium in zero oxidation state Se (0), which has significantly lower toxicity without affecting the ability of upregulation of selenoenzymes at nutritional levels and induction of phase II enzymes at supranutritional levels [82]. Nano-Se which is bright red, highly stable and soluble, has been developed for pharmaceutical and medical applications due to its anticancer, antimicrobial, antioxidant, and antidiabetic effects [83,84]. Although Se (0) is unstable and easily reoxidized into inactive forms, proteins and polysaccharides are mainly used as nano-vehicles: chitosan [44,85], egg white lysozyme [86], beta-lactoglobulin (Blg) [87], acacia gum (ACG) and carboxymethyl cellulose (CMC) [88].

Prior research has thoroughly investigated the effects of Nano-Se at cellular and tissue levels, for example, in type 2 diabetes mellitus (T2DM) treatment [68], immune and antioxidative responses [89,90], atherosclerosis treatment [91], and semen quality and testis ultrastructure study

[92]. Several studies have indicated that Nano-Se is gaining attention as dietary supplements and therapeutic agents [71]. In addition, its immunostimulatory [57] and protective effects against metal intoxication [93–95] have been well documented. Sheiha et al. (2020) reported the effects of Nano-Se supplementation on growth performance, kidney and liver functions, carcass traits, antioxidants indices, and inflammatory cytokines of growing rabbits during thermal stress. Furthermore, Tran et al. (2010) combined the carcinostatic activity of Se nanoclusters with the mechanical properties of titanium to build a new anticancer bone implant. Bartůněk et al. (2019) evaluated the use of nano-selenium-PEG composite network for specific antimicrobial coatings. In addition to the above-mentioned studies, SeNPs were used as coatings to inhibit biofilm formation [50,99,100]. Some of the properties of SeNPs found in scientific research are summarized in Fig. 3.

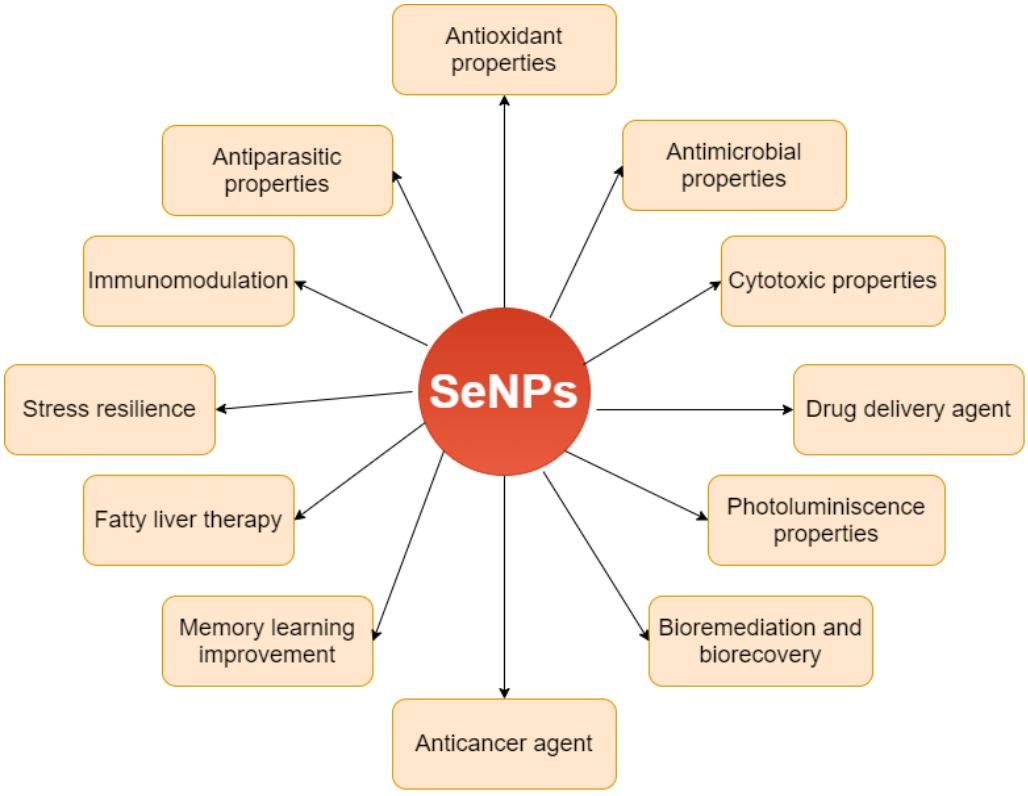

Figure 3. Schematic diagram that shows the principal properties of SeNPs.

7. Materials and Methods used for the Synthesis of SeNPs

Selenium nanoparticles (SeNPs) offer some advantages over bulk materials such as higher biological activity, stronger catalytic efficacy, greater bioavailability, lower toxicity, more surface activity and higher particle dispersion [101]. The ultimate outlook of precise nanomedicine has been the design and construction of intelligent nanoparticles for future clinical translations. However, the ability to fabricate nanoparticles free of any toxic or hazardous

substance is very challenging, especially for applications in nanomedicine. Various chemical, physical and biological methods to synthesize SeNPs will be reviewed.

7.1 Physical Methods

The physical techniques include microwave irradiation, ultraviolet irradiation, laser ablation and ultrasonic field treatment [83]. Yu et al. (2016) showed the synthesis of bright red selenium nanoballs, nanotubes and multi-armed nanorods of diameter ranging from 20 to 130 nm via a microwave assistant approach. According to the results, the L-asparagine/H_2SeO_3 concentration ratio and the irradiation time controlled the diameter and morphology of selenium nanoparticles. Similarly, [103] fabricated pure hexagonal SeNPs by employing microwave irradiation with aid of selenium tetrachloride as an initiating reagent in distilled water. El-Batal et al. (2020) reported the synthesis of aqueous dispersed Se NPs using gamma rays with the aid of various natural macromolecules such as citrus pectin (CP), sodium alginate (Alg), chitosan (CS) and aqueous extract of fermented fenugreek powder (AEFFP). Moreover, Lara (2018) documented that the SeNPs were synthesized by irradiating selenium pellets in a technique based on the nanosecond pulsed laser ablation in liquid chitosan as a capping agent. Similar studies reported on the fabrication of Se nanostructures by laser ablation to analyze the antibacterial effect [105–107].

In addition, Luesakul et al. (2016) fabricated cubic-like SeNPs employing a self-assembly process and Panahi-Kalamuei et al. (2015) synthesized SeNPs via a sonochemical (ultrasonic) method using $SeCl_4$ as starting precursor and hydrazine, potassium borohydride, and thioglycolic acid as reducing reagents. Physical procedures offer advantages over the chemical ones, since these often require a calcination step at the end of the process, which makes them unsuitable for targeted applications [53]. Nevertheless, physical procedures are not frequently used to fabricate SeNPs.

7.2 Chemical Methods

Chemical synthesis of SeNPs is the most conventional method that comprises the reduction of metal salts using chemical reducing agents in aqueous or organic media [110]. The chemical reduction of metal salts in the presence of stabilizers to avoid particle aggregation is of current interest for the fabrication of metal NPs [111,112]. It is basically a time-saving strategy but highly expensive and environmentally harmful [113]. Several authors have shown the chemical synthesis of SeNPs [41,48,114]. A solution-phase approach fabricated monodispesed spherical SeNPs of 20 nm by reducing selenious acid solution using ascorbic acid and water-soluble polysaccharides, such as chitosan (CTS), konjac glucomannan, acacia gum, and carboxymethyl cellulose [88]. Another solution-phase approach synthesized spherical narrowly size distributed SeNPs of 46 nm by reducing selenium tetrachloride in the presence of ascorbic

acid [115]. Moreover, the electrochemical synthesis using selenium powder doped carbon paste electrode was confirmed to be a versatile and facile approach to produce spherical SeNPs of 85, 43 and 60 nm. A simple wet chemical method by employing a reaction of ionic liquid with sodium selenosulphate was reported [116]. The resulting SeNPs were spherical in the size range of 76–150 nm.

It has been extensively explored the use of CTS as an effective material to synthesize nanoparticles due to its exceptional properties of biocompatibility, biodegradation and resistance to certain enzymes [117]. CTS has potential applications in diversified biomedical fields such as tissue engineering, drug delivery, wound healing, and gene therapy [118]. For example, crystal SeNPs spheres were manufactured in aqueous chitosan and then embedded into CTS microspheres through a spray-drying method [119]. The authors revealed a new path for oral delivery of Se with a higher efficient and better biosafety. Luo et al. (2010) showed the successful selenium nanoencapsulation in CTS with decreased toxicity, enhanced antioxidant activity and controlled release in vitro. Zhang et al. (2011) assessed the effects of selenium-loaded CTS nanoparticles in cellular selenium retention, cell survival and DNA damage response to selenium exposure. This study contributed to the investigation of novel selenium delivery systems with high specificity and low toxicity for dietary and therapeutic applications.

To explain why SeNPs are promising candidates for the treatment of cancer, Cui et al. (2018) synthesized ferulic acid modified SeNPs of 105 nm via a low-cost and simple synthetic approach, and investigated its antitumor properties and DNA-binding affinity. Moreover, a novel room-temperature procedure fabricated SeNPs using selenium oxide as precursor and lignosulfonate as a stabilizer [122]. The authors presented a facile method that may be useful for the large-scale preparation of SeNPs.

7.3 Biological Methods

7.3.1 Biosynthesis Using Microorganisms

The synthesis of SeNPs via biological procedures, the so-called green synthesis or sustainable synthesis, is getting more attention in comparison to physical and chemical methods. Researchers have found that some biological sources such as microbes, plants, seaweeds, among others can be cost-effective for NPs synthesis, have fewer side effects, and comprises a one-step method [123]. The process typically reduces selenite (Se(IV)) or selenate (Se(VI)) species into elemental selenium (Se(0)). In recent years, the biosynthesis of Se-containing NPs using harmless bacteria has been reported as a new environmentally-friendly route that offers tremendous advantages, such as easy handling, short synthesis times and simple genetic manipulation [124]. Various bacteria reduce inorganic selenite (SeO_3^{2-}) and/or selenate (SeO_4^{2-}) to elemental red selenium Se(0) nanoparticles of various morphologies including spherical, hexagonal, polygonal

and triangular nanoparticles [125]. The academic community has extensively explored the aerobic and anaerobic bacteria involved in the production of SeNPs. There are various reduction pathways in bacteria under both aerobic and anaerobic conditions [126–131]. However, further investigations are required to fully determine the underlying biochemical pathways and the biochemicals that govern these processes. The general process of biofabrication through SeNPs is shown in Fig. 4.

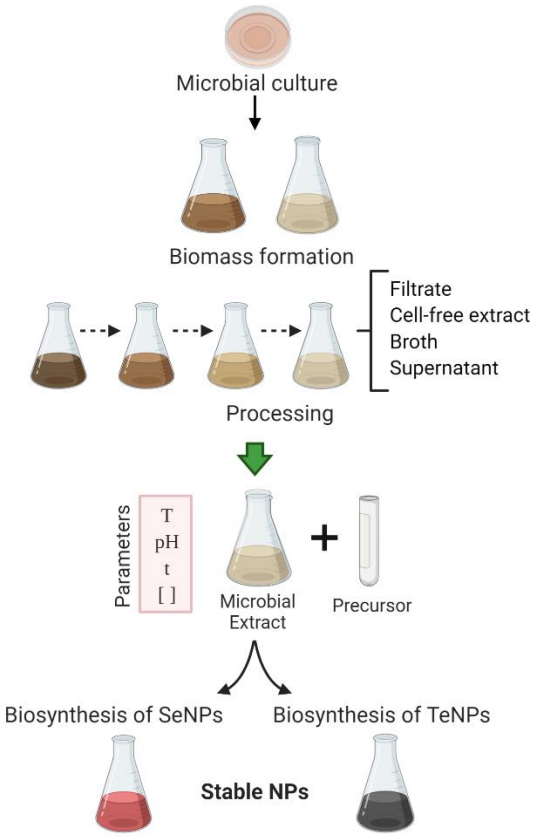

Figure 4. Biosynthesis of metalloid NPs: Se Nanoparticles (SeNPs) and Tellurium Nanoparticles (TeNPs)

Estevam et al. (2017) produced SeNPs intracellularly using Staphylococcus carnosus TM300 that were harvested by first sonicating the pellet and then separating the NPs by subsequent centrifugations. Cocktails of proteins were attached to the SeNP surface to act as potential natural stabilizers that prevent the formation of precipitates at the bottom of the flasks. Moreover, these SeNPs exhibited nematicidal activity against the non-pathogenic nematode S. feltiae and biological activity against E. coli and S. cerevisiae for bacterial and yeast infections. Wadhwani et al. (2018) detailed the process of SeNPs synthesis by challenging the cell suspension and total cell proteins (TCP) of Acinetobacter sp. SW30 with sodium selenate. This cell suspension formed spherical SeNPs of 78 nm after 6 h incubation and transformed into rod-like structures after 48 h. These selenium structures were observed at different pH values (ranging from 6-10) and precursor

concentrations (1.5 mM and 3.0 mM) (Fig. 5.). On the other hand, polygonal-shaped SeNPs of 79 nm in size were obtained in the supernatant at 4 mg mL^{-1} of TCP.

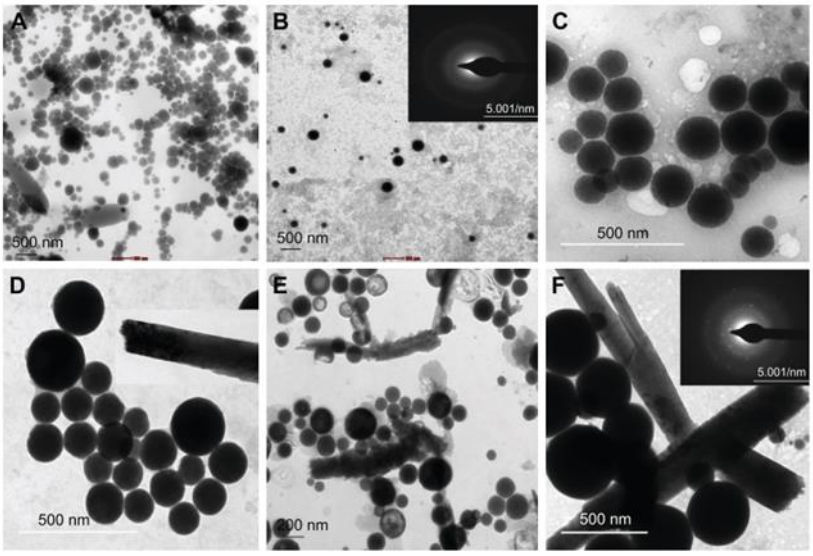

Figure 5. TEM micrographs of SeNPs biofabricated with Acinetobacter sp. SW30 at 37 °C in 1.5 mM Na_2SeO_3 concentration incubated at: (A) pH 6, (B) pH 7 and (C) pH 9. TEM micrographs of SeNPs synthesized at 37 °C using 3.0 mM Na_2SeO_3 incubated at: (D) pH 6, (E) pH 7 and (F) pH 9 (Reproduced from Wadhwani et al. 2018).

7.3.2 Plant-mediated Synthesis

Several papers have reported the plant-derived SeNPs with varying sizes and morphologies (Table 4). For instance, Hibiscus sabdariffa fabricated spherical, triangular and hexagonal SeNPs with a size of 20-50 nm [133], whereas Azadirachta indica has been used as a rapid and efficient biosystem to produce crystalline and spherical SeNPs with a smooth surface [134]. *Withania somnifera* was the best adaptogen herb with active withanolide and flavonoids, used as a bio-reductant system to fabricate SeNPs of 40-90 nm [135]. Although plants offer the most suitable green synthesis protocols, the mode of action of plant-produced SeNPs against bacteria remains unknown; it is suggested that the nanoparticles interact with the peptidoglycan layer and break up the bacterial cell wall [136]. The SeNPs are able to induce apoptosis or programmed cell death [137]. Anu et al. (2016) reported spherical SeNPs produced by a cheap aqueous extract of garlic cloves, A. sativum, that acted as both the reducing and capping agent. These biogenic SeNPs showed lower cytotoxicity against the vero cancer cell line than those chemically synthesized. Anu et al. (2020) took advantage of the medicinal properties of Cassia auriculata to prove the anticancer and antiproliferative characteristics of functionalized SeNPs. Kokila, Elavarasan, and Sujatha (2017) reported on Se-NPs using the leaves of Diospyros montana as a biocidal agent against both gram positive Staphylococcus aureus and gram negative *Escherichia coli* and the fungus *Aspergillus niger*.

Table 2. Different species of plants used for the biosynthesis of SeNPs.

Plant species	Part	Metabolite	Shape	Size (nm)	Application	Ref
Withania somnifera	Leaves extract	Flavonoids, phenolics and tannins	Spherical	40-90	Antibacterial, antioxidant and anticancer	[135]
Guava *(Psidium guajava)*	Leaves extract	N/a	Spherical	8–20	Antibacterial	[136]
Garlic *(Allium sativum)*	Cloves	N/a	Spherical	40-100	Cytotoxic activity against Vero Cells	[138]
Cassia auriculata	Leaves extract	N/a	Amorphous	10-20	Anti-leukemia	[139]
Bittermelon *(Momordica charantia)*	Roots and shoot	Terpenoid and phenolic	Spherical	10-30	Toxicological studies	[141]
Hawthorn fruit *induced (HE)*	Fruit	N/a	Spherical	113	Antitumor activity against HepG2 cells.	[142]
Bougainvillea spectabilis	Flower broth	alcohols, amines and ketones	Hollow and spherical	24.24 ± 2.95	N/a	[143]
Catharanthus roseus, Peltophorum pterocarpum	Flowers	esters, ketones, primary, secondary and tertiary amides	Spherical	23.2 ± 6.06 and 30.44 ± 2.89	N/a	[144]
Hibiscus sabdariffa (roselle plant)	Leaves extract	Phenols and alcohols	Spherical, triangular and hexagonal	20-50	Reduce oxidative damage in testicular tissue	[133]
Pelargonium zonale	Leaves extract	N/A	Spherical	40-60	Antibacterial and antifungal	[145]
Aloe vera	Leaves extract	Hydroxyl and amide I	Spherical	121-3243	Antibacterial and antifungal	[146]
Emblica officinali	Fruit extract	Phenolics, flavonoids, Tannins	Spherical	20-60	Antimicrobial	[147]
Moringa oleifera	Leaves extract	Phenolics, flavones	Spherical	23-35	Anticancer	[148]
Triticum aestivum L.	Roots	N/A	Spherical	140 ± 40	Fertilizers	[149]
Broccoli	N/A	Carotenes, glucosinolates Polyphenols	Spherical	50-150	Antioxidant and anticancer	[150]
Leucas lavandulifolia Sm.	Leaf and stem Extract	Polyphenols, alkaloid, flavones, flavonoids, alkaloids and fatty acids	Spherical	56-75	Antibacterial	[151]
Diospyros montana	Leaves extract	Phenolics, flavonoids	Spherical	4-16	Antibacterial and anticancer	[140]
Ocimum tenuiflorum	Leaves extract	Polyphenols	Spherical	15-20	Inhibitor of CaC_2O_4 urinary stones	[152]
Petroselinum crispum	Leaves extract	Phenols	Spherical	50-100	Crop bio-fortification agent	[153]
Theobroma cacao L.	Shell	Polysaccharides, proteins and phenolics	Spherical, trigonal	1-3	N/A	[154]
Zingiber officinale	Root	Flavonoids, terpenoids	Spherical	100-150	Antimicrobial and antioxidant	[155]

Azadirachta indica	Leaves extract	Polyphenols, flavonoid, proteins	Spherical	142-168 221-328	Antibacterial	[134]
Radish *(Raphanus sativus)*	Taproot	N/A	Spherical	26±3	Anticancer	[156]
Vitis vinifera (Raisin)	N/A	Lignin biopolymer	Spherical	3-18	N/a	[157]
Java tea *(Orthosiphon stamineus)*	Leaves	Alkaloids, flavonoids, tannins, phenols	Trigonal	88-141	Insulin mimic activity	[158]
Clausena dentata	Leaf extract	Flavonoids, triterpenoids, polyphenols	Spherical	46.32-78.88	Larvicidal activity	[159]
Clostridium Botulinum	Leaf extract	Proteins	Spherical	26-41	Antimicrobial	[160]
Spermacoce hispida	Leaf extract	Polyol, saponins	Rod-shaped	120 ± 15	Anti-inflammatory, antibacterial, anticancer	[161]
Allium sativum	Buds	N/A	Hollow and spherical	8-52	Antimicrobial	[162]
Aloe vera	Leaf extract	N/A	Hollow and spherical	9-58	N/a	[163]
Rosa roxburghii	N/A	Polysaccharide (RTFP-3)	Spherical	104.5	Treatment of ROS-mediated diabetes	[164]
Lycium barbarum	Wolfberry	Flavonols (catechins)	Spherical and triangular	83–160	Antioxidant activity (DPPH and ABTS free radical scavenging)	[165]
Fenugreek	Seed	Phenol, flavonol	Oval	50–150	Anticancer	[166]
Garlic *(Allium sativum)*	N/a	N/A	Spherical	21-50	Antibacterial	[167]
Allium sativum	Garlic bulbs	Alcohols, phenols	Spherical	205	Antioxidant and anticancer	[168]

8. Properties of Selenium Nanoparticles

The morphology, size and properties (i.e. physical, chemical, biological) of nanomaterials are determined by different factors and reaction parameters such as synthesis techniques, starting materials, specific surfactant or additive, pH, reaction time, reaction temperature, reaction media and nature of the solvent. This section reviews several physical, chemical, optical and biological properties of the SeNPs that will help in understanding the biomedical applications.

8.1 Physico-chemical Properties

Selenium (Se) is a semi metal that possesses intermediate properties between a metal and a non-metal. It is stable and does not oxidize at ordinary temperature [36]. Se shares several chemical and physical properties with its other non-metal counterparts found in the Oxygen Family (Group 16): the sulfur and tellurium. The atomic number and weight of Se is 34 and 78.96 respectively [169]. Selenium possesses over 20 different isotopes, but only 6 of them are stable: ^{74}Se, ^{76}Se, ^{77}Se, ^{78}Se, ^{80}Se and ^{82}Se, showing $4s_2$ and $4p_4$ outer electronic configuration (Nayak et

al., 2021). The melting point of Se is relatively low (~217 °C) and the photoconductivity is high (~ 8 x 10^4 S/cm) [170]. Moreover, Se has shown a catalytic activity toward organic hydration and oxidation reactions, intrinsic chirality, high refraction coefficient in devices and large birefringence, and relatively large piezoelectric, thermoelectric, and nonlinear optical responses [171]. According to its allotropy, Se can exist in amorphous and crystalline varieties: gray (trigonal) selenium (containing Se_n helical chain polymers) known as "metallic" selenium; rhombohedral selenium (containing Se_6 molecules); three deep-red monoclinic forms: α-, β-, and γ-selenium (containing Se_8 molecules); amorphous red selenium and black vitreous selenium [172]. The crystal selenium (c-Se) is the most thermodynamically stable structure, exhibiting an atomic radius of 1.17 A° [173]. Previous studies indicated that the phase transition between c-Se and a-Se existed in the charge/discharge process [37,174,175]. Amorphous selenium (a-Se) has been an efficient photoconversion material, frequently used in several imaging applications, including ultrahigh-sensitivity pickup tubes [176] and solid-state image sensors [177]. Nevertheless, a-Se has a poor spectral response at long wavelengths and needs a high operation voltage [178].

The c-Se structure appears as an alternative to a-Se in the photoconversion layer of solid-state image sensors. Crystalline selenium consists of a long helical chain arranged in a hexagonal Se array, the most stable form of Se [178]. Prior research has investigated the synthesis and properties of c-Se. For instance, Takiguchi et al. (1997) fabricated single crystals of trigonal Se with a cylindrical shape and diameter of about 8 mm. P. Liu et al. (2007) studied the photoconductance of single-crystalline selenium nanotubes (SCSNTs) under a range of illumination intensities of 633 nm. The authors suggested that a SCSNT is potentially a good photo-sensor material as well as a very effective solar cell material. Moreover, [170] documented the synthesis of uniform nanowires of crystalline selenium with uniform lateral dimensions in the range of 10-30 nm: these nanowires can potentially be converted into other functional materials such as ZnSe and CdSe. Another study assembled c-Se films via doping with various halogens, such as chlorine (Cl): 0.50 and 500 ppm, bromine (Br): 50 ppm, and iodine (I): 50 ppm to investigate the details of concentration effects on surface enhancement [178]. This technology is suggested to be helpful for the design of super-high-definition imaging systems.

Moreover, the academic community has extensively explored the physicochemical properties of SeNPs. Chen et al. (2015) indicated that the molecular weight of chitosan (CS) regulates the biological and physicochemical properties including crystallinity, surface charge density, and hydrophobicity. Zhang et al., (2015) proved that Chitosan-Selenium nanoparticles (CS-SeNPs) at different weights exhibited excellent physicochemical stability, with particle sizes of 80–120 nm after 30 days of storage. Yu et al. (2016) showed that Chitosan-Selenium nanoparticles (CS-SeNPs) remained stable with particle size lower than 180 nm for 60 days. In

addition, the effects of pH (6-9) and temperature (20-50 °C) on the structure, morphology and stability of biosynthesized SeNPs were investigated by employing SEM, XRD, and light microscopy [182]. The authors showed that selenium particle crystallinity, shape and color can be controlled by temperature and pH; for instance, grey crystalline hexagonal acicular SeNPs appear at high temperature or high pH, whereas red amorphous nanospheres prevails at low temperature and low pH.

8.2 Optoelectronic Properties

Selenium nanoparticles have distinct striking shape- and size-reliant physical properties because of their inherent quantum confinement nature. Selenium is a typical semiconductor with a band gap energy of 1.6 eV (775 nm) [183]. Due to the its excellent high resistivity, ranging from 10^{12} to 10^{14} Ω, it has been considered an outstanding option for detectors to produce ultra-low dark current along with noise signals. Selenium was found as one of the primary substances that possess photoelectric conductivity i.e., to change in electrical resistance under the action of light [52]. Therefore, prior research has thoroughly investigated the potential detection applications of a-Se mainly due to its ultra-high photosensitivity by using avalanche multiplication inside the solid. For example, imaging photodetectors using low-dose X-ray [184,185], X-ray photoelectron spectroscopy (XPS) and Raman spectroscopy [186], nitrogen (N)-doped diamond cold cathode [187] or driven by a diamond cold cathode [188]. On the other hand, c-Se possess lower concentrations of selenium than a-Se, thus having less non-radiative recombination loss. Therefore, c-Se has been employed to fabricate solar cells [173,189], being even extremely cheap and highly scalable [190].

Moreover, T. Sharma et al. (2019) used genetic algorithm based code which consists of universal structure prediction evolutionary xtallography (USPEX) and molecular dynamics to obtain at least 70 distinct equilibrium geometries for each selenium cluster. The authors analyzed the structural features of Se clusters including the bond length, bond angle, point symmetry and shape of the geometries, demonstrating that the lowest energy geometries are one dimensional rings (buckled or distorted) with each atom possessing two nearest neighbors only.

The optical properties of nanomaterials are highly influenced by multiple factors such as size, shape, surface modifications, doping, and interactions with other materials. Unique features such as the nanoscale dimension, and the increased energy level spacing (quantum effect) and surface plasmon resonance, determine the size-dependent optical properties [192]. There exist several applications based on these properties including biosensing, photocatalysis, imaging, photoelectrochemistry and photocatalysis [193]. The nanoparticle size distribution can be estimated by using optical absorption and luminescence spectra, which is generated by quantum confinement effect [194]. For instance, Rajalakshmi and Arora (1999) found that a blue shift of

0.235 eV appears in the optical absorption and photoluminescence (PL) energy of SeNPs, being useful to estimate the particle size. Lesnichaya et al., (2019) showed that polydispersity of SeNPs creates broadening of the absorption and excitation-dependent luminescence spectra. Also, laser irradiation reduces the size of β-selenium spherical nanoparticles (69 nm) below 3 nm and converts them into more closely packed α-Se quantum dots (QDs); then, surface defect density and electron trap level of QDs increases with the increase of time of irradiation, which cause decreased energy levels [196]. Another study used optical spectroscopy to show a usual blue shift in the optical spectra of α-monoclinic SeNPs of the order of 40 Å, demonstrating an increase in the band gap [171]. This blue shift of the band gap energy of Se in comparison with its bulk counterpart appears when particles size is smaller than its Bohr excitation radius, so the band gap is enlarged due to the quantum confinement effect [183].

Moreover, biomolecules such as proteins and amino-acids absorb light and provide thermodynamic stability [157,197]. An FTIR analysis suggests that a strong interaction between Se atoms and protein molecules present in the *Pseudomonas alcaliphila* may be responsible for a drastically decreased intensity of spectral peaks of SeNPs [198]. The optical properties can promote light induced drug release for both covalently bonded and encapsulated drugs with SeNPs [52]

8.3 Catalytic Properties

Selenium has been considered a platinum-free, methanol-tolerant cathode material with great stability and electrocatalytic activity, generating a chemical resistance to oxidation and hydrolysis. In recent times, nanoforms selenium have been attracting special attention, particularly due to their unique redox properties, large surface area, efficient catalytic activity and low toxicity [199]. Dumore and Mukhopadhyay (2020) employed 1-Diphenyl-2-picrylhydrazyl free radical scavenging (DPPH FRS) reaction as a model to observe the catalytic activity of Aqueous selenium nanoparticles (ASeNPs) from pH 6, 6.5, 7 and buffer 7 via UV-Visible spectroscopy analysis. It was observed that the FRS reaction was dependent on the concentration of DPPH, following pseudo-first-order kinetics. In this study, the rate of DPPH-FRS reaction increased proportionally with concentration of the catalyst ASeNPs, proving that the catalytic reaction occurs at the surface of the nanoparticles.

Good semiconductors chalcogens such as selenium have a direct bandgap and can be potentially used for degradation of dye groups due to its thermoconductivity, anisotropy and high photoconductivity [201–203]. For instance, Ameri et al. (2016) described about photocatalytic decoloration of triphenylmethane dye, bromothymol blue (BTB) using biogenic SeNPs under UV illumination (15 W) after 60 min incubation of dye solution. Another pioneering study conducted by Chiou and Hsu (2011) showed that single-crystalline Se nanorods (NRs) were able to degrade

methylene blue in dark environment after a short period of irradiation; the superb catalytic process of SeNRs over commercial nanoparticles was due to the efficient interior charge carrier transfer and thus the enhanced carrier utilization efficiency. The photocatalytic activity of biogenic fluorescent SeNPs was evaluated by the decomposition of methylene blue (MB) under UV irradiation [206]. Also, the visible-light-driven photocatalytic capacity of super-long single-crystalline t-Se NRs for methyl orange (MO) degradation was determined [40]. A similar study was reported by Che et al. (2017), in which monoclinic Se nanospheres (SeNSs) degraded Rhodamine B (RhB) with H_2O_2 more efficiently than t-Se NRs. This investigation showed that the photo-memory effect mechanism of Se NSs remains in the dark after pre-irradiation.

Furthermore, when doped with selenium, bismuth sulfides increased the degradation rate of methylene blue under visible-light irradiation ($\lambda > 400$ nm). The improvements were presumably caused by photoelectrons and holes generated by Se dopants in Bi_2S_3 photocatalysts [208]. Selenium doped copper oxide nanoparticles (Se-doped CuO NPs)/H2O2/UV were used to build a photo-Fenton based degradation system for 4-bromophenol in 90 min at a rate of 0.057 min^{-1} [209]. Therefore, Se doping possesses extraordinary photo-absorption properties, increases surface area of nanoparticles and enhances the in-situ generation of hydroxyl radicals. Alagesan and Venugopal (2019) found that biosynthesized SeNPs using *Withania somnifera* leaves extract, exert excellent photocatalytic activity identified by the gradual degradation of MB from deep blue to colorless dye solution under sunlight; during the process, the main active species were holes, superoxide radicals, and hydroxyl radical.

SeNPs with a proper reducer were proven to be a suitable adsorbent for the removal of copper from aqueous solution [210,211] and zinc from wastewaters mainly through inner-sphere complexation [212]. Further, negatively charged biogenic SeNPs produced by aerobic granular sludge in a sequencing batch reactor (SBR) removed cadmium Cd(II) metal ions efficiently [213]. The resulted monolayer maximum adsorption capacity was 59.7 mg/g, enhanced by the increasing solution pH but decreased by the increasing adsorbent dosage. In addition to this, selenium combined with ruthenium nanoparticles increased the electrocatalytic oxygen reduction reaction (ORR) through enhancing the oxygen adsorption site and electron bridge features of selenium [214].

8.4 Biological Properties

Selenium is considered as an essential micronutrient of all living organisms. Se is integrated into 25 selenoproteins in the form of the aminoacid selenocystine (SeCys). In addition, Se modulates a myriad of key biological processes such as the cellular response to oxidative stress, cellular differentiation, immune response, redox signaling, and protein folding [70]. To

investigate selenium's biomedical applications, the biological properties should be addressed. Hence, the present critical review outlines key biological features of the selenium nanoparticles.

The most important biological role of selenium is the maintenance of the thyroid, immunity, and homeostasis through the production of oxidoreductases such as glutathione peroxidases (GPx), iodothyronine deiodinase (DIO) and thioredoxine reductase (TRx), and the plasma selenium transport protein (SePP1) [70,74]. The main selenoprotein families are the GPXs that include 5 Se-dependent members and non-Se-dependent GPX isoenzymes, which have oxidoreductase functions and also regulate immune response; the iodothyronine deiodinases (DIOs) that catalyze the conversion of T4 (thyroxine) to T3 (triiodothyronine) and rT3 (reverse T3); and the thioredoxin reductases (TXNRDs), which modulate transcription and signal transduction functions [215,216]. (Table 3).

Table 3. Main types of selenoproteins and their functions.

Selenoproteins	Abbreviation	Localization	Function	Reference
Glutathione peroxidase GPX			Protects against oxidative stress. Catalyzes the reduction of H_2O_2	[70,217]
Cytosolic GPx1	GPX1	Cytoplasm, ubiquitous	Antioxidative defense	
Extracellular GPx	GPX3	Plasma and thyroid follicle	Anti-inflammatory activity	
Phospholipid GPx	GPX4	Mitochondrial membrane	Reduces the phospholipids's hydroperoxides. Membrane antioxidant	
Thioredoxin reductase TXNDRD			Oxidoreductase activity with $NADPH^*$ as a cofactor	[215,218]
TXNRD cytosolic	TXNDRD1	Mainly cytosolic, ubiquitous	Main antioxidant "weapon" at the cellular level. Inhibits apoptosis, redox state of transcription factors	
TXNRD mytochondrial	TXNDRD2	Mitochondrial, ubiquitous	Regulates cell proliferation	
TXNRD mytochondrial	TXNDRD3	Mainly mitochondrial, ubiquitous	Regulates apoptosis and signaling pathway	
Iodothyronine deiodinase DIO			Catalyzes the conversion of T4 and T3	[219]
Type I DIO	DIO1	Liver, lung, eyes, kidney, thyroid gland, pituitary, CNS	Converts T4 into T3, and rT3 and T3 into rT3 or T2	
Type II DIO	DIO2		Produces locally (intracellular) T3 from T4 and T2 from rT3	
Type III DIO	DIO3	Placenta, fetus, liver, gravid uterus, fetal and neonatal brain, skin	Produces T2 from T4, and rT3 from T4	

Selenoprotein P	SePP	Thyroid and blood	Transports selenium and storage, endothelial antioxidant	[220]

*NADPH = nicotinamide adenine dinucleotide phosphate (reduced form of the redox coenzyme nicotinamide adenine dinucleotide phosphate)

8.4.1 Antioxidant Properties and Prooxidant Properties

8.4.1.1 Antioxidant Properties

An antioxidant is a substance that greatly inhibits or delays the oxidation mechanism and the antioxidant activity means measure this inhibition rate of the oxidation process (Menon et al., 2018). The antioxidant activity of SeNPs is principally associated to the mammalian selenoenzymes: glutathione peroxidase family (GPXs), thioredoxin reductase (TXNDRD), and iodothyronine deiodinase (ID).

Selenium is part of the antioxidant defense system in the liver and plays an essential role in protection against oxidative stress. Prior research has demonstrated that Se supplementation can enhance enzyme levels like GPx that prevent ROS accumulation and decrease cellular damage [221,222]. The GPXs are able to detoxify actively a variety of peroxides such as H_2O_2, phospholipid hydroperoxidase, fatty acids hydroperoxidases, and hydroperoxyl groups of thymine [193]. The TXNDRD also possesses detoxification action by forming a redox system with its substrate thioredoxin. These metabolic processes produce the most common free radicals in nature: reactive nitrogen and oxygen species (RNS and ROS). They are derived from oxygen including peroxyl radical, superoxide radical, per hydroxyl radical, hydroxyl radical and non-free radical species such as hydrogen peroxide and singlet oxygen. The RNS and ROS are highly unstable as the outermost shell is occupied with an unpaired electron; this leads to a removal of electrons from other compounds to get stability, which leads to a chain reaction cascade that may produce more reactive species.

Prior research has documented that excessive levels of ROS may cause oxidative stress and redox disbalance in the cell. This can disrupt or damage proteins, DNA and lipids resulting in cardiovascular and neurodegenerative diseases i.e. Parkinson's and Alzheimer's [223]. Selenium has attracted attention because its antioxidant properties are predominantly exerted by its incorporation into selenoproteins that can catalyze the reduction of disulfide bonds in proteins and peptides [224,225]. Indeed, Se is the main component of the antioxidant enzymes GPXs, TXNDRD and DIO that protect cells from oxidative stress. For example, selenite which is an essential dietary element for mammals, is present in the active center of the antioxidant enzyme GPX and protects membrane lipids and macromolecules from oxidative stress [226]. Notably, *in vitro* and *in vivo* investigations have demonstrated that all selenium compounds with their different oxidation states (-2, 0, +4 and +6) are involved in enhanced selenoprotein expression;

thus, different oxidation states have shown a great bioavailability for selenoprotein biosynthesis [81].

SeNPs have demonstrated to enhance the activity of selenoenzymes (for combating oxidative stress) with equal effectiveness and less toxicity when compared to Se-methyl, selenocysteine, selenomethionine and selenite [68] The SeNPs possess radical scavenging properties and reduce oxidants including 1,1-diphenyl-2-picrylhydrazyl (DPPH), superoxide anion (O_2^-•), singlet oxygen ($^1O_2$), and carbon-centered free radicals [101]. This function is size-dependent, which means that smaller SeNPs possess higher free radical scavenging potential. Moreover, SeNPs is considered to restore the T3, T4, GSH, superoxide dismutase (SOD), and catalase levels in manipulated animals and decrease the $K_2Cr_2O_7$ induced oxidative stress in thyroid glands [68].

8.4.1.2 ROS Scavenging Mechanism

Reactive Oxygen Species (ROS) are chemically reactive molecules produced through a myriad of extracellular and intracellular pathways that include at least one oxygen atom in each molecule [10]. They include free radicals, a species containing one or more unpaired electrons of oxygen such as superoxide ($O_2^{\bullet-}$), hydroxyl radical ($^{\bullet}OH$), and singlet oxygen, as well as nonradical oxidizing agents such as and hypochlorous acid (HOCl) and hydrogen peroxide (H_2O_2) formed by the partial reduction of oxygen and singlet oxygen [227]. Mitochondria are the main intracellular source of $O_2^{\bullet-}$, produced by a side reaction of the respiratory chain. The superoxide anions are formed through the conversion of a small percentage of oxygen molecules (1%-2%) that are not reduced to water in the mitochondrial electron transport chain (ETC) [227].

The ability of Se compounds to scavenge ROS is widely accepted [44,226–228]. The evaluation of dose-dependent free radical scavenging activity (FRS) of Aq SeNPs (ASeNPs) by using 1,1-diphenyl-2-picrylhydrazyl (DPPH) and 2,2'-azinobis (3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) was reported [200]. The results revealed a gradual color change of DPPH from intense purple to light yellow, and of ABTS radical, from bluish-green to colorless in the presence of ASeNPs at pH 6, 6.5, 7 and buffer 7. The scavenging ability of the nanoparticles were stronger compared to sodium selenite.

Furthermore, Zhai et al. (2017) synthesized SeNPs of 103 nm stabilized using chitosan (CS) (CS-SeNPs) with different molecular weights; the antioxidant assessments showed that the nanoparticles were capable of scavenge free radicals at different levels DPPH, ABTS, and lipid peroxide models. The authors also found that the efficient penetration of CS-SeNPs in cells and tissues prevents the accumulation of ROS and Lipofusin (LF), protects GPx activity and decreases Se cytotoxicity *in vitro* or *in vivo*. Another study proved that Nano-Se of different sizes, ranging

from 5 nm to 200 nm, possesses important effects both on scavenging free radicals and protecting DNA from oxidation in a size-dependent fashion in an *in vitro* model: the smaller, the better [229].

Neuroprotective drugs combined with ROS scavenging nanocarriers constitute excellent agents for synergistically protection of neuron cells and retrieval of nerve function. Multifunctional SeNPs were modified with the soluble polysaccharide–protein complex (PTW) and PG-6 peptide (PLGLAG) and loaded with the therapeutic agents monosialotetrahexosylganglioside (GM1) and tetramethylpyrazine (TMP) for an effective treatment of spinal cord injury (SCI) [230] (Fig. 6). These SeNPs@GM1/TMP were found to attenuate ROS overproduction, prevent mitochondrial dysfunction via up-regulating the expression of pro-apoptotic proteins Bcl-2 (B-cell lymphoma-2) and Bcl-xl (B-cell lymphoma-extra-large), and down-regulating the expression of anti-apoptotic proteins Bax (Bcl-2 associated X) and Bad (Bcl-2 associated agonist of cell death), inhibit the activation of p53 and mitogen-activated protein kinase (MAPK) pathways, and have protective effects against the tert-butyl hydroperoxide (t-BOOH)-induced G2/M phase arrest and apoptosis (Fig. 6). The results of behavioral assessments in mice demonstrated that SeNPs@GM1/TMP are promising therapeutic agents that improve the functional recovery of rats after SCI [230].

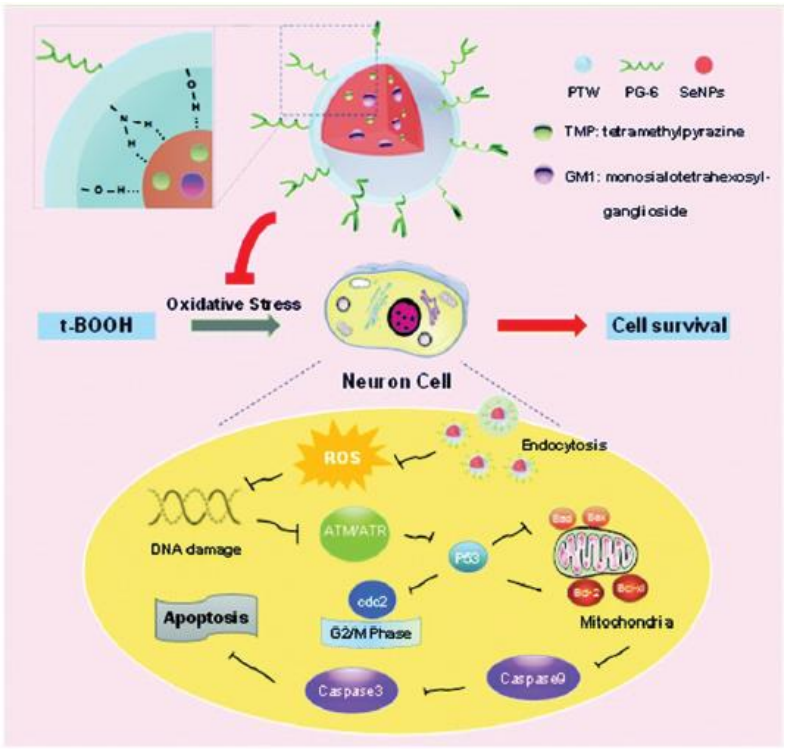

Figure 6. Structure of SeNPs@GM1/TMP and its protective activity against t-BOOH induced neuron cell death. Reproduced from Rao et al. (2019).

8.4.1.3 Pro-oxidant Activity

Selenium execute dual effects: at low concentrations it possesses antioxidant activity, maintaining the intracellular redox status in the cells, whereas at higher concentrations, it acts as a pro-oxidant, producing oxygen radicals and provoking an apoptotic cell death [220]. Among all the explored inorganic nanoparticles, much attention has been drawn to selenium nanoparticles due to their cytotoxicity activity by generating ROS inside the malignant cells. Furthermore, SeNPs are found to be potential tools in fighting drug resistance, reducing the toxicity compared to chemotherapeutic agents and being an excellent carrier for gene and drug delivery [193].

Recent studies have shown that the initial major cellular event prior to cell cycle arrest and/or apoptosis is the ROS generation by SeNPs [231]. Indeed, the SeNPs are able to enter the malignant cells via receptor mediated endocytosis, mainly due to an acidic pH state with redox imbalance. This process leads to a pro-oxidant behaviour of the NPs by free radical generation on one side, which produce mitochondrial membrane disruption and consequently, the leakage of mitochondrial proteins and the endoplasmic reticulum (ER) stress. Hence, several apoptotic molecular pathways which are regulated by SeNPs are activated including NFκB (nuclear factor kappa-light-chain-enhancer of activated B cells), Wnt (wingless-related integration site)/β-catenin, MAPK/Erk (mitogen-activated protein kinases/extracellular signal-regulated kinases) and PI3K/Akt/Mtor (phosphatidylinositol 3-kinases/protein kinase B/mammalian target of rapamycin). The regulation of these pathways are crucial for oncogenic signaling due to a considerable decrease of cellular proliferation and angiogenic signalling by obstructing the growth-promoting signaling in the vicinity of tumor cells. For instance, Pi et al. (2013) reported that SeNPs significantly reduce the adhesion force and Young's modulus of MCF-7 cells leading to a diminished expression of trans-membrane CD44 molecules and necrosis of MCF-7 cells. Zeebaree et al., (2020) demonstrated that spherical biogenic SeNPs synthesized by *Asteriscus graveolens* leaves, enhance the level of ROS and lipid peroxidation, while causing the HepG2 apoptosis by glutathione depletion and decrease of potential of mitochondrial membrane.

Besides, the pro-oxidant mechanism of SeNPs involves the reduction of nano selenium by the Trx/TrxR/Trx/GSH/GR/GRx pathway (thioredoxins/thioredoxim reductases/Glutathione/glucocorticoid receptor/glutaredoxins) and the utilization of the $NADPH+H^+$ to generate selenide (Se-) anion for the further production of free radical (O^{2-}) and ROS [72,76].

8.4.1.4 ROS Production

ROS has gained much importance in recent years as novel signal mediators implicated in growth, differentiation, progression, and death of the cells. In regards to oxidative stress, the

overaccumulation of ROS in cells leads to a reaction with different cellular components to cause oxidative cellular injury and cell death [234].

The term “oxidative stress” is attributed to the perturbations of the physiological redox homeostasis when the rate of cellular reduction is overwhelmed by the rate of cellular oxidation [220]. When ROS overwhelm the cellular antioxidant defense system, either through enhanced ROS levels or a decreased cellular antioxidant capacity, oxidative stress occurs. Particularly, selenium compounds possess a high capacity of exerting oxidative stress by oxidizing thiols and generating ROS, thereby termed as redox-active selenium compounds (i.e. selenocystine, selenite, methylseleninic acid and Se-methylselenocysteine) [81]. This is a clear evidence that selenium does not have only an antioxidant, but pro-oxidant properties. Thus, when so ever applicable, redox-active selenium compounds are not antioxidant by themselves, but only when supplied at dietary dose levels equivalent to physiological optima and incorporated into selenoproteins with oxidoreductase functions; whereas at supra-physiological levels, redox-active selenium compounds can induce oxidative stress, becoming a novel tool for cancer therapeutics based on ROS-mediated mechanisms [235]. The effectiveness of Se compounds for *in vivo* chemoprevention, relies on their capability to regulate the cell cycle, stimulate apoptosis and restrain tumor cell migration and invasion *in vitro* [82,236].

The encapsulation of Se at nanoparticle size (Nano-Se) upregulates selenoenzyme activity with more efficiency and less toxicity compared to other seleno-compounds. SeNPs can be reduced by the thioredoxin (Trx)- or glutaredoxin (Grx)-coupled glutathione system to produce ROS more efficiently than selenite, especially at low levels of NADPH. This is because elemental selenium requires only a single step reduction to selenide anion, thereby triggering redox cycling with oxygen. [237]. This process leads to a rapid and selective hyper-accumulation of SeNPs in cancer cells, which causes catastrophic oxidative stress and cell death. This underlying concept relies on two observations: first, the presence of higher basal levels of ROS in cancer cells compared to normal cells; secondly, the cancer cells possess lower tolerance to increased levels of ROS than normal cells [235,238,239]. The process of ROS production is illustrated in Fig. 7.

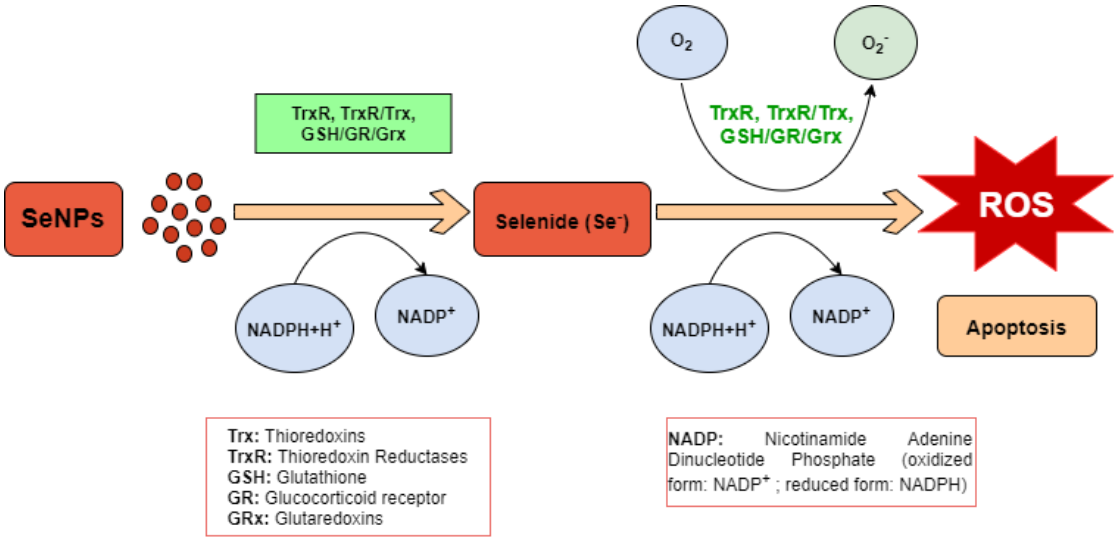

Figure 7. The mechanism of production of ROS through SeNPs.

The intraperitoneal delivery of SeNPs has emerged as an effective and safe approach with promising cancer therapeutic effects. For example, G. Zhao et al. (2020) demonstrated that SeNPs delivered to hepatocarcinoma-22 cells (H22 cells) in the peritoneal cavity of mice induce ROS production and cause protein degradation and apoptotic response. This study showed that GSH can dose-dependently stimulate redox and biotransformation of SeNPs to generate ROS in a pure enzyme system, especially when GSH is the most abundant thiol-containing small molecule in cells. Moreover, Sonkusre and Cameotra (2017) indicated that a minimal concentration of 2 ug Se/ml of biogenic SeNPs prevent and inhibit the proliferation of prostate adenocarcinoma cell line, PC-3, by a ROS-mediated activation of necroptosis.

The process of Se-induced apoptosis is associated with chemical varieties of Se and their metabolism, altering some cellular morphologies including nuclear breakdown, condensation of chromatin, membrane blebbing, cell rounding and formation of apoptotic bodies that are eliminated via phagocytosis [226]. It is well-known that apoptotic cascades can be originated by intrinsic mitochondria-mediated, extrinsic receptor-mediated or endoplasmic reticulum (ER) stress-mediated signaling pathways [241]. Although there exist different proposed mechanisms to explain the key role of Se on cell cycle and apoptosis, the complete process is complex and not yet fully understood. It is correlated with their chemical forms and doses, and encompasses the activation of caspases, protein kinases signaling, p53 phosphorylation and ROS generation [224,239,241–243]. Prior research confirms that Se compounds possess caspase modulation activity causing a programmed cell death. For instance, heterocycles containing Se such as 1,2-[Bis(1,2-benzisoselenazolone-3-(2*H*)-ketone)] ethane (BBSKE) fosters the activity of caspase-3 against tongue cancer Tca8113 [244]; 2,5-bis(5-hydroxymethyl-2-selenienyl)-3-hydroxymethyl-N-methylpyrrole (D-501036) increases the activity of caspase-3 and -9 [245]; and methylselenic

acid (MSA) activates caspase-8 and -9, working with tamoxifen in both tamoxifen-sensitive and tamoxifen-resistant breast cancer cells [236].

The effect of Se compounds in caspases, also known as cysteine-aspartic-specific proteases, includes the fragmentation of internucleosomal DNA and the mitochondrial-dependent/independent apoptosis. The intrinsic mitochondrial pathway is the main process for apoptotic caspase activation in mammals, especially owing to the mitochondrial release of cytochrome c (cyt-c) that creates an apoptosome complex through the oligomerization with Apaf-1 and procaspase-9 [241]. For example, Se containing polysaccharide (SeGLP-2B-1) disrupted the mitochondrial membrane potential and enhanced the cyt-c cytosolic levels and the activity of caspase-9 and -3 [246,247] .

Chapter IV

9. Pharmacokinetic Activity and Cellular Interaction of Selenium Nanoparticles

Nanomedicine is increasingly offering novel nanoparticle-based technologies for the treatment of diseases and diagnosis. The extraordinary properties of nanoscale materials provide a safe and efficient personalized medicine, which promotes tailored therapies to the specific characteristics of patients for the best response and highest safety margin [248,249]. In vitro and in vivo ADME (Absorption, Distribution, Metabolism and Excretion) studies are necessary for pharmaceutical organic drugs. Likewise, nanomaterials should be subjected to both in vitro and in vivo ADME studies [20,250]. NPs need to reach the targeted organ or tissue in order to accomplish the desired function. Therefore, nanotherapeutics rely on effective cellular uptake and tumor permeability of NPs, which both depend on different factors such as size, shape, surface chemistry of NPs, as well as the biological environment, the specific location and type of targeted tissue [251–253].

9.1 Selenium nanoparticles-cell Interactions

The interaction of nanomaterials with cells and lipid bilayers is crucial in several biomedical applications such as drug and gene delivery, phototherapy and imaging. Besides interacting with biological entities (i.e. organs and tissues), NPs cross the cellular barriers and are internalized by cells through endocytosis, accumulate in targeted organs, and are later eliminated [254]. The different manners of internalization of nanoparticles inside cells and the human body is shown in Fig. 8. Although this particular capacity leads to beneficial therapeutic applications, some potential adverse effects regarding the toxicity of NPs have been observed. In consequence, the investigation of the interaction of nanoparticles with their ecosystem, mainly with other nanomaterials and biomolecules is crucial to determine the efficacy of nanoscale materials [252,254,255]

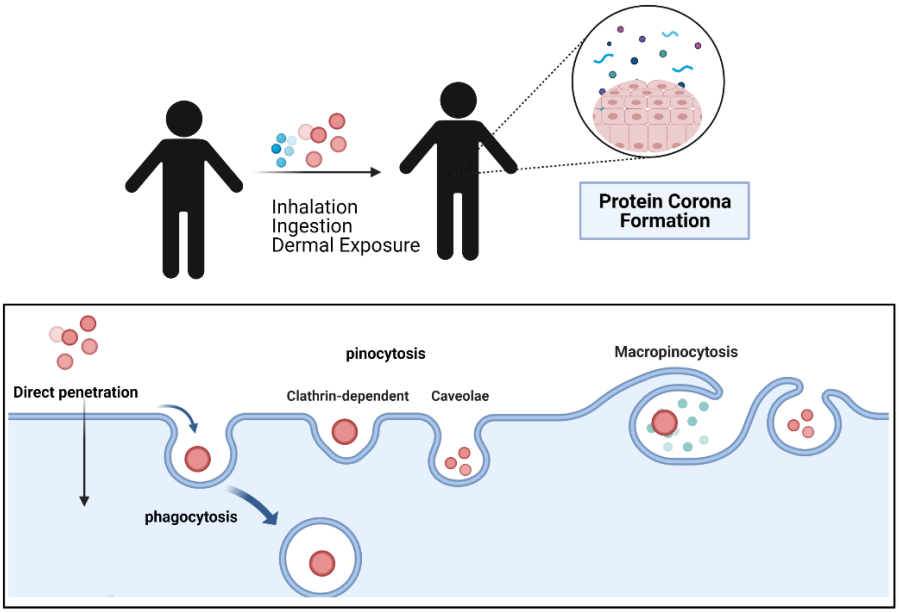

Figure 8. Schematic representation of the different manners to enter the NPs in the human body and inside the cells.

Several factors are involved in determining the success of the uptake and interaction with cells including the intrinsic physicochemical properties of NPs such as shape, size, coating and morphology, crystalline structure, characteristics of the biological environment, and the transformation of NPs during the test, i.e. owing to the formation of protein corona [256,257]. The size and shape of the NPs directly affects the cellular uptake rate of the NPs and is influenced by the time the nanoparticle remains in the circulatory system [248]. The shape also plays an important role in the internalization interaction between the NPs and cells. The symmetry of the NPs controls the trajectory throughout the body because the hydrodynamic forces regulate the transport of NPs [258]. For example, several studies agree that spheres are most effective at cellular uptake mainly due to the symmetry in shape, which allows a constant distribution of acting forces and a tendency to remain in the blood flow [259,260]. Spherical NPs must overcome a minimal membrane bending energy barrier, compared to the non-spherical counterparts.

The importance of cell-nanoparticles interactions has been acknowledged by several authors [255,261–263]. However, little research has been conducted to show the quantitative analysis of nanomedical and nanotoxicological results [256]. The analysis of NP uptake and biodistribution has gained much importance in recent years, mainly to evaluate the medically effective concentration of administered NPs. According to literature, the most remarkable interacting biomolecules to the NP surfaces are nucleic acids and proteins [264,265]. Nucleic acids are convenient receptors for molecular nano-construction demonstrating potent synergistic activity due to their mechanical rigidity, physicochemical stability and high specificity of base pairing [266]. On the other hand, proteins possess various binding sites because of post-

translational modifications, specific and non-specific adsorption capability and confer immune-biocompatibility to nanomaterials [267,268].

The main factors that influence coupling NPs with biomolecules or other nanoparticles are the interaction drivers including Van der Waals forces, electrostatic or magnetic interactions and molecular forces, the complementarity between nanomaterials, their distance and geometry [269]. Furthermore, the interaction between molecules on surfaces is greatly dependent on surface functionalization with one or different chemical reactive groups [270]. For instance, NPs in biological entities are surrounded by interacting biomolecules that are able to change or saturate their surface. NPs surface coating modification alters chemical, electrical, optical and magnetic properties, as well as cytotoxicity by influencing distribution, pharmacokinetics, accumulation and toxicity [271].

Surface modification of NPs by functional molecules/particles/polymers can increase cellular interactions and uptake through tuning the overall properties of particles to fit targeted applications [272]. Multifunctional NPs have various and different interactions with biomolecules and are embedded in human proximal fluids, inside cells, and inside culture media [248,266]. In order to achieve this multifunctionality, nanoparticles include the diagnostic imaging domain, the targeting ligand and therapeutic (Fig. 9). Then, these multifunctional formulations constitute therapeutic-loaded NPs, known also as theranostic NPs, which lead the nanomedicine towards a "personalized medicine" with promising applications in drug delivery, cancer treatment, and diagnosis among others [8,20,248].

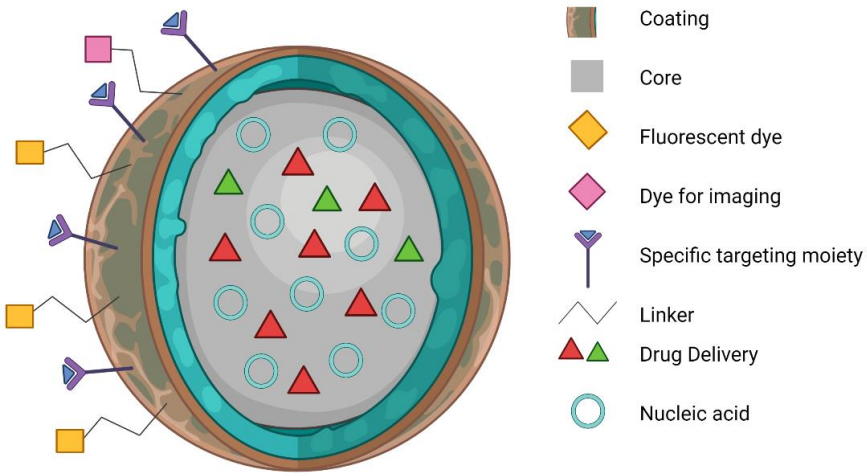

Figure 9. Schematic representation of multi-functional nanoparticles. It includes an imaging component, a targeting element and a therapeutic constituent.

For instance, multifunctional monodisperse and homogeneous spherical SeNPs have been successfully modified with a dinuclear luminescent ruthenium (II) complex [273]. The resulted

NPs (Ru@L-SeNP/Ru@D-SeNP) act as a multifunctional nanocarrier-based delivery system (NDS) to deliver siRNA targeting tumor-MDR1 gene in cisplatinresistant adenocarcinomic human alveolar basal epithelial cells (A549 cells). A similar study fabricated amine-terminated generation 5 polyamidoamine (PAMAM) dendrimers (G5.NH2)-modified SeNPs (G5@Se NP) for the systemic dual delivery of mdr1 siRNA and cisplatin (cis-diamminedichloroplatinum-(II), DDP) for reversal multridug resistance [274]. Through a gel retardation assay, cellular uptake and transfection studies, the authors demonstrated that the multifunctional G5@Se and G5@Se-DDP NP enhance siRNA loading, releasing efficiency and gene-silencing efficacy. Also, Y. Li et al. (2016) showed that siRNAs with polyethylenimine (PEI)-modified SeNPs (Se@PEI@siRNA) improve the apoptosis of HepG2 cells. Therefore, all these studies demonstrate that multifunctional SeNPs are effective nanosystems for chemotherapy and gene therapy technology.

When the nanoparticles interact with plasma proteins, a protein layer known as “protein corona” is formed on the nanoparticle surface. This protein corona has been widely studied due to the significant therapeutic effects on nanoparticles [276–279]. Indeed, it can considerably modify the shape, size, surface charge distribution and susceptibility to the aggregation of nanoparticles. Corona formation also dictates the subsequent biological fate of nanoparticles within the body [253,262] and modulates various biological behaviours such as cell-uptake, toxicity, and immunogenicity [280]. Since this protein is important in the nanoparticle-cell interactions, various studies have investigated the parameters affecting the adsorption of proteins on the surface of nanoparticles in physiological fluids and the role of corona on the nanoparticle cell uptake mechanism [281]. Recently, the academic community has indicated that personalized protein corona formation is useful for targeted medicine, and consequently, for personalized medicine approaches [282].

Regarding SeNPs, biocorona formation of the most abundant serum proteins i.e. human serum albumin (HSA), Immunoglobulin-G (IgG) and transferrin on functionalized SeNPs was reported [283]. For SeNPs functionalization, cationic (CTAB), anionic (SDS), and non-ionic (brij-58) surfactants were used. In this study, HAS was found to increase the antioxidant property of SeNPs, whereas the presence of IgG and transferrin reduced the radical scavenging activity (RSA) activity. Moreover, the authors observed that protein corona formation over functionalized SeNPs enhanced their size and decreased its cellular uptake and its subsequent toxicity, excepting transferrin-coronated nanoparticles that showed increased uptake and cytotoxicity. Another study revealed that protein coronation is significantly influenced via functionalization of NPs [284]. In particular, a protein quantification and densitometry study showed that cationic SeNPs (CTAB-SeNPs) promote maximum corona formation and possess higher affinity towards predominant negative surface potential of serum albumin. The authors suggested that binding factors such as

electrostatic forces, attachment via cysteine group hydrogen bonding and entropy-driven binding governs the process of protein coronation [284].

Furthermore, Borowska et al., (2020) evaluated the molecular interaction between biogenic SeNPs -synthesized using yeast extract- and human serum albumin by employing a microwave plasma optical emission spectrometry operating in a single-particle mode. This study documented that the biomedical application potential of SeNPs deeply depends on their surface functionalization and capability to form protein corona.

Polysaccharides have been widely used as functionalizing agents for nanomaterials, specially due to their unique properties including excellent biocompatibility, nontoxicity, stability and biodegradability [286–288]. NPs functionalized with bioadhesive polysaccharides could increase the residence time and absorption of loaded drugs or biomolecules [289], enhance the specific interaction with biological targets [290], and improve cell-permeability and cancer-targeting ability [287]. For example, Wu et al. (2012) documented that decorated SeNPs with mushroom polysaccharides–protein complexes (PSP) achieve remarkably enhanced cellular uptake via endocytosis and thus antiproliferative activity. The capping with PSP was done through strong physical adsorption of hydroxyl groups of polysaccharides and imino groups of proteins [42]. The authors observed that lysosomes are the main target organelles of PSP–SeNPs on the MCF-7 human breast carcinoma cells.

Moreover, Spirulina polysaccharides (SPS) from food-grade blue-green microalga *Spirulina platensis* is suggested to have an essential biological role in free radical scavenging activity, deoxyribonucleic acid (DNA) repairing, immunostimulation and antiviral effect [291,292]. Thus, SPS could be employed as surface decorator of nanoparticles to improve cell-penetrating capabilities, upgrade circulation time, and avoid plasma protein adsorption. For instance, Yang et al. (2012) showed that monodisperse and homogeneous spherical SeNPs were successfully functionalized with SPS, enhancing the cellular uptake capability and cytotoxicity towards various human cancer cell lines, including A375 melanoma cells.

9.2 Key role of Selenoproteins in the Pharmacological Activity of SeNPs

Selenium is a unique trace element which presents a pleiotropic pharmacological behaviour by its incorporation into selenoproteins. Several selenoproteins are essential enzymes that include at least one SeCys in their active sites to exert catalytic and antioxidant activities [294–296]. Selenoproteins have a crucial role in regulating immune cell functions [297], protection against oxidative stress [298], and cardiovascular disorders [299], thyroid hormone metabolism [300], chemoprevention and chemotherapy [296], and male-fertility enhancement [301]. Excellent reviews have been published on the physiological roles selenoproteins [297,302–304]. However,

there is no much information on how SeNPs affect the pharmacokinetics and pharmacodynamics of selenoproteins [68].

Furthermore, H. Wang et al. (2007) compared the effect of SeNPs and selenoproteins on Glutathione S-transferase (GST) activity and preferred the SeNP function irrespective of supranutritional or toxic level. H. Liu et al. (2020) designed a safe and effective strategy using SeNPs for a highly therapeutic efficacy of cytokine-induced killer (CIK)-based cancer immunotherapy. Since the safety profile of nanomaterials considerably determines their biomedical applications, the authors evaluated the hemocompatibility of SeNPs and found no hemolysis induction when incubated with human blood. This study also revealed that SeNPs are gradually metabolized into selenocystine ($SeCys_2$), which will subsequently regulate the expressions of multiple selenoproteins and other metabolisms in CIK and tumour cells. This unique strategy allows a CIK + SeNPs co-treatment that induces specific immune responses against tumour progression via the production of natural killer cells and shaping of tumor-associated macrophages. All these findings are helpful in translational medicine to develop efficient treatments for diseases associated with Se metabolism [24].

On top of that, Se nanosystems have demonstrated to improve Se bioavailability and facilitate selenoprotein expression when Se level is low [117]. Indeed, the encapsulation of Se in chitosan nanoparticles (CS-SeNPs) is likely to increase Se retention or delivery that can promote selenoprotein expression, as well as protects cells from selenium-induced DNA damage response [117].

9.3 Selenium Nanoparticle Biodistribution and Pharmacokinetics

The science of investigating the scale and rate of ADME of drugs in the body through precise and rigorous experimental methods is known as pharmacokinetics [306]. By nanosizing the formulation, the drug dissolution rate can be increased promoting improved drug absorption and bioavailability. Therefore, NPs are useful to deliver drugs and enhance tissue selectivity due to the selective uptake of NPs in specific tissues [236]. Despite the improved protection or decreased renal clearance for short half-life drugs (i.e. small peptides, nucleic acids), NPs can cause new side effects. The pharmacokinetic profiles of the parent drug and the drug encapsulated in the NP is often different. Thus, studying the pharmacokinetics (PK) and biodistribution of NPs is essential to comprehend and predict their effectiveness and side effects. For delivery, an optimal theranostic NP model should display suitable release kinetics of the drug in specific concentrations on the target site [20].

The physicochemical properties of NPs are essential for PK modulation because they dictate the immediate pharmacological response in the body after administration. For instance, the shape, size, surface chemistry (PEGylation, ligand conjugation), surface charge and

composition influences the pharmacokinetics, biodistribution (BD), intracellular penetration and tumor bioavailability [252]. Moreover, NPs are able to prolong the half-life of drugs in blood circulation, decrease the apparent volume of distribution, and significantly reduce the clearance and degradation. Depending on the method of preparation and the desired therapeutic effect, the drug can be dissolved, adsorbed, entrapped, attached or encapsulated into a NP (Singh & Lillard, 2009). Therefore, the encapsulation of drug molecules in NPs improves the potential cumulative drug delivery to the target tissues, thereby promoting an enhanced drug exposure with NPs [307].

Generally, in spite of their compositions, all NPs must possess a reasonable half-life in blood, selective targetability, and efficacious elimination from the body after delivery to target tissues [308–312]. To obtain these PK behaviors of NPs for clinical applications, it is required to regulate the hydrodynamic diameter (HD), shape and surface properties of NPs. NPs exhibit distinctive PK and BD compared to small molecules, and the toxicity and efficacy profile of each drug are altered by the *in vivo* biofate [252]. The general process includes: (1) systemic circulation and reticuloendothelial system (RES) interaction, (2) extravasation and tumor penetration, and (3) interaction with the target cells. The specific pharmacokinetic parameters include the volume of distribution (Vd), half-life (T1/2), mean residence time (MRT), maximum concentration (Cmax), clearance (Cl), bioavailability (F), permeability and area under the time-concentration curve (AUC).

Current studies on the metabolism of Se have indicated that the metabolic cycle and excretion from humans include both inorganic and organic molecular species of Se present at different oxidation states including -2, +2, +4 and +6. Nevertheless, little research has been conducted to show the formation of elemental Se (Se^0) as part of metabolic processes [313]. Se-methylselenocysteine (SeMC), an organic Se compound with potential anticancer activity, was found to be an advantageous supplementation of Se due to its lowest toxicity among all the selenocompounds while still being greatly bioavailable [78]. In this study, the positive effects of various selenocompounds on GPX1 activity and glycoprotein selenoprotein P (SEPP) generation did not correlate to their toxicity levels but rather were molecule-specific qualities. H. Yang and Jia (2014) revealed that SeMC has minor sub-chronic oral toxicity and no genotoxicity at doses far beyond the nutritional selenium level (0.5, 0.7, 0.9 mg/kg BW/day) after 90-day oral exposure.

Although the pharmacokinetics of sodium selenite in various animals have been investigated, the biosafety dose of Se is still unclear due to the narrow safe dose range of Se and the distinct physiological and pathological conditions of animals [315]. Prior research has investigated the in vivo biodistribution of Se after administration of different supplements in different animals. S. Zheng et al. (2019) reported the PK characteristics of sodium selenite in the blood and tissues of Se-deficient ducklings. S. Q. Zhang, Shen, and Zhang (2020) demonstrated

that selenium-enriched yeast (SeY) has higher bioavailability in rats than sodium selenite and found free SeMet is the ideal biomarker of SeY status in vivo. H. Xing et al. (2019) showed the rapid absorption and slow excretion of sodium selenate in healthy piglet blood, whose pharmacokinetic process conforms to the two-chamber open model. This study also found variations of antioxidant systems in piglets according to Se levels, thereby providing a more complete understanding of risk assessment and clinical application of Se supplementation.

Moreover, the safe dose level of iv administered sodium selenite, defined as maximum tolerated dose (MTD), was reported to be 10.2 mg/m^2 in terminal cancer patients [318]. The pharmacokinetic results of this study demonstrated a linear increase in plasma Se concentration with respect to total dose and suggested the importance of kidney in excretion of Se from selenite. Also, no apparent adverse effects of high dose of repeated selenite administration on physiological selenium homeostasis were reported [318].

The pharmacokinetic and pharmacodynamics profiles of two high doses of parenteral selenite in patients with systemic inflammatory response syndrome (SIRS) showed that maximum glutathione peroxidase activity appeared only with very high dose (VHD) [319]. The authors also documented that the very high dose of 2000 µg (25.30 µmol) of Se as selenious acid, supplied by short-term bolus injection, followed by a continuous intravenous infusion (CIV) of 1600 µg/d (20.24 µmol/d) for 10 d, was most effective in replenish serum selenium to physiological levels and safely maximize the antioxidant selenoenzyme GPx-3 activity.

Regarding SeNPs, Loeschner et al. (2014) compared the distribution of Se following oral administration of elemental SeNPs and selenite in rats and found that both of them were equally adsorbed, distributed, metabolized, and excreted. The authors observed selenoprotein-P (SelP), a transport protein for Se, in plasma corroborating the bioavailability of nanoparticulate elemental Se and that Se was mainly accumulated in the liver and kidneys of animals. Finally, the presence of urinary metabolites Se-methylseleno-N-acetylgalactosamine and trimethylselenonium-ion ($TMSe^+$) proved the entry of SeNPs into the metabolic pathway and its subsequent excretion after dosage. However, it is necessary further studies to deeply understand the fate of the administered elemental Se or selenite in the gastro-intestinal tract. L. Rao et al. (2014) found that chitosan-decorated SeNPs are excellent protein carriers for the therapeutic peptide BAY 55-9837 for type 2 diabetes mellitus by decreasing its renal clearance rate.

In addition, insulin-loaded SeNPs fabricated by using ionic cross-linking/in situ reduction, exhibited enhanced antidiabetic effect through a controllable insulin delivery and outstanding stability in the digestive fluids [321]. This study employed ex vivo intestinal imaging and cellular internalization to evaluate the transepithelial transport ability of nanoparticles to overcome the absorption barrier. Finally, the authors found that INS-SeNPs demonstrate excellent

hypoglycemic effect after oral administration, requiring a lower oral dose of INS-SeNPs to achieve a long-acting glycemic reduction. Kojouri and Sharifi (2013) reported that serum Se concentration was significantly increased in response to SeNPs supplementation and intense exercise in donkey. The findings suggested that SeNPs diet supplementation for 10 consecutive days prevent radical changes in blood urea nitrogen (BUN), creatinine, and total protein concentration in response to intense exercise.

Chapter V

10. Green Nanotechnology: A Better Approach for SeNPs Bioapplications

Despite the tremendous advances in recent years on the application of nanotechnology with regards to treatment and diagnosis of different diseases, there are still many challenges in bio- and cytocompatibility, as well as the selectivity and efficiency of NPs [323]. Conventional synthesis of nanomaterials requires the employment of toxic/harmful reagents and substances (i.e. solvents, catalysis, reducing, and capping agents), which affects the environment and the patient response. Moreover, progress running of nanomaterials from laboratory to clinical or industrial applications has been slow and difficult due to the poor understanding of the new hazards introduced by nanotechnology and the absence of suitable policies to manage several new risks [324]. Hence, green nanotechnology has been introduced as a sustainable alternative offering better and safer processing methods of NPs production [54,325–327]. Green nanotechnology represents a new effort by researchers to utilize the ability of nature to eliminate or reduce environmental and human health risks caused by using nanomaterials, and to promote the substitution of existing toxic products with new environmentally friendly nanoproducts [328].

In the light of enhancing the quality of NPs for making them benign, eco-friendly, biocompatible, and safe agents, the sustainable synthesis of NPs by using natural resources has emerged as a promising field in nanobiotechnology [329]. According to Mostafavi et al. (2020), the presence of organic and non-toxic stabilizing agents in biogenic NPs leads to tailored biological responses (i.e. cytotoxicity, inflammation), enhanced biodistribution, and controlled size and shape of NPs. Nanomedicine is a cutting-edge research field with important opportunities for development and improvement of the identification and therapy of human diseases. Green nanomaterials have demonstrated potential applications in medicine, agriculture, energy, etc. including anticancer, antidiabetic and antioxidant effects, as well as bio-sensing applications [330]. For instance, green nanodrug delivery systems have been revolutionizing the nanomedicine through their good targeted recognition and controlled release, high biocompatibility and decreased toxicity [331]. Thus, there has been a great demand for green nanotechnology-driven drug delivery systems, which has led to the development of diverse delivery devices such as inorganic (metallic) nanoparticles, quantum dots, organic polymeric nanoparticles, mesoporous silica nanoparticles, dendrimers, nanostructured lipid carriers, solid lipid nanoparticles, etc. [332]. Further, the emergence of sustainable, low-energy, and low-cost procedures for the manufacturing of different tissues that diminish the consumption of toxic materials was shown [333].

It has been found that green synthesis approaches produce highly stable and biocompatible SeNPs that increase efficiency and minimize side effects [147,334]. Due to biosynthesized SeNPs are less polydisperse and do not form aggregations at physiological conditions, they have become an efficacious and specific agent against different diseases such as cancer [137]. Indeed, some metabolites from plant extracts such as saponins, minerals, vitamins, carbohydrates, flavonoids, tannins, etc. are known to be excellent reducing and capping agents of SeNPs, making them more stable and safe [335]. Biogenic SeNPs and their potential applications in biomedical sciences have been extensively explored by researchers [34,54,55,57,204,325,326,336,337]. Moreover, green SeNPs has emerged as a major therapeutic tool to treat different diseases, appearing effective in medicine sciences as well as in pharmaceutical and cosmetics industry [55]. It is stated that eco-friendly metallic NPs are safely translated in medicine and serve as safe nanotheranostic agents/platforms [338–340]. However, some important issues need to be considered prior to the use of SeNPs in clinic translational applications such as the safety profile, pharmacokinetics and pharmacodynamics, specificity and the sensitivity in the biological environment. Therefore, these aspects will be addressed in the subsequent sections and we will also discuss in detail different biomedical applications of biosynthesized SeNPs, highlighting the therapeutic and diagnostic potential.

11. Targeted Biomedical Applications of Biogenic Selenium Nanoparticles

Selenium nanoparticles have attracted considerable interest due to their exceptional properties and enhanced bioavailability with the advantage of decreased toxicity. Therefore, SeNPs have found potential applications in various domains such as biomedical, environmental, agricultural, among others. The prooxidant and antioxidant properties provide different throughways for SeNPs study in a myriad of pathological conditions. The present section specifically discusses biomedical applications of SeNPs by focusing on the variety of therapeutic and diagnostic aspects. Further, this review highlights the applications of those synthesized SeNPs through green chemistry.

11.1 Therapeutic Applications

SeNPs are bioactive and biologically available that play a crucial role in many oxidoreductive processes. The nanostructured Se possesses a regulative effect to support the correct functioning of the body (plants and animals) and offers health benefits for treatment/cure of various diseases. This review covers in detail the use of biogenic SeNPs for different therapeutic purposes including the anticancer, antimicrobial, anti-diabetic activity, delivery of gene and drugs, etc.,

11.1.1 Antioxidant Applications

Antioxidants are compounds that prevent the generation of free radicals as well as scavenge free radicals produced during various biochemical reactions in animals and plants [53]. Selenium is implicated in antioxidant defense systems, and significantly contributes in maintaining the redox homeostasis. Nano-Se avoids toxicity damage, offering protective activity against cellular damages by regulating ROS and GPx. The antioxidant potential of biogenic NPs relies on the redox potential of phenolic and flavonoid compounds [118]. Thus, they play a significant role in protecting against oxidative stress diseases, neurodegenerative diseases, and cardiovascular diseases [341].

To date, an overwhelming number of studies indicated that SeNPs possess high antioxidant ability and free radical scavenging efficiency, which can protect tissues and cells from oxidative damage [135] (see Table. 4). Earlier studies confirmed that SeNPs exhibited antioxidant activity with lesser toxic effect than selenium [44] and sodium selenite [147]. Also, biogenic SeNPs demonstrated to have higher antioxidant action with lesser toxicity to normal cells than selenium dioxide [342]. Another study proved that SeNPs fabricated using *Theobroma cacao* L. bean shell (CBSE) extract as bio-reductant and capping agent, possessed a high stability and more antioxidant activity than the extract itself [343]. Likewise, other studies reported similar behaviors for SeNPs fabricated with different natural extracts [135,140,344,345]. However, El-Zayat et al. (2021) documented a lower antioxidant activity of selenium nano-solution of *Ephedra aphylla* extract than the water extract. The authors suggested that phenolics, flavonoids, and tannins in the plant's extract offer a high antioxidant activity due to presence of hydroxyl groups.

The size of the SeNPs has a considerable effect on the antioxidant properties due to the more efficient capture of free radicals by smaller nanoparticles [347]. For instance, P. Liu et al. (2007) mentioned that the size of SeNPs notably affects their biological activity, and, as expected, SeNPs of 5-200 nm can directly scavenge free radicals in vitro. Similar studies confirmed the dependency of antioxidant activity on particle size and concentration [100,140,348]. Table 4 summarizes different antioxidant studies of SeNPs with their respective size. Additionally, [349]Mittal et al., (2014) found that the capping constituents of quercetin and gallic acid present on the nanoparticles surface play an important role in the antioxidant potential of ecofriendly Ag-SeNPs.

Table 4. Methods of antioxidant capacity determination of prepared biogenic selenium nanoparticles.

Biological system used for synthesis	Shape and size of SeNPs	Antioxidant Measurement Technique	Antioxidant activity	IC50 (µg/mL)	EC50 (µg/mL)	Ref

Bacillus sp. MSh-1.	Spherical; 80-220 nm	DPPH and reducing power assays.	RSA of 23.1 ± 3.4%. Reducing power in a dose-dependent manner in concentration range of 0–200 μg/mL.	41.5 ± 0.9	N/A	[342]
Saccharomyces cerevisiae	Spherical; 50 nm	DPPH	RSA of 21.7-48.5% , increasing in a dose-dependent manner	N/A	N/A	[350]
Bacillus sp. EKT1	Spherical; 31-335 nm	DPPH	RSA was up to 56.5 ± 5% at 400 μg/mL	322.8	N/A	[348]
Quercetin and gallic acid	Bimettalic Ag-Se NPs capped by flavonoid and phenolics; 30-35 nm	ABTS, DPPH and MTT assays	T-AOC was in the range of 59 to 62 %.	30- 66	N/A	[349]
Aqueous chitosan microspheres	Spherical; 36-95 nm	H_2O_2 levels; measurement of GSH, TBARS (MDA equivalent), GSH-Px, SOD and CAT	Increase of both intracorporal Se retention and the levels of GSH-Px, SOD and CAT; lower levels of TBARS.	N/A	N/A	[119]
Emblica officinalis extract	Spherical; 15-40 nm	DPPH and ABTS radical scavenging assays.	RSA in dose-dependent manner, directly proportional to the concentration of NPs.	127.28 ± 3.73	DPPH: 15.67 ± 1.41 mg/mL ABTS: 18.84 ± 1.02 mg/mL	[147]
Lactobacillus Casei ATCC 393	50-80 nm	Cellular methods: T-AOC MDA T-SOD GSH-Px levels TrxR	Increase T-AOC, T-SOD, TrxR and GSH-Px. Reduced MDA levels in serum and jejunum.	N/A	N/A	[351]
Pantoea agglomerans	Spherical; 30-300 nm	Production of ROS using HUVEC. Fluorescence determined using a microplate reader (Bio-Rad) at 485-nm excitation and 583-nm emission.	Decrease in fluorescence resulting from the oxidation of intracellular probe dichlorofluorescein (DCF).	N/A	N/A	[347]
Lactobacillus Casei ATCC 393	Spherical capped with proteins and polysaccharides; 50~80 nm	H_2O_2 levels	Increased the activity of GPx, and reduce MDA.	N/A	N/A	[352]

Lactobacillus Casei ATCC 393	Spherical capped with proteins and polysaccharides; 50~80 nm	H_2O_2- induced oxidative damage model of human colon mucosal epithelial cells	Alleviate increase of ROS, reduce ATP and MMP. Improve the protein levels of Nrf2, HO-1, and NQO-1.	N/A	N/A	[353]
Lactococcus lactis NZ9000	Spherical; 38-152 nm	H_2O_2 levels measurement. MDA T-SOD GPx	Alleviate IPEC-J2 cell oxidative damage caused by H_2O_2. Inhibition of intracellular ROS production	N/A	N/A	[354]
Cordyceps sinensis exopolysaccharide (EPS) conjugation	Amorphous & monoclinic; 80–125 nm.	ABTS and superoxide anion radical (O_2•−) scavenging assays	Smaller SeNPs present high O_2•− scavenging ability. Se/P ratios (1:3, 1:1 and 4:3) had a higher $ABTS^{•+}$ scavenging ability, and could reach 88.89%,85.53% and 69.88% at 0.2 mg/mL	N/A	N/A	[355]
Ephedra aphylla extract	Spherical and tetragonal; 13.95-26.26 nm	DPPH assay	The Se nano-solution of E. aphylla extract showed lower activity than the water extract.	0.213 and 0.296 mg/mL	N/A	[346]
Green tea extract and *Lycium barbarum* polysaccharides	Spherical and triangular; 83-160 nm	DPPH and ABTS assays	Strong DPPH-scavenging activity in a concentration-dependent manner at 5–25 μM. High antioxidant activity with low EC50. Inhibition of ABTS free radicals in a dose-dependent manner.	N/A	22 μ M	[356]
Theobroma cacao L. Bean Shell Extract	Spherical; 1-3 nm	ABTS and FRAP assays	ABTS: 28.6 ± 0.1 mg TE/g FRAP: 12.4 ± 0.2 mg TE/g	N/A	N/A	[343]
Chitosan	Spherical; 102-104 nm	DPPH, ABTS and superoxide anion radical (O_2•−) scavenging assays	**DPPH:** 83.06% at 0.5 mM **ABTS:** 74.33, 80.23 and 81.99% at 2 mmol/l **Superoxide:** 25.20, 27.54, 31.44% at 1 mM	**DPPH:** 0.296, 0.306, 0.325, 0.370 mM **ABTS**: 1.314, 1.249, 1.143 and 1.101 mM	N/A	[345]
Streptomyces minutiscleroticus M10A62	Spherical; 100-250 nm	DPPH; Reducing power assay;	All measurements increase in a dose-dependent manner.	N/A	N/A	[357]

		T-AOC: Phosphomolybdenum method	T-AOC was more or less equal to the standard ascorbic acid.			
Saccharomyces cerevisiae	Spherical; 45–90 nm	DPPH	RSA increase in a dose-dependent manner at 20 and 100 mg/ml.	14.81 µg/mg	N/A	[135]
Diospyros montana leaf extract	Spherical; 4 to 16 nm	DPPH and FRAP assays	**DPPH:** color change from purple to pale yellow. RSA of 61.12% at 200 µg/mL **FRAP:** color change from yellow to shades of green and blue	0.225	0.435	[140]
Corbicula fluminea	Spherical; 40-70 nm	DPPH, TEAC and FRAP of plasma assays.	**DPPH RSA:** 70, 77, 83, 79, and 53% at 1.5 mg/mL. Increase in a dose-dependent manner **TEAC:** highest RSA at 226 µmol Trolox/g sample **FRAP**: highest RSA at 150 µmol Fe2+/g sample	1.5 mg/mL	N/A	[344]
Murraya koenigii	Spherical; 50-150 nm	DPPH and Superoxide anion (O_2^-) scavenging assay	RSA increased with increase in concentration,	25 and 50	N/A	[100]
Ginger plant (Z. officinale) extract	Spherical; 100-150 nm	DPPH	RSA increase in a dose-dependent manner and is indicated by the degree of discoloration (disappearance of the purple color). SeNPs are free radical inhibitor or scavenger acting possibly as primary antioxidants	125	N/A	[155]

Abbreviations:

IC50: Half maximal inhibitory concentration; EC50: Effective concentration required to inhibit 50% of free radicals; RSA: Radical Scavenging activity; DPPH: 2,2-diphenyl-1-picrylhydrazyl; ABTS: 2,20-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid); FRAP: Ferric reducing antioxidant power; TEA: Trolox equivalent antioxidant; POX: Peroxidase; APX: Ascorbate peroxidase; CAT: Catalase; T-AOC: Total antioxidant capacity; MDA: Malondialdehyde assay; SOD: Superoxide dismutase; T-SOD: Total superoxide dismutase; GSH: Glutathione; GSH-Px: Glutathione peroxidase; TrxR: Thioredoxin reductase DAO: Diamine oxidase assay; HUVEC: Human umbilical vein endothelial cells; MMP: Mitochondrial membrane potential.

The most used technique to measure the free radical scavenging of SeNPs is DPPH due to its simple, rapid, facile, sensitive and stable activity [43]. This method is based on the reduction

of methanolic DPPH solution by donating an electron or hydrogen atom to form a non-radical and colorless stable molecule 2, 2-diphenyl-1-hydrazine. [140,357].

The academic community has extensively explored the strong antioxidative activity of biogenic SeNPs synthesized by Lactobacillus Casei ATCC 393 to alleviate oxidative stress-caused intestinal epithelial barrier dysfunction [351,352,354]. These studies documented that nanoparticles can alleviate ROS mediated mitochondrial dysfunction via Nrf2-mediated signaling pathway, increase the number of goblet cells, reduce the production of ROS, increase GPs activity and preserve the mitochondrial functions. Therefore, SeNPs could be employed to treat oxidative stress-related intestinal disorders. Similarly, [354]Xu et al., (2019) [2] studied the antioxidative and anti-inflammatory effect of biogenic SeNPs mainly coated by polysaccharides to protect intestinal epithelial cells against H_2O_2 and ETEC K88-caused injury and maintains the intestinal epithelial barrier integrity.

The consensus has been that biogenic SeNPs present significant antioxidant activity and serve as a potential antioxidant supplement or ingredient [147,344], nano-biomedicine [100], antibacterial agent [135] and neuroprotective agent [356].

11.1.2 Antimicrobial Activity

The antimicrobial capability of SeNPs has propelled to the forefront in investigations of plant disease management due to their large surface area to volume ratio, which allows them to set better contact with microorganisms, thus leading to improved antimicrobial activity [358]. Therefore, SeNPs can be used in several fields including infectious control, food manufacturers, treatment of the biomedical instruments, cosmetics and the pharmaceutical products [147].

11.1.2.1 Antibacterial Activity

The antibacterial activity of selenium compounds has been attributed to the generation of free radicals, including Se oxyanions [341]. Increasing emergence of drug-resistant microorganisms constitutes a great concern to clinicians; hence, novel active products are necessary to treat a diverse of infectious disease cases [336]. The unique antibacterial effect of biosynthesized SeNPs has been extensively explored by researchers on the basis of morphological and structural changes in the bacterial cells [135,140,346,349,357,359].

Phytofabricated selenium nanoparticles fabricated from aqueous fruit extract of *Emblica officinalis* were found to possess antimicrobial activity on both bacterial and fungal pathogens [147]. In this study, the antibacterial activity was observed against Gram-positive and Gram-negative bacteria. The MIC and MBC values were 09.16 ± 0.76 and 19.83 ± 1.25 μg/mL against *S. aureus* MTCC 96, and 59.83 ± 2.56 and 97.50 ± 3.27 μg/mL against *E. coli* MTCC 41. A similar study indicated the MIC of manufactured SeNPs by aqueous extract of fermented Lupin

(AEFL) against *A. calcoaceticus* (2.343 μg/ml), *C. albicans* (2.343 μg/mL) and *S. aureus* (1.171 μg/mL) [360]. The same study reported that the antifungal activity of the SeNPs upon *Aspergillus* species was effective only against *A. flavus* (29.6 mm ZOI) and no activity was shown towards *A. niger*.

Prior research generally confirms that the antimicrobial activity is size-dependent [86,105,147]. Smaller NPs can easily cross the cell wall and membrane and provoke cell lysis. For instance, Zonaro et al. (2015) showed that the smallest SeNPs fabricated by using *Stenotrophomonas maltophilia* SeITE02, exhibited strongest antimicrobial activity with an EC50 of 26.32 mg/L for *E. coli*, 7.59 mg/L for *S.aureus* and 62.37mg/L for *P.aeruginosa*. San Keskin, Akbal Vural, and Abaci (2020) suggested that large surface area, small size and spherical shape of SeNPs fabricated from the supernatant of *Lysinibacillus* sp. NOSK strain is probably responsible for the good antimicrobial activity against *E. coli* ATCC 125922 and *S.aureus* ATCC 29213 bacteria. Moreover, this study determined the anti-biofilm activity of different concentrations (0–2 mg/mL) of the biogenic SeNPs against strong-biofilm producer *P. aeruginosa*.

Besides the dimensions of the NPs, further important features such as the elemental structure (purity) and the shape of SeNPs should be taken into consideration [147]. For example, the antimicrobial and antibiofilm ability of SeNPs, manufactured with *S. maltophilia* SeITE02, against different pathogenic bacteria seems to be strictly linked to the organic cap surrounding biogenic NPs [56]. This characteristic was tested through exposing NPs to progressively stronger protocols for the denaturation of the external organic coating; this resulted in increased MIC values with progressive denaturation.

Moreover, SeNPs synthesized from *C. bulbosa* tuber aqueous extract were found to promote growth inhibitory effects of certain clinical pathogens such as *Bacillus subtilis* and *E.coli*, as well as a strong larvicidal activity in *Aedes albopictus* against the dengue vector with a maximum of 250 g/mL mortality concentration [362]. The bacterial biofilm inhibition assay results in a gradual decline of biofilm thickness at 25 μg mL^{-1} (80-70% reduction) and 50 μg/mL (extreme reduction), thus inhibiting further proliferation of bacteria (Fig. 10).

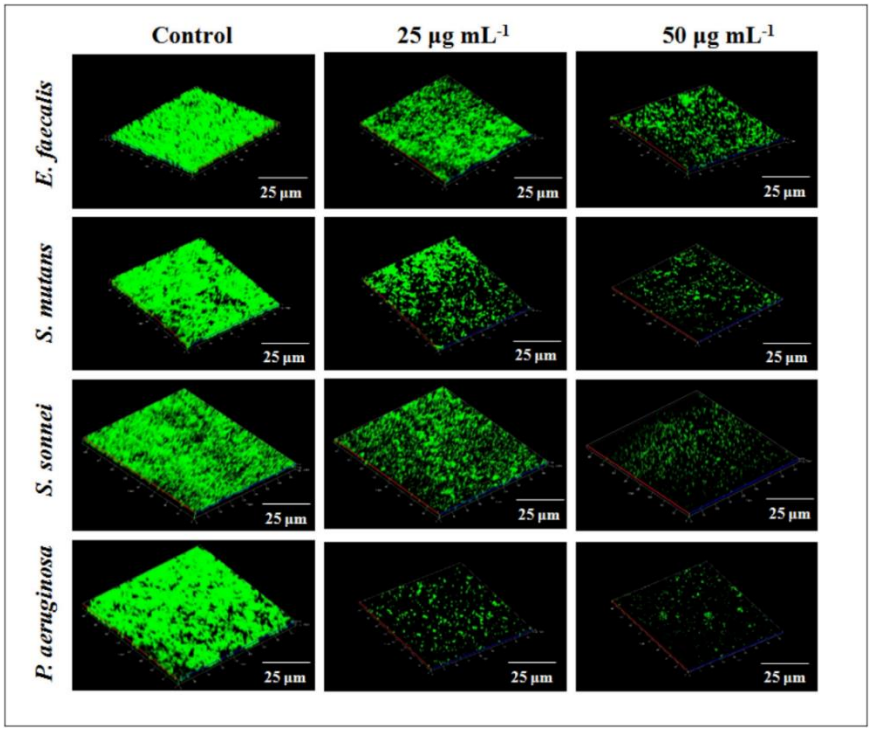

Figure 10. Confocal laser scanning microscopic images of antibiofilm activity of Mk-SeNPs against Gram-positive (*E. faecalis* & *S. mutans*) and Gram-negative (*S. sonnei* & *P. aeruginosa*) bacteria [100].

Sonkusre and Singh Cameotra (2015) showed *that Bacillus licheniformis* JS2 derived SeNPs inhibit *Staphylococcus aureus* adherence and micro-colony formation on polystyrene, glass, and catheter surface. Similarly, at a concentration of 300 µM, 23.7 µg mL^{-1}, SeNPs totally inhibited *S. aureus* bacterial growth mainly due to the interactions with DNA and proteins [364]. The 100, 100, 250 and 100 µg/ml SeNPs, fabricated by non-pathogenic and inexpensive bacterium *Ralstonia eutropha*, were found to inhibit 99% growth of *Pseudomonas aeruginosa, S. aureus, E. coli* and *Streptococcus pyogenes*, respectively [202]. The same study found that 500 µg/ml of SeNPps inhibit the growth of pathogenic fungi *Aspergillus clavatus* (MTCC 1323).

Moreover, Menon et al. (2018) tested the anti-microbial activity of SeNPs synthesized by *Z.officinale* root extract on one Gram-positive bacteria (*S. aureus*) and five Gram-negative bacteria (*Escherichia coli, Klebsiella sp., Pseudomonas sp., Serratia sp.* and *Proteus sp.),* resulting in MIC values from 150 µg/mL to 500 µg/mL. Medina, et al. (2018) produced SeNPs by using *E. coli, Pseudomonas aeruginosa, S. aureus* and Methicillin-resistant *Staphylococcus aureus* (MRSA) and tested for their ability to inhibit bacterial growth. In this study, the biogenic SeNPs may alter the bacterial growth cycle through the synthesis of RNA, enzymes or other molecules involved in the cell division. Also, the authors hypothesized that SeNPs cause a systematic failure of the intern metabolism that leads to cell death by inducing the formation of ROS. Another study demonstrated that SeNPs fabricated by the whole cell lysate of *Bacillus sp.*

MSh-1, inhibited the biofilm of *S. aureus*, *P. aeruginosa*, and *P. mirabilis* by 12 42%, 34.3%, and 53.4%, respectively.

Furthermore, phytosynthesized SeNPs using *Cinnamomum zeylanicum* bark extract (CIE-SeNPs) were evaluated as antimicrobial agents against bacterial foodborne pathogens: *E. coli*, *Salmonella typhimurium, S. aureus, and Listeria monocytogenes* and as potential edible coating (EC) basements [366]. Menon et al. (2020) fabricated SeNPs by the aqueous extract of cow urine and analyzed the antimicrobial activity by determining the ZOI of Gram-negative bacteria *E.coli* (9 ± 0.3 mm), *Klebsiella* sp. (10.5 ± 2.8 mm), *Pseudomonas* sp. (7.5 ± 6.8 mm) and *Serratia* sp. (8 ± 0.8 mm), and Gram-positive bacteria *Staphylococcus aureus (*8.4 ± 5.7 mm*).*

Environmentally friendly SeNPs manufactured by *Bacillus* sp. MSh-1 showed effective and accurate prophylactic effects on acute toxoplasmosis, thereby offering a potential alternative for the treatment with pyrimethamine and sulfadiazine, which presents serious side effects [368]. Beheshti et al. (2013) confirmed the in vitro and in vivo efficacy of biogenic SeNPs against *Leishmania major*, becoming a novel therapeutic agent for treatment of the localized lesions typical of cutaneous leishmaniasis.

11.1.2.2 Antifungal Activity

Several investigations have reported the antimicrobial activity of biogenic SeNPs; for example, Joshi et al. (2019) revealed the in vitro antifungal activity of spherical mycosynthesized SeNPs against *Pyricularia grisea* and *Colletotrichum capsici* and *Alternaria solani* in one-month-old chili and tomato leaves. This study also demonstrated the inhibition of the sporulation of late blight of tomato by treating with the *P. infestans* zoospores with different concentrations. Kheradmand et al. (2014) found that selenium nanoparticle-enriched probiotics (*Lactobacillus plantarum* and *L. johnsonii*) and their exametabolites inhibited the growth of *Candida albicans* ATCC 14053 (*C. albicans*). The authors observed that selenium dioxide in culture supernatants of strains enhanced production of soluble metabolites involved in killing *C. albicans* cells. A similar study determined that the size and crystallinity of chitosan-stabilized SeNPs greatly influenced the synergistic antifungal effect against *C. albicans* biofilms in a dose–response manner [371].

Trichoderma harzianum-derived selenium nanoparticles (TSNP) showed excellent antifungal activity and dramatically increasing control functionalities against *Alternaria* toxins (83% of TeA and 79% of AOH reduction), fumonisin B1 (63% of FB1 reduction) and deoxynivalenol (76% of DON reduction) [372]. In this study, the TSNP were suggested to be applicable as bifunctional nanomaterials for biocontrol of phytopathogens and mycotoxins in agriculture and food safety. El-Zayat et al. (2021) documented that SeNPs fabricated using *Ephedra aphylla* extract displayed potent antimicrobial activity against several bacterial and

fungal species with enhanced inhibition zone diameter within 19.33–39.33 mm. Kokila et al. (2017) evaluated the antimicrobial activity of biosynthesized SeNPs using the leaves of *Diospyros montana* against *S. aureus*, *E. coli* and the fungus *Aspergillus niger* using disc diffusion method; the results indicated that the highest inhibition zone was for *Aspergillus niger* (12 mm) at different concentrations (10, 20, 30 and 40 μg/mL).

11.1.3 Anticancer Activity

Cancer has emerged as a major global challenge and embraces near 100 types characterized by an uncontrolled division of abnormal cells with the ability to metastasize to other parts of the body [373]. Meanwhile, nanotechnology has gained much importance worldwide in recent years as a novel approach to combat cancer. Cancer nanomedicine holds potential to improve anticancer therapy because the unique properties of NPs such as small size, large surface-to-volume ratio, the ability to encapsulate various drugs, and tunable surface chemistry, confer them many advantages over their bulk counterparts [374]. A full understanding of nano-bio interactions leads to safer and more efficacious nanotherapeutics by overcoming physiological barriers posed by the tumour microenvironment, which will facilitate clinical development [375]. On the other hand, green nanomaterials are currently greatly investigated for the treatment and diagnosis of cancer owing to their high biocompatibility and effectiveness [376].

Much attention has been drawn to anticancer effects of biologically synthesized SeNPs (Table 5). SeNPs have shown to be better anticancer, nontoxic, and biocompatible operators than selenite and selenate compounds [43]. *Bacillus licheniformis* derived biogenic SeNPs emerge as the safest form of selenium supplementation with potent necroptosis activity against LNCaP-FGC cells, without affecting the RBC integrity [377]. *Streptomyces bikiniensis*-derived SeNPs demonstrated excellent anticancer effect against Hep-G2 and MCF-7 cells under in vitro conditions through a suggested mechanism of mobilization of increased endogenous copper (possibly chromatin-bound copper) of cancer cells and consequent prooxidant action [378] (Fig. 11.). Another anticancer mechanism proposed for biogenic SeNPs fabricated by *Idiomarina* sp. PR58-8 is activation of apoptotic pathway by a decreased expression of pro-caspase 3 [379]. This was corroborated by determining the expression of pro-polymerase (PARP), and cleaved PARP, as the activated form of caspase-3 catalyzes the cleavage of pro-PARP. Caspases are a family of intracellular proteases, essential for the initiation and execution of apoptosis or programmed cell death through activation by proteolytic cleavage [380]. A similar study found that biosynthesized SeNPs + X-ray combination were involved in caspase-3 activation and downstream target that inhibited the lung cancer cell proliferation with high cytotoxic effect [381].

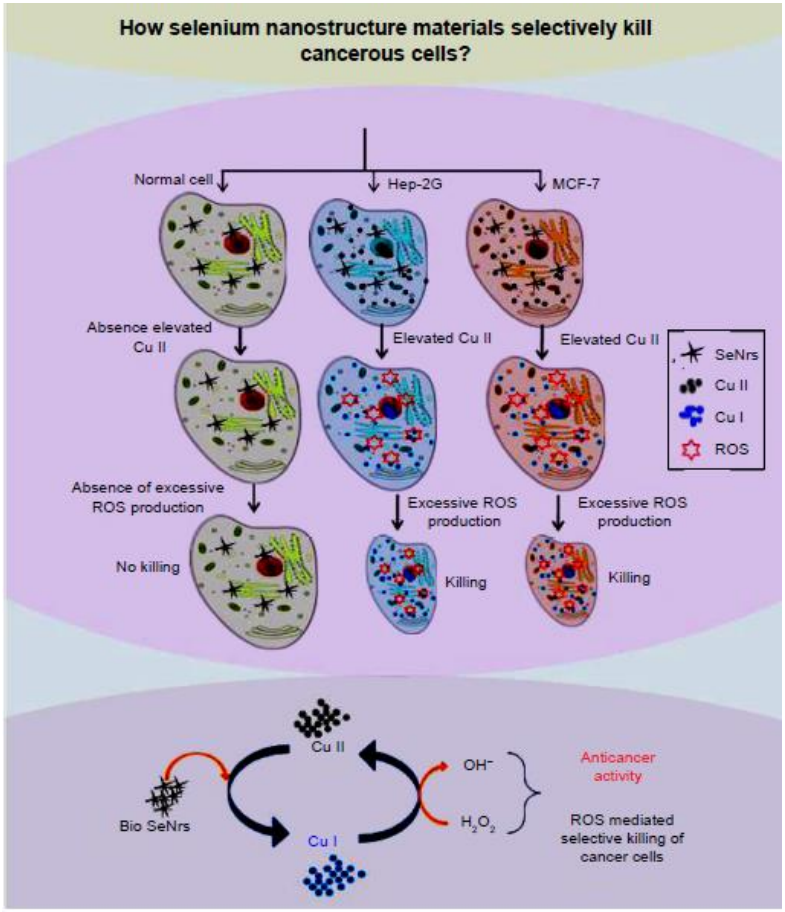

Figure 11. Anticancer effect of green synthesized Se Nanorods (SeNrs) on Hep-G2 and MCF-7 cells that encompasses a mechanism of mobilization of endogenous Cu and a further prooxidant action [378]

Table 5. Anticancer Activity of several Biogenic Selenium Nanoparticles in different cell cancer lines.

Biological system/Green method	Shape and Size (nm)	Concentration/Dosage	Pathway	Cell line	Key Outcomes	Reference
Streptomyces bikiniensis	Nanorods; 17 nm	10, 25, 50, and 100 µg/mL	MTT dye reduction assay	Hep-G2 and MCF-7 human cancer cells	$ID_{50\%}$: 75.96 µg/Ml and 61.86 µg/mL. Loss of cell-to-cell contact, cell shrinkage, and formation of apoptotic bodies. Higher reduction of cell viability in Hep-G2 (42.3-86.9%) than MCF-7 (37.5-69.1%).	[378]
Cassia auriculata leaf extract	10–20 nm	0.5 to 150 µg/mL	MTT assay	Human leukemia (HL-60) and Vero cell line	Antileukemia activity in a dose-dependent manner with a CC50: 7.01 µg/ml (HL-60) and 109.13 µg/ml (Vero cells)	[139]
Garlic cloves *Allium sativum extract*	Spherical; 40-100 nm	15, 30, 60 and 90 µg/ml	MTT assay	Vero cell line	CC50 of 31.8 ± 0.6 µg/ml	[138]
Chitosan (CH-SeNPs) and *Pleurotus ostreatus* fermented fenugreek (SeNPs-AEFFP)	Spherical; CH-SeNPs: 45 nm SeNPs-AEFFP: 11.8nm	**CH-SeNPs:** 1.187-38 µg/mL **SeNPs-AEFFP:** 0.594-19 µg/Ml NPs exposed at gamma ray doses of 60 kGy and 15kGy, respectively against EAC and CACO cells	Trypan blue (0.5%) assay	Ehrlich Ascites Carcinoma (EAC) and human Colon Adenocarcinoma (CACO)	For EAC: **CH-SeNPs:** IC_{50}=23.12% **SeNPs-AEFFP:** IC_{50}=7.21% For CACO: **CH-SeNPs:** IC_{50}=25.32% **SeNPs-AEFFP:** IC_{50}=8.57% Biogenic Se NPs exhibit a repression of concentration dependent against cells of EAC and CACO and a selective cytotoxic effect.	[104]
E.Coli	Spherical, elliptical and nanorods; 60 nm	20, 60, and 100 µg/ml	MTT and addition of DMSO. Apoptosis pathway involved caspase-3	A549 lung cancer cells and IMR-90 normal fibroblast cells	Cell viability of ~70%, ~45% and ~25%, high generation of ROS and elevated caspase-3 activity.	[381]
PLAL method	Spherical; 144 ± 46 nm	0.05 to 1 ppm for between 24 and 72 h	MTS assay	Human melanoma and glioblastoma cells, and primary human dermal fibroblasts (HDF)	Increase in the production of ROS in a dose-dependent manner	[382]
Bacillus licheniformis JS2	Spherical; 110 nm	1, 2, 4, 6, 50, or 200 µg Se/ml for 24 h	Colorimetric XTT assay, activation of caspase-3/7	A human prostate epithelial carcinoma	Overexpression of TNF and interferon regulatory factor (IRF1), reducing the expression of androgen receptors.	[377]

			activity, DMSO treatment and hemolysis assays	cell line (LNCaP-FGC)	SeNPs decreases the cell viability independent to apoptosis and necrosis. SeNP induces cell death neither through apoptosis nor necrosis.	
Streptomyces minutiscleroticus M10A62	Spherical; 10-250 nm	50-100 µg/ml	MTT	Hep-G2 (Hepatic carcinoma) and HELA (cervical carcinoma) cell lines	50 µg concentration of SeNPs was required for 99.5% HepG2 growth inhibition and 100 µg for 100 % growth inhibition of HeLa.	[357]
Bacillus licheniformis JS2	110 nm	Minimum [] of 2 µg Se/ml	Real-time qPCR analysis; confocal microscopy; treatment with cytochalasin D	Human prostate adenocarcinoma cell line (PC-3);	ROS mediated necroptosis of PC-3 cells independent to RIP3 and MLKL and regulated by a RIP1 kinase. Increased expression of necroptosis associated TNF and IRF1	[240]
Fenugreek seed extract	Amorphous; 50–150 nm.	25, 50, 75, and 100 µg/ml for 24 h	MTT assay	MCF-7 breast-cancer cells	SeNPs augment the cytotoxicity of doxorubicin and induces MCF 7 cell death through apoptosis.	[166]
Idiomarina sp. PR58-8	Spherical; 150-350 nm.	5-100 µg/ml for 24 h	MTT assay, ROS assay, apoptotic index assay, and western blot analysis.	Normal human epidermal keratinocyte cell line, HaCaT, and HeLa cells	Caspase-dependent apoptosis in HeLa cell lines: decrease in expression of pro-caspase 3. SeNPs exhibited dose-dependent cytotoxicity with only 3% viability at 100 µg/ml.	[379]
Acinetobacter sp. SW30	Nanospheres and crystalline nanorods of 78 nm. Polygonal-shaped SeNPs of 79 nm.	0–100 µg/mL	MTT assay	Cancer cells (4T1, MCF-7) and noncancer cells (NIH/3T3, HEK293)	Antiproliferative activity	[34]
Bacillus sp. MSh-1	Spherical; 80–220 nm	10, 20, 50 and 100 µg/mL	MTT assay and gelatin zymography	Human fibrosarcoma cell line (HT-1080)	The presence of 100 µg/ml of NPs decreases the viability percentage of the cell line to 50%, whereas lower dose levels (10 µg/ml) shows a small amount of cytotoxicity with a viability percentage of more than 80 %.	[383]
Asteriscus graveolens extract	Spherical; 20 nm	25–125 mg/mL for 24 h.	MTT assay, flow cytometry analysis, Measurement of ROS (conversion from DCFH-DA to DCF); measurement of	HepG2 cells line	Cell viability (IC50): 51.8% at 3.98 µg/Ml Se-NPs inhibits the growth of the HepG2 cell mainly by induction of the apoptosis. They also significantly and rapidly increase the level of ROS	[233]

			MMP and lipid peroxidation			
M. Oleifera extract	Spherical; 23-35 nm Polygonal; 25-45	N/A	MTT assay	CACO-2 cells, HepG2 cells, and MCF-7 cells	IC50: 50.3% at 392.57 µg/mL	[148]
Penicillium corylophilum	Spherical; 29.1–48.9 nm	1000, 500, 250, 125, 62.5 and 31.25 ppm incubated in 5% CO_2 incubator at 37 °C for 1 day	MTT assay	Normal Wi 38 and human cancer colorectal adenocarcinoma epithelial (Caco-2) cell line	IC50: 171.8 ppm (Wi 38) and 104.3 ppm (Caco-2)	[384]
Hawthorn fruit extract (HE)	113 nm	0, 5, 10 and 20 µg/mL for 24 h	MTT assay; Flow cytometric analysis; ROS detection; MMP measurement; Western Blotting	HepG2 cells line	IC50: 54.2 % at 19.22 ± 5.3 lg/mL.	[142]
Lactobacillus casei 393	Spherical; 50~80 nm	4, 8, and 16 µg/ml for 12 h	Real-time PCR analysis; the mRNA expression levels of Bax, Caspase-3, P53 and Bcl-2.	HepG2 cell line, NCM460.	Endocytosis of SeNPs induces cell death by reducing the viability of HepG2, increasing the mRNA levels of caspase 3, bax, and p53, and reducing the mRNA expression of bcl-2.	[352]
Carica papaya latex	Spherical; 70 nm	5, 10, 15, 20, 25, 30, 35, 40, 45, and 50 µg/mL at 48 h	MTT assay	Normal (HBL100) and cell type of breast cancer (MDA-MB-231)	IC50 (HBL100): 50 µg/mL IC50 (MDA-MB-231): 34 µg/mL	[385]
Spermacoce hispida aqueous leaf extract (Sh-SeNPs) + S-allyl glutathione conjugation *(*SAG-Sh-SeNPs*)*	Sh-SeNPs: aggregation SAG-Sh-SeNPs: spherical; 50 nm	HepG2 cells: 1.88, 3.75, 7.5, 15 and 30 µg/ml for 24 h Vero cells: 3.7–60 µg/ml for 48 h	MTT assay; Determination of intracellular ROS production and MMP; Cell cycle analysis by flow cytometry; DNA fragmentation assay; determination of apoptosis by	HepG2 cell line and Vero cells	IC50 (Sh-SeNPs): 30 µg/ ml IC50 (SAG-Sh-SeNPs): 18.7 µg/ ml SAG-Sh-SeNPs induce cell cycle arrest at sub-G1 phase and further lead to apoptosis. The NPs increase ROS levels, disrupt MMP, initiate DNA fragmentation and decrease the endogenous antioxidants level such as GSH, superoxide dismutase, catalase and GSH peroxidase.	[386]

			acridine orange/ethidium bromide staining;			
Undaria pinnatifida polysaccharides	Spherical; 44-92 nm (average of 59 nm)	N/A	MTT assay; Flow cytometric analysis; *Annexin-V-FLUOS staining assay; Measurement of ROS levels; MMP evaluation*	A375, CNE2, Hep G2 and MCF-7 cancer cells	IC50 values ranging from 3.0 to 14.1μM. Apoptosis with the involvement of oxidative stress and mitochondrial dysfunction.	[387]
Ceropegia bulbosa tuber's aqueous extracts	Spherical; 55.9 nm	0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50 μg/mL	MTT assay	Human breast malignance cells (MDA-MB-231) and epithelial cell line (HBL-100 cells)	IC50 (MDA-MB-231): 34 μg/mL for 48 h. IC50 (HBL-100): more than 50 μg/mL at 48 h.	[362]
Diospyros montana leaf extract	4 to 16 nm	50, 150, 250, 350 μg/mL	MTT assay	MCF-7 cancer cells	IC50: 80.83 μg/mL, SeNPs can enhance the cytotoxicity.	[140]
Chitosan decoraction	Spherical; 50 nm	10, 50, 100 μM	WST-1 assay	HepG2 cell line	SeNPs decrease the cell viability to 76.63, 63.31 and 56.34% and inhibit the growth of HepG2 cells in a time- and dose-dependent manner.	[345]
Ephedra aphylla Extract	Spherical and tetragonal; 13.95-26.26	N/A	MTT assay	HePG-2, HeLa, MCF-7, Colorectal carcinoma (HCT-116), Epidermoid larynx carcinoma (HEP2), Human prostate cancer (PC3)	IC50 (HePG-2): 7.56 ± 0.6 μg/mL IC50 (MCF-7): 15.65 ± 1.4 μg/mL IC50 (HCT-116): 10.02 ± 0.9 μg/mL IC50 (HeLa): 9.23 ± 0.8 μg/mL IC50 (PC3): 18.63 ± 1.5 μg/mL IC50 (HeP2): 12.10 ± 1.2 μg/mL	[346]
β-glucan with triple helical conformation (Lentinan)	Spherical; 28 nm	N/A	MTT assay	HeLa cells	IC50 of three complexes Se/s-LNT-1, Se/s-LNT-2, Se/s-LNT-3 were estimated to be 85, 37,and 19 μM. SeNPs with small uniform size largely enhanced the antitumor activity and bioavailability.	[388]
Two phytochemicals: quercetin and gallic acid	Bimetallic Ag-Se NPs of 30–35 nm and capped by	50, 100, 250 and 500 μg/mL	MTT assay	Dalton lymphoma (DL) cells	The viability of DL cells was 20% at 50 μg/mL Ag-SeNPs, while at 100 μg/mL, it is significantly reduced to 15%. The Ag-SeNPs showed strong anticancer activity at a lower concentration.	[349]

	flavonoid and phenolics.					
Cationic pullulan (CP)	Spherical and microflowers; 50 nm	N/A	MTT assay; AnnexinV-FITC and propidium iodide (PI) staining	Normal cells (L929) and KB (cervical carcinoma) human cancer cell line	IC50: 0.060 μM. The early- and late-stage apoptotic rates of KB cells treated with doxorubicin only reached 0.52% and 4.64%, respectively and the highest induction of 55.8% was arrested in the necrosis rate.	[389]
Walnut peptides	Spherical; 89.22 nm	200 μL/mL	MTT assay; POM, Flow cytometry; MMP assay; Nuclear morphology analysis by Hoechst 33258; Measurement of ROS Production; DNA fragmentation assay; Caspase activity assay; Western Blot	HL-7702 (L02) cell, MCF-7 cell, SGC-7901 cell, A549 cell, PC3 cell, and HeLa cell.	MCF-7 cell was most sensitive to SeNPs. The apoptosis-inducing activity was proved by the accumulation of S-phase cell arrest, nuclear condensation, and DNA breakage. The intrinsic signal pathway was through the activation of FADD and caspases 3, 8, and 9, in combination with the MMP depletion and ROS generation.	[390]

Moreover, green-produced SeNPs using garlic *Allium sativum* demonstrated less cytotoxic effect against Vero cells than conventional chemically synthesized SeNPs [138]. Biogenic SeNPs fabricated using the reducing power of fenugreek seed extract, were able to inhibit the cell growth of human breast-cancer cells (MCF-7) by dose-dependent manner [166]. Elemental SeNPs were injected into the abdominal cavity of mice, following the inoculation of highly malignant H22 hepatocarcinoma cells, revealing that the cytotoxic effect is linked to Se-mediated production of ROS [391]. The SeNPs of *Ephedra aphylla* extract revealed very strong cytotoxicity against HePG-2 cells with high inhibition values and low relative viability at different concentrations (1.56–100 μg/mL) [346].

According to [233] green spherical SeNPs synthesized using *Asteriscus graveolens* leaves extract induced ROS over production and mitochondrial membrane potential (MMP) disruption, thus evidencing high antitumour activity through the activation of apoptosis pathways of downstream signalling in HepG2 cells (Fig. 12). D. Cui, Liang, et al. (2018) reported increased apoptosis rates in HepG2 cells after treated with biogenic SeNPs from extract of hawthorn fruit, exhibiting up-regulation of caspase-9 and down-regulation of Bcl-2. Krishnan et al., (2019) conjugated S-allyl glutathione (SAG) with SeNPs biosynthesized using *Spermacoce hispida* aqueous leaf extract (SAG-Sh-SeNPs) and tested their anticancer effect and induction of cell cycle arrest.

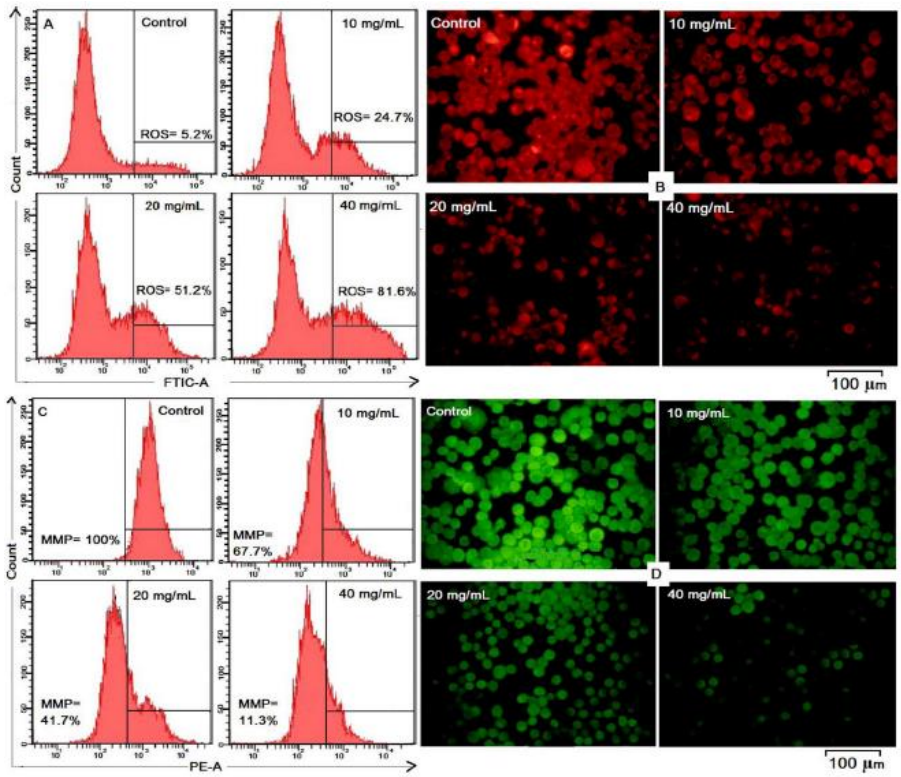

Figure 12. Measurement of the Generating A) MMP and C) ROS induced by various concentrations (10–40 mg/mL) of Se-NPs using flow cytometry: B & C microscopy illustration of MMP and ROS production. [233]

11.1.4 Protective Role of Selenium Nanoparticles in Drug Induced Toxicity

Notwithstanding the widespread application of chemotherapeutic drugs in clinic tumor treatment, serious toxicity, dose-dependent side effects and non-specific targeting restricts their therapeutic efficacy [392]. Thus, Nano-Se has been considered a potent chemotherapy preventive agent due to its high bioavailability and low toxicity. For example, SeNPs induced a significant tumor cell apoptosis and impressive enhancement of therapeutic effect of irinotecan by a selective modulation of Nrf2-ARE pathway in tumor tissue and normal tissue [393]. Anastrozole is an aromatase inhibitor drug mainly used for breast cancer treatment. In an experiment, SeNPs (1 mg/kg/day) efficiently alleviated anastrozole induced bone toxicity, preventing the occurrence of osteoporosis in ovariectomized female SD rats [394]. This study indicates that bone loss for estrogen can be successfully solved by using SeNPs. Moreover, encapsulated nanoepigallocatechin-3-gallate and elemental SeNPs dispersed by BSA showed notably superior chemopreventive effects [82].

Moreover, Shirsat et al. (2016) synthesized SeNPs by using *Pentoea agglomerance* strain E and investigated their protective role in immunological and oxidative stress generated by Enrofloxacin (EFX) in broiler chicken with a simultaneous exposure of SeNPs (0.6 mg/Kg of feed). Dahdouh et al. (2019) reported on the protective effects of SeNPs against Gentamycin-induced nephrotoxicity and hematotoxicity in female swiss albino mice. SeNPs demonstrated to have protective effect on hexavalent chromium-induced thyroid damage [94].

Cisplatin (CIS) is a highly used alkylating agent for cancer treatment such as testicular, ovarian, head and neck, among others [397]. Despite its widely clinical applications, CIS produces many side effects including the obstruction of some metabolic cellular processes i.e. DNA replication and transcription by inducing DNA adducts and establishing DNA cross-links [398]. Prior research has thoroughly investigated the protective activity of SeNPs against CIS toxicity [274,399,400]. For example, Rezvanfar et al. (2013) demonstrated that SeNPs possess a strong antioxidant potential to prevent CIS-induced gonadotoxicity. Another study employed 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (trolox) surface-functionalized SeNPs (Se@Trolox) to block the cisplatin-induced ROS accumulation [401].

SeNPs decorated with amantadine (Se@AM) remarkably prevented the caspase-3 activation and decreased ROS levels to inhibit the ability of H1N1 influenza virus to infect host cell, thereby overcoming the emergence of drug-resistant viruses [402]. SeNPs showed protective effects in the progression of diabetic nephropathy (DN) by increasing the levels of heat shock protein (HSP-70) (Kumar et al., 2014). Another study documented that Nano-Se increased the number and the survival duration of neutrophils in healthy sheep using thiobarbituric acid reactive substances (TBARS) assay [403].

Arsenic (As) cell exposure induces DNA damage by inhibiting repair proteins such as excision repair cross-complement 1 (ERCC1) and zinc fingers DNA repair proteins [75,404]. Biogenic SeNPs synthesized with *Terminalia arjuna* leaf extract showed protective and antigenotoxic effects [93]. Cadmium (Cd) exposure produces high ROS levels, regarded as Cd-induced neurotoxicity and nephrotoxicity [405]. Se has been recognized as an effective chemo-protectant against Cd toxicity, for example, Cong Zhang et al. (2020) demonstrated that Nano-Se, sodium selenite and Yeast-Se diet had different protective proficiency in Cd induced testicular damage by improving the selenoprotein expression via regulating the SEPSecS and other selenoprotein synthesis. Another study indicated the chemoprotective effects of SeNPs against neuro- and nephrotoxicity of subchronic cadmium chloride, mainly due to the inhibition of lipid peroxidation (LPO) and regulation of genes encoding numerous detoxifying and antioxidant enzymes [405].

Trichoderma harzianum-derived SeNPs (TSNPs) exhibited high protective effects in infected foodstuffs with main hosts of the *Fusarium* and *Alternaria*, maize and pear [372]. Thus, the proposed TSNPs may be applicable as bifunctional nanomaterials for biocontrol of phytopathogens and mycotoxins in agriculture and food safety. Furthermore, the potential ability of biologically synthesized SeNPs by terrestrial actinomycete *Streptomyces griseobrunneus* strain FSHH12, for elimination of diclofenac (DCF) in the presence of UV light was assessed [407]. In this study, a high concentration of Se NPs (64 μg/mL) could remove 94% of the DCF through hydroxylation, oxidation, and decarboxylation reactions.

11.1.5 Anti-inflammatory Activity

Trachyspermum ammi derived biogenic SeNPs exhibited anti-rheumatic and immunomodulatory properties in arthritic Balb/c mice [408]. The results showed that SeNPs treatment reduced paw edema along with decreased lymphocytic cellular infiltration in the histopathological finding, as well as improved the redox state of inflamed synovium. A similar study confirmed that SeNPs dispersed in phytochemical P-Coumaric acid (CA) exert anti-inflammatory activity by modulating catalase, GPx1, and COX-2 gene expression in a rheumatoid arthritis rat model [409].

Biogenic SeNPs synthesized by *L. casei* ATCC 393 possessed strong antioxidant and anti-inflammatory activity to effectively protect human colon epithelial cells against H_2O_2 induced injury [353]. X. Yuan et al. (2020) mentioned that SeNPs are a promising anticonvulsant agent due to their potent antioxidant, anti-inflammatory, and neuromodulatory activities against pentylenetetrazole (PTZ)-mediated epileptic seizures in mice hippocampus. Alkhudhayri, Dkhil, and Al-Quraisy (2018) demonstrated that SeNPs are more effective than sodium selenite with regard to their anti-oxidant, and anti-inflammatory role against eimeriosis induced in the jejunum

of mice, and therefore could be used in immunoregulation. El-Ghazaly et al. (2017) corroborated that Nano-Se possesses a potential anti-inflammatory activity through down-regulation of the pro-inflammatory genes and mediators (i.e. TNF-α, PGE2, TBAR, and NOx) and/or in addition to its anti-oxidant activity. Moreover, SeNPs were found to ameliorate streptozotocin-instigated brain oxidative-inflammatory stress and neurobehavioral alterations in rats by regulating molecular markers of oxidant stress and tissue damage, Nrf2, caspase-3, and parvalbumin proteins [413].

Macrophages play a vital role in chronic inflammatory diseases (CIDs), so regulating activated macrophage is crucial into detecting and reducing chronic inflammation [414,415]. *Ulva lactuca* polysaccharide decorated SeNPs displayed anti-inflammatory effects to diminish the symptoms of acute colitis through inhibition of the hyper activation of NF-κB in colonic tissues and macrophages [416]. SeNPs reduced H_2O_2 produced by the pro-inflammatory-activated macrophages and selectively imaged and killed pro-inflammatory-activated macrophages under photodynamic treatment [417]. Stable SeNPs decorated by sulfated *Ganoderma Lucidum* polysaccharides inhibited inflammation caused by over-activated macrophages for Raw 264.7 cells in a dose-dependent manner [418].

11.1.6 Antidiabetic Activity

Diabetes mellitus (DM) is defined as a group of metabolic disorders characterized by decrease in insulin secretion by pancreatic islet cells leading to high blood glucose levels (hyperglycemia) [419]. Diabetes is classified into two major types: type-I diabetes mellitus or insulin dependent diabetes, and type-II or non-insulin dependent diabetes. Type-I diabetes mellitus cause a deficiency of insulin due to autoimmune or genetic disorders, and type-II generates an insulin resistance or reduced insulin sensitivity as a result of inappropriate diet or lack of physical activity [420]. Advances in nanotechnology, molecular and biomedical imaging tools, and drug delivery systems are offering new opportunities for early diagnosis and monitoring of disease progression for patients with type 1 or type 2 diabetes combined with diminished insulin secretion [421].

Prior research has thoroughly explored the association between selenium concentration and diabetes [422–427]. Patients with DM are often affected by oxidative stress, requiring more antioxidant species to reduce the oxidative and inflammatory response [428]. Se has been confirmed to possess excellent antioxidant and anti-inflammatory effects against DM [429,430]. Therefore, several studies investigated the pivotal therapeutic role of SeNPs in alleviating most of diabetic complications and insulin resistance [46,321,431,432]. Recent research has demonstrated the antidiabetic potency of elemental SeNPs to increment insulin secretion by preserving pancreatic β cell integrity, repressing oxidative stress, inducing glucose depletion and inhibiting pancreatic inflammation [433].

Biosynthesized SeNPs by using *Hibiscus sabdariffa (roselle plant*) leaf extract could significantly reduce the oxidative stress indicators of the testicular tissue in streptozotocin (STZ) induced diabetic rats such as nitric oxide and lipid peroxidation [133]. This experimental work found the promising effects of SeNPs in attenuating oxidative damage induced by diabetes, especially in testicular tissue. A similar research revealed that administration of SeNPs prepared with *Catathelasma ventricosum* polysaccharides (CVPs-SeNPs) could significantly ameliorate the body weight, blood sugar, antioxidant enzyme activities and lipid levels of STZ-induced diabetes mice, indicating the dramatically antidiabetic activity of the nanoparticles [431]. The authors suggested the natural synergy of CVPs-SeNPs and Vitamin E in antidiabetic activity. Nevertheless, the mechanisms are not yet clearly understood, thus further studies should be conducted to investigate action mechanisms deeply.

A novel peptide-conjugated, chitosan-modified SeNPs (SCD), consisting of a recombinant PACAP-derived peptide DBAYL capable of specifically activating VPAC2 receptor, and chitosan-modified SeNPs enhanced insulin sensitivity, hyperglycemia and lipid profiles, thus demonstrating the potential to become a long-acting anti-T2D therapeutic [432]. Chitosan-decorated SeNPs (CH-SeNPs) were used to treat diabetes mellitus by reducing its renal clearance rate [320] . This study proved that BAY-CS-SeNPs possessed a desirable sustained-release profile, high stability and could enhance the half-life of low-molecular-weight therapeutics by increasing their apparent molecular size. Abd El-Hakim et al. (2021) demonstrated that CH-SeNPs in combination with metformin (MF) was an effective treatment for T2DM by limiting the diabetic complications largely than monotherapeutic approach. and considerably rescued the T2DM-induced sperm abnormalities, reduced sperm motility, diminished sexual hormones level, testicular oxidative damage, and steroidogenesis-related genes dysregulation. Further, similar studies showed the antidiabetic effect of CH-SeNPs as monotherapy or combined therapy with drugs able to decrease fasting blood glucose and insulin levels (Abdel-Rahman Mohamed et al., 2020) and nanohybrid systems to treat diabetic wound infection at mild stage [435].

11.2 Diagnostic Applications

Nanotechnology has led to the development of various NP formulations for diagnostic applications, thereby revolutionizing treatment strategies of relevant diseases such as cancer [21,196], gastrointestinal disorders [436] and infectious diseases [437]. Imaging and point of care technologies are two specific fields that could benefit from utilization of NPs. However, nanodiagnostics are useful in limited clinical situations due to complex demands on pharmacokinetic activity and clearance [438]. The application of SeNPs is of particular interest as it has high photoconductivity, piezoelectricity, thermoelectricity and spectral sensitivity

properties. For instance, optical and photoluminescence properties of Se nanomaterials can be exploited for the fabrication of nanosensors and imaging markers, eliminating the requirement for additional fluorescent tags including protens or dyes [203]. In the subsequent sections, some diagnostics applications of biogenic SeNPs will be addressed.

11.2.1 Detection and Biosensors

Recent studies have been developing innovative and sophisticated devices, named nanobiosensors, due to the increasing demand for sensing a great variety of molecules at low concentrations with high specificity and good biocompatibility [330,439,440]. Nanobiosensors are basically the sensors which are made up of nanomaterials due to their electronic and mechanical properties for their use in enhanced biological signaling and transduction mechanisms [441]. The main contribution of NPs is immobilizing bioreceptors, catalyzing bioreactions, mediating electron transfer, amplifying mass change, and enhancing refractive index changes [440]. Conventional techniques for immobilizing enzymes are physical adsorption, entrapment and covalent cross-linking, which present shortcomings like the leakage and partial denaturation of the enzyme. Compared with classical macroscopic materials, nanomaterials possess large surface-to-volume ratios, which enable them to serve as superior enzyme supports [442].

Biogenic NPs offer significant advantages over those synthesized by conventional methods such as their stability up to months that leads to simple, rapid, nontoxic, cost-effective and handy sensing strategies [34,326,327,341]. Indeed, the proteins and biomolecules in the nanoformulation bind to the surface of the NPs, preventing aggregation or flocculation and conferring a long-term stability [443,444]. Furthermore, green-chemistry techniques can potentially improve biosensing applications such as transducers or electroactive labels, especially in nanoparticle-based electrochemical detection systems [439,445]. Thus, the emerging greener biosensor chemistry can be relevant for point-of-care handling due to nontoxic activity [446].

Recently, hydrogen peroxide (H_2O_2) has received somewhat greater attention as an important analyte for human metabolism because any imbalance can cause the damage of lysosomal membrane and genomic DNA or induction of apoptosis [447–449]. Therefore, reliable, accurate and rapid sensing techniques for cellular peroxide detection is of practical importance [450]. For instance, Biogenic capped Se nanorods fabricated by using citric acid and flavonoids from lemon juice, served as H_2O_2 spectrometric sensor with interfering ions and naked eye visual color change technique from reddish to faint pink [451]. This study also demonstrated a morphology change by chemical surface leaching from nano-rod to nano-oval, proving the selectivity of Se nanomaterials to peroxide and other cations. Moreover, spherical monoclinic SeNPs synthesized by the *Bacillus subtilis* exhibited high electrocatalytic activities to detect H_2O_2 and showed good adhesive ability and biocompatibility [124]. Prasad et al. (2015) reported that

biosynthesized, colloidally stable SeNPs from *Bacillus pumilus* sp. BAB-3706 cell-free extracts were employed to fabricate a low cost, sensitive and reproducible H_2O_2 biosensor.

Green Se nanospheres fabricated using the bacterial isolate *Pseudomonas aeruginosa* strain JS-11 were used to construct a biosensor for nanotoxicity assessment, involving the inhibition of SeO_3^{2-} bioreduction process in NPs treated bacterial cell culture supernatant, as a toxicity end point [453]. This novel Se-bioassay could be easily applicable for prescreening of a plethora of environmental toxicants including nanostructures prior to intensive toxicity investigations. H. Cao, Xiao, and Liu (2019) reported the improved oxidase-like activity of SeNPs stabilized by chitosan by providing an economical colorimetric method for Hg^{2+} detection with a detection limit of 0.12 μM. This investigation broadens the application of SeNPs in chemical sensors.

11.2.2 Cellular Imaging

SeNPs have become one of the most prospective and potential tools for cancer diagnosis and therapy. For example, Korany et al. (2020) fabricated SeNPs capped with glutathione as a novel radio-platform for tumor imaging by studying the radiochemical yield of radioactive technetium-99m (^{99m}Tc) in intravenous (I.V.) and intratumoral (I.T.) routes. D. Sun et al. (2014) showed that luminescent Ru(II)-thiols SeNPs possessed high tumor-targeted fluorescence imaging in HepG2 and HUVECs cells, and displayed improved antitumor efficacy and decreased systemic toxicity. In this study, the functionalized SeNPs exhibited well-defined time-dependent increase in fluorescence intensity from 115 ± 17 after 0.5 h to 1171 ± 127 after 4 h. J. Huang et al. (2019) synthesized SeNPs with epidermal growth factor receptor (EGFR) to construct a smart drug-delivered nanoplatform and achieve simultaneous diagnosis, real-time monitoring and therapy of cancer. EGFR was used as the targeting molecule, gadolinium chelate as the magnetic resonance imaging contrast agent, polyamidoamine (PAMAM) and 3,3′-dithiobis (sulfosuccinimidyl propionate) as the response agents of intratumoral glutathione, 5-fluorouracil (5Fu) and cetuximab as drug payloads, and pH for the treatment and diagnosis of nasopharyngeal carcinoma (NPC).

Vitamin C is a notable antioxidant human vitamin highly employed as coating in NPS to prevent aggregation and achieve enhanced control and stabilization. Vitamin C-stabilized selenium nanoparticles, Vit_C (SeNPs) were manufactured and labeled with ^{99m}Tc for further in vivo studies on normal and solid tumor induced mice [51]. The authors found an increased antioxidant activity of the resulting nanoparticles leading to improved uptake and retention by tumor cells. Another study developed an siRNA-delivery system for vascular endothelial growth factor (VEGF), a known signaling molecule involved in cancer, that comprises two nanostructures, SeNPs@siRNA and G2/PAH-Cit/SeNPs@siRNA [457]. The component

G2/PAH-Cit/SeNP is a pH-sensitive delivery system able to improve siRNA loading [457]. This study also demonstrated that the utilization of the pH-sensitive functional SeNPs results in no occurrence of lesions in major target organs, thereby offering a novel and promising alternative for cancer treatment.

Furthermore, photodynamic SeNPs with photosensitive and macrophage-targeting bilayers for controlling activated macrophage and quenched the intracellular H_2O_2 and NO that are associated with chronic inflammation diseases (CIDs) were developed [417]. The first layer of the photosensitive system consisted of principally of a conjugate of a photosensitizer (rose bengal, RB) and a thiolated chitosan (chitosan-glutathione), and the second layer was fabricated by conjugation of hyaluronic acid with folic acid using an ethylenediamine linker. Khalid et al. (2016) reported the intrinsic fluorescence intensities and lifetimes of individual SeNPs in the visible to near infrared range, which allows their application for real-time tracking and imaging in cells, without the addition of chemical tags or dyes that serve to change the biological environment under study [458].

Biogenic SeNPs produced by the Se-tolerant *Stenotrophomonas maltophilia* SeITE02 strain, showed higher ability to emit light (photoluminescence [PL]) than their chemical counterparts (i.e. fluorophores) thus representing potential markers for bioimaging and Fluorescence Lifetime Microscopy (FLIM) [203]. Y. Zhao et al. (2018) performed a green and controlled synthesis of SeNPs through a self-assembled method on molecular imprinting sites of zeolite-chitosan-TiO2 microspheres by coupling chitosan biosorption and TiO2 photocatalysis. Cruz et al. (2019) biosynthesized SeNPs from *E. coli* culture and evaluated their radio-sensitizing effect in the presence of X-rays against A549 lung cancer cell line, revealing their high cytotoxic potential. Besides, SeNPs fabricated by the marine selenite-reducing bacterium *Lysinibacillus* sp. ZYM-1 showed visible light-driven photocatalytic activity for Rhodamine B (RhB) degradation with H_2O_2 [207].

Chapter VI

12. Role of SeNPs against SARS-CoV-2

Since November 2019, the pandemic outbreak of coronavirus disease 2019 (Covid-19), with millions of infected patients worldwide, has recently become a public health emergency of international concern [460]. It arose from the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, whose rate of spread is greater than that for severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory coronavirus (MERS-CoV) [461,462]. The clinical manifestations of SARS-CoV-2 infected patients include fatigue, fever, pneumonia, dry cough, diarrhea, strokes, loss of taste or smell, conjunctivitis, leucopenia, and lymphopenia [463,464]. Coronaviruses are common human pathogens as enveloped, positive-sense and single-stranded RNS viruses that belong to the family Coronavirdiae [465]. They are the largest known group of viruses causing acute respiratory, gastrointestinal, and neurological diseases with varying severity in humans as well as animals [466]. Also, coronaviruses possess a cell membrane structure with three kind of proteins: spike glycoprotein (S, Spike Protein), membrane glycoprotein (M, Membrane Protein), small envelope glycoprotein (E, Envelope Protein), and a few types present hemagglutinin glycoprotein (HE protein, Haemaglutinin-esterase) [467]. Besides the mediating virus entry, the spike is an essential determinant of viral host range and tissue tropism and a major inducer of host immune responses [468].

The accelerated and continuous increase of global pandemic has generated serious problems for countries' health organizations and caused a profound socio-economic crisis due to the quarantine [469–471]. Quarantine has been associated with stress and depression leading to unhealthy diet, anxiety, and low physical activity. In consequence, it carries some long-term effects on cardiovascular diseases [472,473]. Therefore, emergent attempts for controlling the virus incidence by rapid diagnosis of the new cases and developing effective therapeutics are fundamental. The focus should be on designing and adopting safe approaches from a cellular and molecular level to characterize the nascent nano-drug agents as diagnostics, therapeutics or viral entry inhibitors [474,475].

In this regard, nanobiotechnology by linking nanoscience and virology has shown tremendous promising potential to present a smart molecular diagnosis/treatment for pandemic viral infections [476–478]. For example, synthetic NPs have demonstrated to have high antiviral activity and can closely mimic the virus and interact strongly with its virulent proteins due to their morphological similarities [479]. This would be advantageous for early detection and the development of safe and useful therapeutic management of COVID-19. Also, nanostructures are able to deliver viral antigens in a controlled manner, activate follicular dendritic cells or B cells, antigen cross-presentation, as well as produce humoral/cellular immune responses [480].

Among the investigated nanoparticle-based strategies to combat COVID-19, there are NPs for diagnostics (metal NPs and metal nanoislands, magnetic NPs, quantum dots), NPs for therapeutics that block cell attachment, viral entry, and viral replication and proliferation, and NPs as immunogenic agents for vaccines (virus-like particles or chitosan, protein cage, and polymer NPs for targeted vaccine delivery) [481]. For instance, a colorimetric AuNP-based assay conjugated with thiol-modified antisense oligonucleotides to detect the gene of SARS-CoV-2 N protein was developed [482]. Also, a nanoparticle-based lateral flow biosensor integrated with multiplex reverse transcription loop-mediated isothermal amplification was constructed for the diagnosis of COVID-19 [483]. Abo-zeid et al. (2020) reported a docking model study of the interactions between iron oxide nanoparticles ($Fe2O_3$ and $Fe3O_4$) with the spike protein of SARS-CoV2 that is responsible for its attachment and entry into host cells.

A large number of reports indicated the direct association between selenium and SARS-CoV-2 [485–491]. For instance, Zhang et al. (2020) documented that synthetic redox-active selenium compound, ebselen, is a strong inhibitor of the main SARS-CoV-2 protease that enables viral maturation within the host. This study suggested that high Se intake might hypothetically inhibit SARS-CoV-2 proteases and promote a higher cure rate. Poor Se status is linked with viral virulence, thus intravenous Se therapy and high-dose selenite pharmaconutrition have been proposed to be effective at reducing the occurrence and the progression of multiorgan failure, and new infections in Covid-19 patients [493]. Overall, human Se levels are crucial in antioxidant, anti-inflammatory, and immune effects in COVID-19, thus it is important to study Se-deficient and Se-enrichment areas, especially those with patients with pre-existing comorbidities or long diseases [494].

Recently, Nano-Se has been suggested to be an ideal tool to fight against SARS-CoV-2 and improve the health outcomes of COVID-19 patients due to its particularities such as low toxicity, antioxidant effect, high sensitivity, high selectivity, and immunity-boosting capabilities [495,496]. Nano-Se was found to possess much lower acute toxicity than other Se compounds

with similar bioavailability and antioxidant effects [497]. Also, SeNPs have shown significant anti-viral, antibacterial and cytotoxic activity [48,357,468,498]. For example, SeNPs decorated with amantadine (AM) were fabricated to reverse drug resistance caused by HI1N1 influenza virus infection through inhibition of caspase-3 activity and suppression of the neuraminidase activity [402]. A similar study demonstrated the superior antiviral capability of SeNPs against HI1N1 via regulation of AKT and p53 signaling pathways [496].

Moreover, SeNPs have been found to integrate simultaneous treatments of immunotherapy, chemotherapy, and radiotherapy because they not only possess a sensitive response to radiation stimuli but also excellent anticancer activity and immune checkpoint inhibitor effect with radiotherapy [499] . Indeed, SeNPs are able to deliver the chemotherapeutic drug doxorubicin (DOX) to tumor sites by systemic administration, thereby exerting immunomodulatory activity through enhancing NK cells function [499]. Moreover, SeNPs can effectively increment the persistence of cytokine-induced killer (CIK) cells in peripheral blood in the body. For instance, the combination of Nano-Se and CIK cells induce natural killer cells infiltrating in tumours and shape tumour-associated macrophages to trigger powerful immune responses for effective cancer immunotherapy [500]. Another study showed that SeNPs allow the signal transduction from lysosomes to the nucleus and further potentiate γδ T cell ati-tumor cytotoxicity, including the promotion of NKG2D, CD16, CD44, and IFN-γ production and inhibition of PD-1 expression [501]. Nano-Se has also been found to have good biocompatibility and can also be employed as an antiviral drug carrier. Therefore, contemplating all these distinctive characteristics and applications of Se nanostructure, it constitutes a promising tool for developing accurate diagnosis and thus, combating COVID-19.

The unique experimental study using selenium nanoparticle-based test for the combined detection of anti-SARS-CoV-2 IgM and anti-SARS-CoV-2 IgG in human serum was performed by [496]. The authors showed that lateral flow immunoassay kits (LFIA) with SeNPs modified with SARS-CoV-2 nucleoprotein, exhibit recent SARS-CoV-2 infection in just 10 minutes by the naked eye. Besides, the sensitivity and specificity of the kits were clinically performed with RT-PCR test in 90 COVID-19-diagnosed patients and 263 non-infected controls, resulting in 93.33% and 97.34% respectively. Finally, there were no cross-reactions with rheumatoid factor and positive serum for influenza A, influenza B, and anti-nuclear antibodies [496]. Similar studies have also shown point-of-care systems for detection of Immunoglobulin-G and –M against SARS-CoV-2 [502,503]. Hence, although little research has been conducted to show the potential of SeNPs to control COVID-19, it clearly shows superior antiviral nanotherapeutics for combating viral pandemic. By using Se nanobiotechnology to develop efficient and smart molecular and diagnosis treatments, the government and hospitals could formulate reasonable

prevention policies and treatment plans. The Fig. 13. indicates the biomedical role of SeNPs in diagnosis and therapeutics of viral infection of SARS-Cov-2.

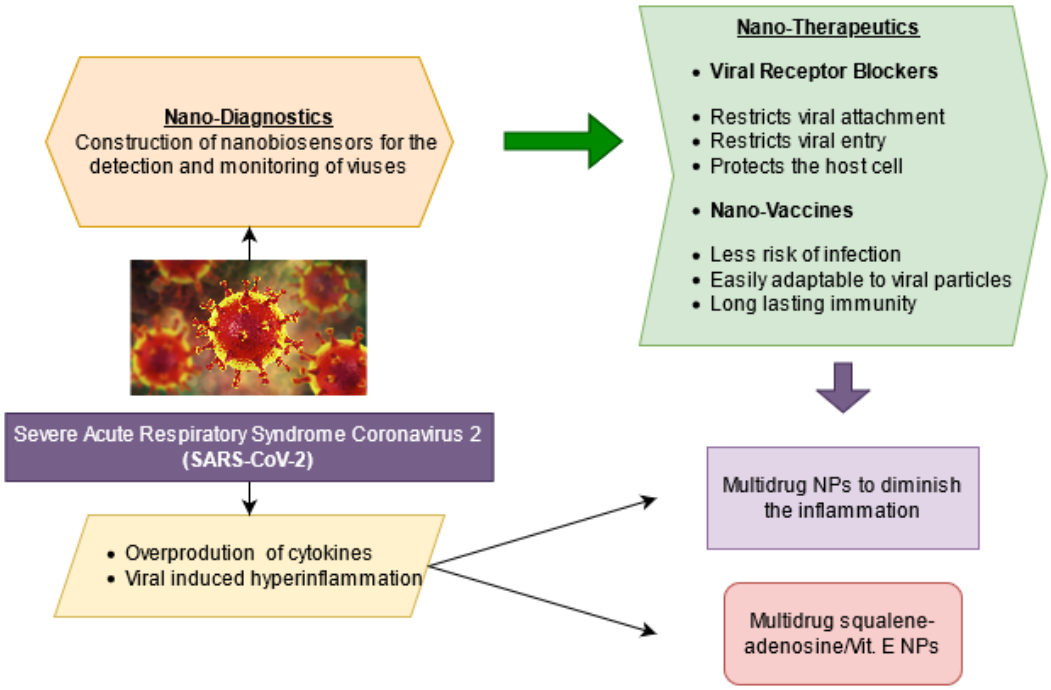

Figure 13. Biomedical application of SeNPs against SARS-CoV-2

13. Translational Nanomedicine: Challenges, Recent Progress and Future Prospects for biogenic SeNPs

Nanotechnology has been a pioneering technology with important benefits in different fields of science especially in biomedicine. To improve human health, scientific discoveries, which start at “the bench” with basic research, must be translated into practical applications by progressing to the clinical level named “bedside” [504]. Among the plethora of advantages of using nanotechnology in molecular medicine are: local and ultrafast strategies at the nanometer length scale (i.e. diffusion, intermixing, sensoric response), controlled and intensified physical and chemical processes, direct access to biomarkers and real time studies [505]. Successfully translating nanomedicines from pre-clinical proof-of-concept to demonstration of therapeutic value in the clinic is challenging. It is highly important to develop more precise and improved translatable nanodevices to build a patient-focused and disease-driven mindset from the outset [260,506]. Hence, nanosystems must grow substantially in safety and sophistication before we can experience focused smart nanomedicines in which a single platform performs seamless processes ranging from ultrasensitive diagnosis to pinpoint therapy [507]. For enhanced nanomedicine translation and performance, the targeted therapies should employ a specific decision-making framework: correct tissue/exposure, correct target/efficacy, correct safety,

correct patient, correct commercial potential [508]. Moreover, the translation strategies usually require innovation in the laboratory that must be supported by the pillars of evidence-based medicine for predictable regulatory pathways.

Extensive research on engineered nanomaterials (ENMs) has led to the design of numerous nano-based formulations for theranostic applications [509]. A significant benefit found in some nanomedicines is the ability to formulate a drug without using dose-limiting toxic excipients present in current marketed formulations, often enhancing tolerability and containing more drug to be administered to patients [508]. SeNPs have demonstrated great preclinical applications in gene and drug delivery for anticancer effects [510]. To date, most of the SeNPs have been applied to diagnosis and treatment of cancer, particularly due to the selective and effective accumulation in tumour cells through the enhanced permeability and retention (EPR) effect [511]. Unfortunately, there is a lack of research about the benefits of SeNPs in clinical settings. However, it has been anticipated that green SeNPs can be a good candidate for advanced clinical research due to the low toxicity and excellent biocompatibility [55,61,512].

To develop safer SeNPs with enhanced therapeutic efficacy in clinical settings, a better understanding of the toxicity, possible side effects, and interaction with the biological environment is required. Thus, it is important to test their biosafety, degradation rate, long term metabolic activity, pharmacokinetics and pharmacodynamics, interaction with cells, sustainable circulation in the organism, etc, previous their application in humans [513]. NMs usually interact with biomolecules in the physiological system such as plasma proteins, which allows corona formation in the surface due to the protein adsorption [509]. Then, the protein corona can modify nanomaterial stability, targeting ability, bio-identity, cellular uptake, dissolution properties, and change their biodistribution and toxicity in vivo [20,253,514–516]. Therefore, the nano-bio interface of SeNPs needs further investigation regarding the safety assessments of NPs in biomedicine.

Design and delivery of therapeutics to the brain has been an ongoing challenge in the treatment of brain tumours, especially due to the blood–brain barrier (BBB) that impedes a proper local concentration of drugs. Nanotechnology advacements such as the functionalization of the NPs surface have improved penetration across the BBB by receptor-mediated transcytosis [280,517]. For example, SeNPs coated with B6 peptide and functionalized with sialic acid (B6-SA-SeNPs) inhibited Aβ aggregation and passed the BBB, becoming a potential therapeutic nanovehicle to treat Alzheirmer Disease [518].

Despite the fact that green synthesis of NPs is inexpensive, facile, clean, non-toxic and ease scalable, there has not been much work in this field at diagnostics and therapeutics, especially at the clinical stage. The promising clinical applications of phytosynthesized metallic NPs as a

continuously increasing field switching from routine antioxidant or antimicrobial studies on trivial microbial lines to antibiotic-resistant and antitumoral studies have been mentioned [519]. Also, biogenic colloidal metallic NPs (silver and gold) were found as multifunctional theranostic agents [340]. However, more research should be directed towards developing facile and greener techniques of SeNPs at large scale fabrication using natural resources (microorganisms, plants, microalgae, yeasts, etc). We have reviewed the potential applications of green SeNPs in different aspects of nanomedicine, especially in combating cancer disease (Table 5). Indeed, there is a significant interest of oncologists in the following clinical aspects of Selenium: radioprotection of normal tissues, radiosensitizing in malignant tumors, antiedematous activity, prognostic impact of Se, and effects in primary and secondary cancer prevention [520].

In a comprehensive review on strategies to enhance the translation success of cancer nanomedicines, Van der Meel et al. (2019) stated 4 important factors for successful clinical translation: stratification and selection of patients likely to respond to nanomedicine-based therapy, rational drug choice rather than opportunistic preferences, combination and multimodal therapies for synergistic effects, and empowering immunotherapy. Hence, NPs engineering strategy needs to meet important goals to boost the desirable effect and achieve transformation from formulation-driven research to disease-driven rational development. These goals include high stable association of drug and carrier in circulation, enhanced drug delivery in cancer cells, and controlled release of active drug in affected tissues [521]. Furthermore, the benefits of nanostructure-based diagnostics lie in their potentially higher sensitivity and selectivity compared to classical methods, thus enabling earlier diagnosis of diseases [505,522,523]. The enhanced resolution and sensitivity will lead to novel, fast, convenient, and inexpensive screening and diagnostic tools in medicine.

Another challenge of the “next-generation nanomedicines” is the regulatory classification because lack of knowledge about safety and long-term effects of nanomaterials leads to a regulatory uncertainty and deficient standards and protocols for manufacturing scale-up and safe clinical use [524]. This failure in the nanomedicine market affects the effective collaborative work between stakeholders from industrial/academic R&D, professionals in the health system, regulatory bodies, and society (Fig. 14). Also, classical methods for drug-development and (non-) clinical assessments are somewhat erroneous and expensive, delaying innovative approaches and safety concerns. For instance, the wrong information or the lack of full characterization of current nanoparticle-drug products conducts to failures in follow-on versions, making further evaluation and manufacturing processes tedious before regulatory approval and marketing [525].

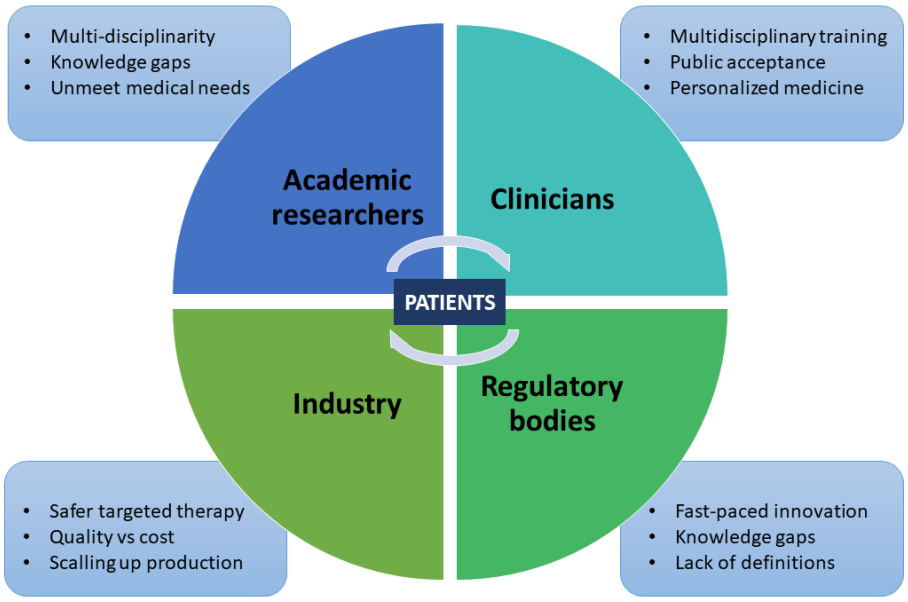

Figure 14. Stakeholders (academic researchers, clinicians and patients, industry, regulatory bodies) and the main challenges faced in the translation of nanomedicine.

Benefiting from advances in nanosciences and nanobiotechnology, as well as the call for personalized medicine nanoparticle-based theranostics has already been a cutting-edge research area. It is necessary to utilize precisely engineered, nanotechnology-enabled solutions to face the challenges of the current drug delivery, imaging, therapeutics, and diagnostics procedures. Therefore, nanomedicine can lead the next generation of biomedical advances by accelerating the translation of therapies with greater efficacy and less side effects. Innovative and clinically effective nanotherapeutics have the potential to revolutionize the nanoscale healthcare and pharmaceutical applications and products.

14. Conclusions and Perspectives

Selenium is a significant trace element with unique biological properties for the proper function of the body. Due to its high bioavailability, low toxicity, and affordability, nano-sized selenium has proven to be a proper supplement and an efficient theranostic agent. Recently, SeNPs have appeared as a research hotspot in nanomedicine that open promising benefits in clinical settings. Since biogenic SeNPs are free from toxic/hazard components, they are well suited in medical sciences and therapeutics. The present review is organized in a way to show the most relevant properties and biomedical applications of biogenic SeNPs including pharmaceutical, therapeutic and diagnostic applications. SeNPs have been shown to combat cancer, diabetes, inflammatory syndromes, cardiovascular and neurological diseases, drug induced toxicity and genotoxicity, among others. Also, SeNPs possess a potential utility in the ongoing pandemic scenario of Covid-19. SeNPs have emerged as suitable nanoplatforms with all

the properties for clinical translation. However, researchers are still investigating possible side effects due to the small therapeutic window of Se compounds. Se nanoparticle-based diagnosis and therapy are still in their early stages and struggling to progress into clinical trials. Thus it is still necessary to accomplish further preclinical safety studies before these eco-friendly SeNPs are safely translated in medicine.

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