REVIEW ARTICLE

Green Chemistry Approaches towards the Synthesis of Selenium Nanoparticles (SeNPs) as a Metal Nano-Therapy: Possible Mechanisms of Anticancer Action

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Abstract

Cancer is one of the most devastating disorders of the 21st century, creating a major concern among clinicians and researchers. Many different treatment strategies are being tried to fight the war against cancer have been tested. Various inorganic nanoparticles have been investigated to induce cytotoxicity in cancer cells and one of the successfully tried nanoparticles is Selenium Nanoparticles (SeNPs). Green synthesized SeNPs are a promising source of new antioxidant and anti-inflammatory agents, given the multiplicity of its mechanism. SeNPs displayed antiproliferative potential against colon, liver, cervical, breast, melanoma, and prostate cancer cells by several mechanisms, including triggering apoptotic signal transduction pathways or slow down the angiogenic signalling in cancer cells. Metal nano-therapies such as SeNPs are granted research consideration for cancer treatment. The biocompatibility achieved through green synthesis suggests its possible use not only in specific cancer conditions but also in other types of cancer without any risk of toxicity of these molecules.

Keywords: Selenium Nanoparticles; Green Synthesis; Characterization Methods; Anticancer Action.

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Frontiers in BIOMEDICAL TECHNOLOGIES

1. Introduction

The nanotechnology term indicates the nanoscale-level ability to function, calculate, and organize the matter; typically, the scale refers to the material in the nano-size range [1]. It allows to creation of materials with new and very different characters through the processing or self-assembly of individual atoms, molecules, or molecular clusters into particular structures [2]. Lastly, its applications emerge as one of the most pioneer and promising technology [3] spatially in biology which requires more studies for the development of new materials in the nanometric range [4]. Metal nanoparticles are sized between 1-100 nm [5]. They are synthesized by different methods such as conventional chemical synthesis methods and green synthesis methods [6]. They possess special physicochemical characteristics [7]. Several properties of nanoparticles are governed by their size, shape, polydispersity, and surface chemistry [8]. Selenium is an essential element for living beings' life [9] which is required up to 40–300 µg for the human body every day [10]. It helps in the regulation of human metabolism [11] and in the stabilization of the immune system, of which Selenium Nanoparticles (SeNPs) take on great importance in the body [12]. The SeNPs are biosynthesis using natural sources such as plant extract, bacteria, and fungi [13]. In this paper, we have presented the green methods employed for the synthesis of selenium nanoparticles and discussed its biological activities and possible mechanism of anticancer action.

2. Research Methodology

For this review, the literature on the nanotechnology, selenium nanoparticles, characterization, and pharmacological actions was collected, examined, and summarized. All published articles concerning this element have been collected using scientific search engines, including PubMed, Science Direct, Springer Link, Web of Science, Scopus, Wiley Online, Scinder, and Google Scholar (e.g., World Intellectual Property Organization (WIPO), Canadian Intellectual Property Office (CIPO), United States Patent and Trademark Office (USPTO)). These search engines, as well as numerous patient offices, used to use Scopus, Wiley Online, Scifnder, and PubMed. It's common to hear the phrase «selenium nanoparticles," either by itself or in conjunction with the phrases "chemical substances" and "pharmacological activity." There were no restrictions on languages. The obtained data were identified and modified using their titles, abstracts, and contents. To discover if any other papers were pertinent, the reference lists of the papers that were retrieved were also examined.

2.1. Green synthesis of Selenium Nanoparticles

Currently, the synthesis of biogenic Nanoparticles (NPs) has attracted great attention [14] because its method of synthesis is eco-friendly and possesses the advantage of low cost, and relative ease of synthesis when it is completed in minutes to a couple of hours at room temperature in addition to the ease of characterization [15]. Thus, the physio-chemical methods are become least favored because they need a long time and require the use of chemicals that are dangerous to human health and the environment. Also, the high cost and generation of hazardous waste from these methodologies have led to advances towards novel and better approaches to NPs synthesis [16]. Green synthesis uses natural and eco-friendly materials that serve simultaneously as reducing, end-capping, and dispersant agents, which not only avoids the use of toxic and dangerous reagents which are used in other techniques but also reduces energy consumption due to local resource availability. Presently, green synthesis mainly uses extracts from different parts of plants or microorganisms (bacteria, fungi, and algae) which contain proteins and polyphenols that substitute the chemical materials as reducing agents to reduce metal ions into lower valence state [17] Figure 1.

2.2. Synthesis of SeNPs Using Microorganisms

Microorganisms such as bacteria, fungi, yeast, and algae are preferred for the synthesis of nanoparticles (NPs) due to their easier cultivation and fast growth rate at ambient condition of temperature, pH, and pressure [19]. The major routes for the formation of NPs may be by intracellular and extracellular mechanisms [20] through precipitation, bioaccumulation, biosorption, and biomineralization where the reduction of metal ions to metal NPs in the presence of cellular biomolecules [21]. However, the

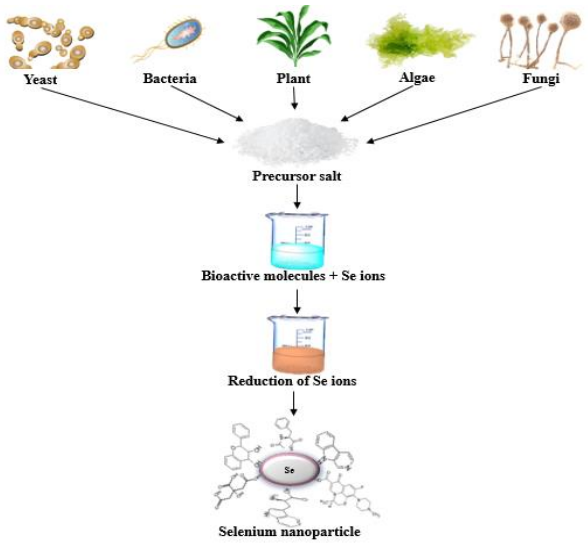

Figure 1. Biological synthesis of selenium nanoparticles [18]

reduction process for the production of SeNPs by microbial method from elementary selenium includes different metabolic pathways, proteins, and enzymes [22]. In the extracellular process, the transformation of added metal salts into NP in the culture broth or attached to the cell membrane. Conversely, in the intracellular process, the transformation of metal ions into NPs inside the cell after their transport across the cell membrane by internalization; then, several procedures are used to release internally formed NPs such as cell lysis into the supernatant, to be recovered and purified [23]. Numerous recent studies revealed the success of microbial use for the synthesis of selenium nanoparticles with different nanosized as presented in Table 1.

The difference between selenium dioxide and sodium selenite, which are used as precursors for SeNPs production, is in the ease and duration of obtaining the ionic form of selenium, whereas the use of sodium selenite allows the synthesis of SeNPs in a short time and with a larger amount than the use selenium dioxide, but the size and morphology of nanoparticles depend on the synthesis conditions, including reducing agent, pH, temperature, and light exposure [32].

2.3. Synthesis from Plant Extract

The use of plant extracts for the synthesis of NPs has become predominant and has more advantages than using of microorganisms due to its simplicity (a single-step method), high yield, and low cost, also it is nonpathogenic and economic method [33, 34]. Phyto-synthesis of SeNPs possesses advantages over other routine methods due to their biocompatibility and in vivo actions [35]. Plant extracts contain various bioactive compounds such as flavonoids, carbohydrates, alkaloids, tannins, proteins, triterpenoids, and polyphenols which participate in the reduction and capping of metal salt precursors for the synthesis of NPs [36, 37]. Current studies employ various parts of plants for the synthesis of SeNPs with different sizes in nanoscale average as presented in Table 2.

Table 1. Green synthesis of Se-NPs using microbial sources

Microorganism	Species	Precursors	Size of SeNPs (nm)	Morphology	References
Fungi	*Rhizopus oryzae*	selenium dioxide (SeO_2)	20 - 200	aggregated spherical shape	[24]
Fungi	*Penicillium expansum* ATTC 36200	selenium dioxide (SeO_2)	4 - 12.7	spherical shape	[25]
Yeast	//////////	Sodium selenite (Na_2SeO_3)	71.14 ± 18.17	spherical shape	[26]
Bacteria	*Bacillus amyloliquefaciens* SRB04	Sodium selenite (Na_2SeO_3)	45.4–68.3	spherical shape	[27]
Bacteria	*Providencia* sp. DCX	Sodium selenite (Na_2SeO_3)	120	spherical shape	[28]
Bacteria	*Bacillus paramycoides* SP3	sodium selenite (Na_2SeO_3)	149.1 ± 29	spherical shape	[29]
Bacteria	*Lactobacillus paracasei HM1*	sodium selenite (Na_2SeO_3)	3.0 - 50.0	hexagonal monodispersed	[30]
Cyanobacteria (blue-green microalgae)	*Spirulina platensis*	sodium selenite (Na_2SeO_3)	79.40 ± 44.26	spherical shape	[31]

Table 2. Green synthesis of Se-NPs using plants source

Species	Precursors	Organ	Size of SeNPs (nm)	Morphology	References
Abelmoschus esculentus	Sodium selenite (Na_2SeO_3)	Whole plant extract	30.7	spherical shape	[38]
Ceropegia bulbosa	Selenous acid (H_2SeO_3)	Tuber's extracts	55.9	spherical shape	[39]
Capparis decidua	Sodium selenite (Na_2SeO_3)	Fruit extract	320	spherical shape	[40]
Azolla pinnata	Selenium dioxide (SeO_2)	Leaves extract	36.45	spherical shape	[41]
Ziziphus spina-christi	Selenium oxide	Callus extract of leaves	15 – 45	low crystallinity as spherical shape	[42]
Psidium guajava	Sodium selenite (Na_2SeO_3)	Leaves extract	40 – 150	Spherical shape	[43]

2.4. Proposed Mechanism for MONPs Synthesis through a Plant Extract

Polyphenols (Quercetin) are the possible phytochemical agent that can reduce metal ions (M2+) to Metal Oxide (MO) during green synthesis of Metal Oxide Nanoparticles (MONPs) and hence aggregates of MO nanoparticles. The plant extract contained large amounts of alkaloids and flavonoids, which were used as stabilizing and capping agents, respectively. The Fourier Transform Infrared (FTIR) signature was revealed in these phytocompounds. In order to synthesize MONPs, it is therefore proposed that metal salt be ionized in an aqueous medium to produce metal ion, which is then reduced by a phytochemical principle found in the plant aqueous extract, specifically the polyphenol quercetin, to generate MO, which then aggregates to form Metal Oxide polymers [44], as shown in Figure 2.

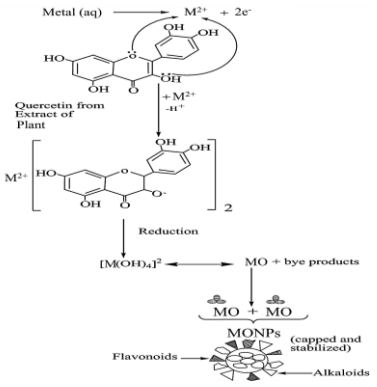

Figure 2. Proposed mechanism of MONPs synthesis through plant extract [44]

2.5. Analytical Characterization Methods

The analytical techniques usually applied for the characterization of Metals Nanoparticles (MNPs) after their synthesis [45], and determination of their particular physicochemical properties (surface area, morphology, structure, size, dispersity, composition, and crystallinity) are Ultraviolet–Visible Spectroscopy (UV-VIS), Fourier Transform Infrared spectroscopy (FTIR), Transmission Electron Microscopy (TEM), Scanning Electron Microscopy (SEM), energy dispersive X-ray (EDX) X-Ray powder Diffraction (XRD), Dynamic Light Scattering (DLS) [46, 47]. The use of each technique is related to the aim of the study, biological and biomedical investigations focus on techniques that determine the size, shape, and purity of the nanoparticles, but physical and chemical studies are concerned with determining the optical and magnetic properties of NPs.

2.6. Ultraviolet–Visible Spectroscopy (UV-VIS)

The UV-Visible spectroscopy technique is used to measure the amount of absorbed and scattered light by a sample. In its simplest form, the intensity of a UV-Vis light ray before and after it passes through a sample can be detected by positioning the sample between a light source and a photodetector [48]. UV–vis analysis is usually the first technique applied in the characterization of Metal Nanoparticles (MNPs), this technique detects a band from which the adsorption peak can be identified to confirm the formation of

respective nanoparticles [49]. Because the positions of absorption peak are dependent upon the size and shape of the particle [50]. Surface Plasmon Resonance (SPR) gives nanometals their striking optical features, where a distinctive SPR absorption band (max) is created by the coupled movements of the free electrons of metal nanoparticles in resonance with the light wave that is dependent the mentioned factors previously of MNPs, the green and blue light rays, are usually employed in a broad spectral range between 300 and 580 nm because they are more diffuse and have a lower intensity [51]. In the UV spectrum, each molecule has a maximum absorption peak at a specific wavelength, different parts of the plant contain biomolecules that differ from each other according to the part, which appear as different peaks in spectra [52]. However, in UV-vis spectrums of SeNPs synthesized by different parts of the plant, a maximum absorption peak of SeNPs is appeared which is probably at the same wavelength but with different intensities related to the amount of SeNPs in the analyzed colloidal solution [53]. The solvents used to extract biomolecules from plants [54] also appear as different peaks in the UV-visible spectrum because each solvent extracts different soluble molecules that differ from one solvent to another. The maximum absorption peak of SeNPs appears in the spectrum as well as the peaks of biomolecules that are responsible for the reduction of selenium to SeNPs [55]. In a recent study by Chetehouna *et al.*, the maximum absorption peak of selenium synthesized using leaves aqueous extract of *Sonchus maritimus* appeared at 300nm [55]. Puri and Patil confirmed that strong absorbance (λmax) at about 285 to 300 nm correspond to the synthesis of SeNPs from phytoconstituents of *Diospyros Montana* bark [56] as presented in Figure 3. In addition, other biosynthetic technique of SeNPs using two marine macro algae *Halimeda opuntia* and algae *Kappaphycus alvarezii* was performed by Rajashree *et al.*, are presented a sharp surface plasmon resonance band at 294 nm and 293nm for *H.opuntia* and *K.alvarezii*, respectively [57].

2.7. Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectroscopy of nanoparticles is performed to determine the possible functional groups included in the stabilization of NPs [58]. This technique is also

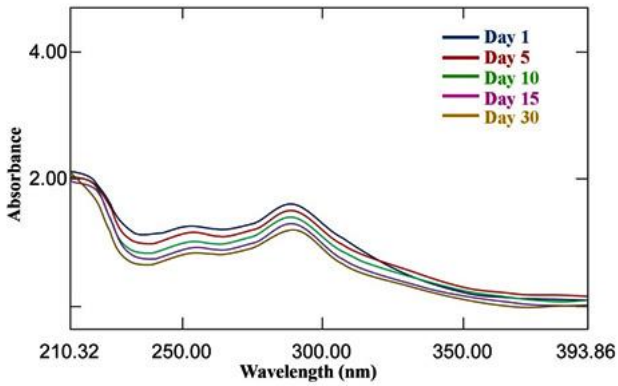

Figure 3. UV-Visible spectrum showing stability of *Diospyros Montana* SeNPs [56]

used to confirm the potential contribution of reducer agents in the synthesis of SeNP through the identification of chemical bond excitations when the chemical information collected facilitates the identification of modifications in the coordination identity of organic molecules on surfaces of SeNPs [59, 60]. The variations in the peaks show that organic elements in the agent used in the synthesis of SeNPs efficiently aid throughout the reduction process, these elements could additionally assist in preventing SeNPs from aggregating and maintaining their stability in the long-term [61]. The Investigation by Hussein *et al.* used the endophytic fungi to create SeNPs shows the appearance of different peaks of functional groups of active compounds on the surface of the nanoparticles as bands of primary amines, phenols, C = O, and C-O in acid (COO−) groups, which determine the role of active metabolites in fungal strains for the synthesis of SeNPs [62] as presented in Figure 4. Other studies of Shahbaz *et al.* depending on the green synthesis of selenium nanoparticles using Melia azedarach extract discovered also many functional groups on the surface of NPs through FTIR analysis of biosynthesized SeNPs that can help in the reduction of bio-fabricated SeNPs [63].

2.8. Transmission Electron Microscopy (TEM)

The TEM technique is a particularly effective method for studying materials that may be characterized by an electron beam traveling through extremely thin samples [64]. It uses a micrograph of the determined area diffraction pattern of metal nanoparticles, which allows to confirm the similarity or difference of size, crystallinity nature, sticking to

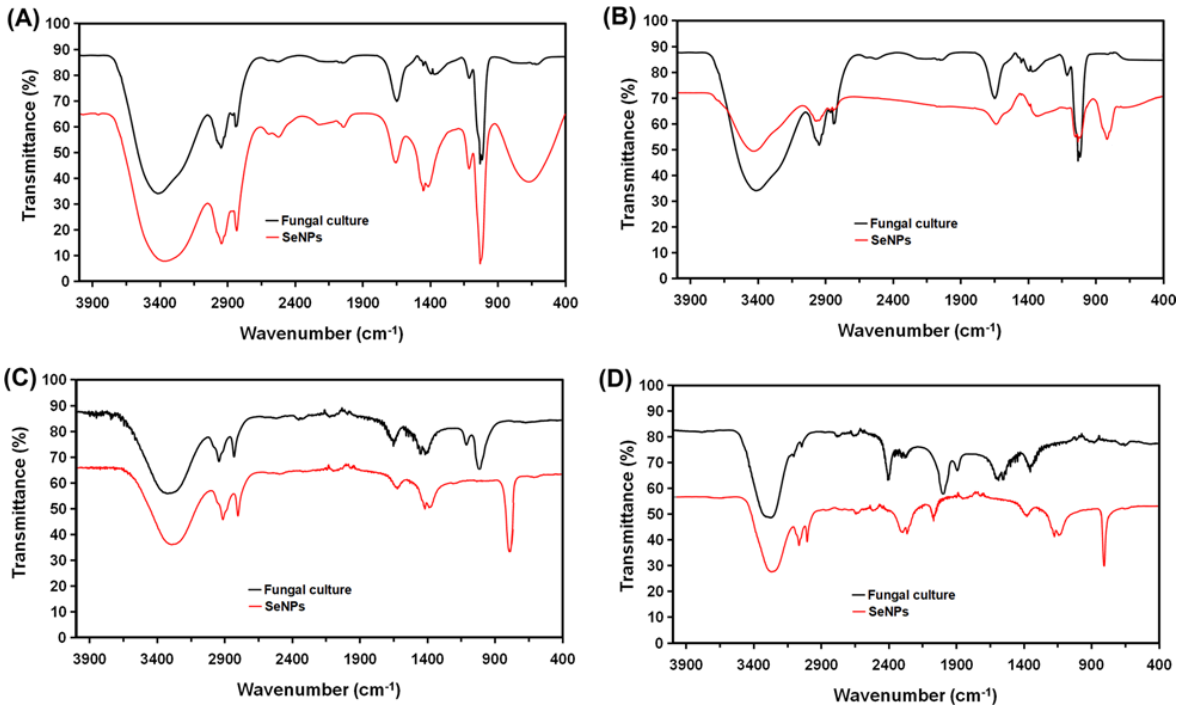

Figure 4. FTIR spectrums of synthesized SeNPs using four fungal strains; using *Aspergillus quadrilineatus* (A), *Aspergillus ochraceus* (B), *Aspergillus terreus* (C), and *Fusarium equiseti* (D) [62]

one another, and agglomeration of nanoparticles [65]. TEM is used to more precisely examine the structure of produced nanoparticles and to observe the morphology and the dispersion of MNPs [66, 67]. In a previous study by Salem *et al.*, the green synthesis method of selenium nanoparticles was used for fungi of Penicillium corylophilum which isolate from soil samples; the results of transmission electron microscopy analysis showed the biofabricated SeNPs had a homogeneous dispersion without aggregations and having a spherical structure with the major average size of mentioned nanoparticles was discovered in the range between 29.1 and 48.9 nm [68]. Mellinas *et al.* depend in their investigation on TEM analysis to study the morphology of SeNPs green synthesized by Theobroma cacao L. extract of bean shell using microwave irradiation and to assess their homogeneity; under optimal conditions, obtained micrographs of SeNPs in different magnifications presented that nanoparticles of selenium were well dispersed and mostly spherical in shape, these nanospheres having a diameter size from 1 to 3 nm, and the predominance of crystalline forms in the SeNPs structure indicating that SeNPs were well-stabilized by Theobroma cacao L. extract [69] as shown in Figure 5. Furthermore, according to Cittrarasu *et al.*, selenium nanoparticles biosynthesized mediated extract of Ceropegia bulbosa Roxb clearly demonstrate from high-resolution TEM photographs that selenium nanoparticles are having uniform spherical morphology and mono scattering [39].

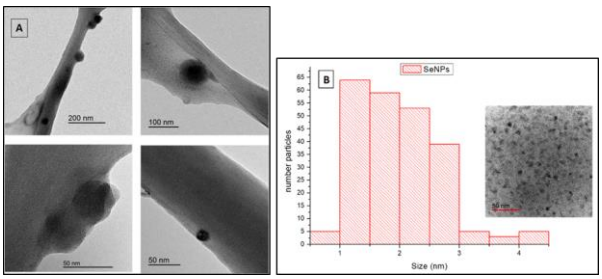

Figure 5. TEM micrographs (**A**) and size distribution (**B**) of green synthesized SeNPs using *Theobroma cacao* L. extract obtained under optimal conditions [69]

2.9. Scanning Electron Microscopy (SEM)

SEM is an important optical technique that is applied to characterize the nanoparticles, this instrumentation aims to determine the morphology, distribution, size, and shape of produced nanoparticles; the SEM analysis can more precisely examine the changes in surface morphology of nanostructures [70]. Field emission scanning electron

microscopy (FE-SEM) is modern SEM with a high resolution using a highly energetic electron beam that can identify the nanoparticle morphology on a very fine scale below 10 nm level. The emitter type is the main difference between FE-SEM and SEM. There are two types of emitter, including field emitter generates electrons without problems induced by thermionic emitter, including relatively low brightness, cathode material evaporation, and thermal drift while operating [71]. In fact, FE-SEM is employed to obtain more accurate surface property data [72]. Figure (6) confirms the resolution quality and clarity of the image taken by FE-SEM. To obtain the micrograph of nanoparticles, the sample should be thin powder and then coated with a layer of heavy metal; electron rays are attacked the coated nanoparticles after they positioned in the SEM stage [73]. Alagesan and Venugopal employed scanning electron microscopy to investigate the shape of the nanoparticles of selenium biosynthesized by leaves aqueous extract of *Withania somnifera*. The obtained micrographs showed agglomerated spherical particles with diameters between 45 and 90 nm and these elements were well dispersed in aggregate form [74]. Previous study by Mahesh and Murthy, scanning electron microscopy analysis, is used to determine shapes, size distribution, and the physical dimensions of selenium nanoparticles produced using bee propolis ethanoic extract, where the obtained result demonstrated that the morphology of the nanoparticles was oval in form with a smooth surface and their size ranged between 52.9 and118 nm [75]. Other findings by Al Jahdaly present that the use of eco-friendly method to produce nanoparticles of selenium gives strict size distribution around 0.47and 0.71 µm with spherical shapes of particles, in addition to the appearance of aggregations as shown in images under scanning electron microscopy at two different magnifications as presented in Figure 7, whereas the grains aggregate throughout the process as a result of the reduction and nucleation outgrowth of the reduced atoms [76].

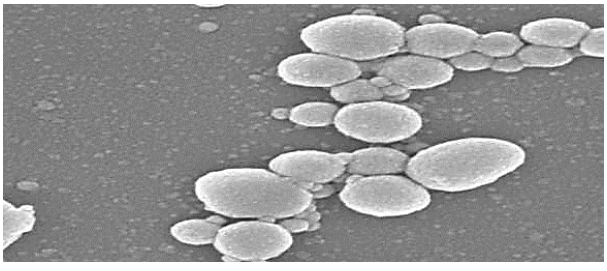

Figure 6. The FE-SEM image of spherical SeNPs [77]

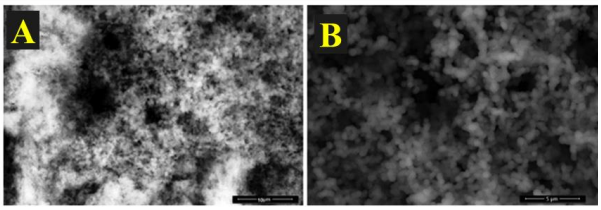

Figure 7. SEM images of prepared SeNPs at 10 µm (A) and 5 µm (B) [76]

2.10. Energy Dispersive X-Ray (EDX)

The Energy Dispersive X-ray technique allows to the confirmation of the formation, to the identification of the conformation and purity, and to the determination of the stoichiometry and the elemental composition of the prepared metal nanostructures [78]. In an EDX spectrum, the metallic nanoparticles produce a distinctive absorption signal of the metal due to Surface Plasmon Resonance (SPR), O peaks are seen as a result of biomolecules adhering to nanoparticles' surface, and carbon peaks discover that biosynthesized nanoparticles are capped in a thin layer of some coating organic component, in addition to carbon tape that employed in the examination of the spectrum [79]. In general, Scanning Electron Microscopy (SEM) is coupled with energy-dispersive X-ray analysis to simultaneously detect the elemental composition and exanimate the morphology of produced nanoparticles [80]. The EDX analysis of biosynthesized selenium nanoparticles based on an aqueous extract of *Portulaca oleracea* revealed that the Se ions constituted the highest weight in the sample with a percentage of 36.49%. The absorption peak at a bending energy of 0.2 KeV indicates the presence of C ions with weight a percentage of 30.68%. The absorption peak at a bending energy of 0.5 KeV indicates the presence of C ions, and additional peaks are present with low weights for Cl and K ions due to dispersion of coating and stabilizing chemicals that are capped the surface of the NPs during EDX measurement [81]. Safaei *et al.* used a microbial method to synthesize selenium NPs using *Halomonas elongata* bacterium, The EDX results of the selenium nanostructure presented in Figure 8 showed that in addition to selenium and oxygen, silicon and carbon elements were also seen in the spectrum, indicating the existence of some impurities from the biological processes that were used produce the nanoparticles [82].

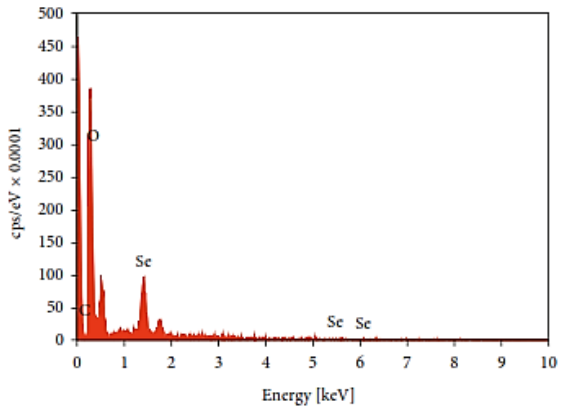

Figure 8. EDX spectrums of SeNPs biosynthesized using *Halomonas elongata* bacterium [82]

2.11. X-Ray Powder Diffraction (XRD)

The crystalline phase and structure of prepared MNPs are analyzed through a recorded XRD pattern [83]. The crystal structure of the samples was documented using an XRD system with a diffractometer that employed radiation with a particular wavelength (nm) [84]. When X-ray light strikes a crystal, diffraction takes position, and the crystal's measured diffraction patterns reveal the properties of the crystal. the machine is operated by determined voltage and current and a particular gauze is used as a filter, a fine layer is drawn using the dipping technique onto the glass plate for performing the XRD examinations [85]. JCPDS files allow to the identification of the shape of crystal metal depending on obtained planes in X-ray diffraction of synthesized metallic nanoparticles [86]. The average crystallite size of the metal nanoparticles is predicted and calculated with the help of the Scherrer Equation [87]. Vu *et al.* confirmed the formulation and crystallinity of Se NPs prepared using the green method by leaf extract of *Cleistocalyx operculatus* through the X-ray diffraction analysis; from XRD pattern of the Se NPs, the diffraction peaks appeared at approximately 20° and 30° are corresponded, respectively to the (100) and (101) planes of metallic Se nanoparticles with trigonal phase containing lattice constants in structure planes of metallic Selenium nanoparticles with a trigonal phase having lattice constants [88], fungal strains called *Candida albicans* used by Bafghi *et al.* to produce Se-NPs which exhibited with crystalline structure as appeared from XRD pattern through the sharp rising of diffraction at a different angle (2θ) and the average size of the nanoparticles was 38 nm (Figure 9), which was calculated using DebyeScherrer formula [$D = 0.9\lambda / (\beta \cos \theta)$] [89].

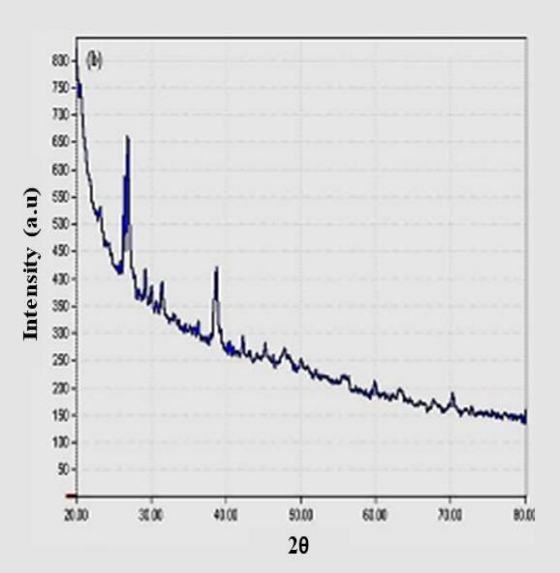

Figure 9. XRD pattern of biosynthesized Se-NPs using the Candida yeast [89]

2.12. Dynamic Light Scattering (DLS)

Dynamic light scattering is a useful technology for precising the properties of nanoparticles. It gives information about the Polydispersity Index (PDI) and hydrodynamic diameter [90]. The aggregation state of the solution of the nanoparticle also could be determined through zeta potential which is linked to the electrostatic force that repels nanoparticles from each other based on the charge that exists on their surface, where the negative or positive charge of all metal NPs is responsible for causing long-term stability of these nanoparticles and preventing their aggregation [91]. Does not only the metallic core of metal NPs play a role in size determination from DLS, but also the organic molecules that are present on the surface of them, and negative zeta potential values were caused by negatively charged functional groups that were present on the surface of NPs [92]. In the previous study, DLS analysis of SeNPs produced using leaf extract *Aloe vera* gave a zeta potential value which was -18 mV indicating that the obtained NPs were bordered with negatively charged groups and possess a high stability, and PDI value which was 0.344 indicating that the formulated metal NPs were monodispersed due to small value of the PDI [93]. The

size of the biosynthesized SeNPe by fruit extract of *Z.officinale* using DLS was between 100 and 120 nm, zeta potential value was −36 mV with electrophoretic mobility of −0.000116 cm^2/Vs and well-dispersed (Figure 10). The aggregation of the selenium nanoparticles caused by the Van der Walls interaction results in dispersions with a lower zeta potential value [94].

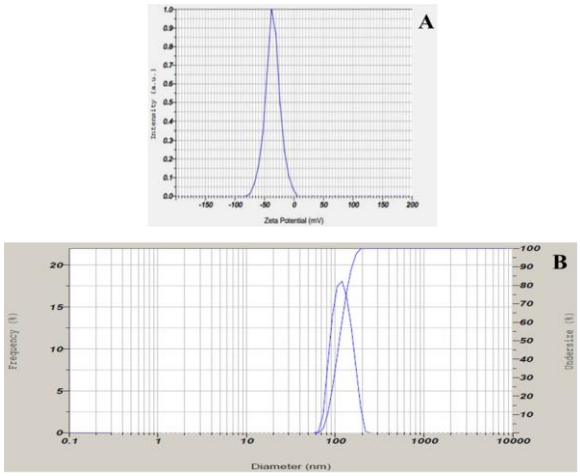

Figure 10. Zeta potential of SeNPs (A) and size distribution of SeNPs using the DLS approach [94]

2.13. Other Analytical Characterization Methods

The Atomic Force Microscopy (AFM) technique is one of the best techniques for studying the size and topography of nanomaterials, allowing to take a 3D view of metal nanoparticles after determination of their size and form using TEM analysis [95]. Shahbaz *et al.* consider Scanning Tunneling Microscopy (STM) analysis to be the first technique used to determine the size, the morphology and to get details surface information of the nanostructures, the main advantage of this approach is that it may be applied to a wide range of materials, including metals and semiconductors [96]. Magnetic Force Microscopy (MFM) is a type of scanning probe microscopy that assesses the magnetic forces exercised on the probe for imaging. For capturing the magnetic stray fields of the magnetic nanoparticles, a nanoscale probe is covered with a few tens of nanometers of magnetic material. The main advantage of this technique is in its ability to photograph the magnetic domains that show the magnetization direction [97]. The Particle Size Analyzer (PSA) technique allows to the examination of the hydrodynamic size distribution of the biosynthesized nanoparticles in the fluid [98]. It is widely known that the critical characteristic of Surface Plasmon Polaritons (SPPs), that is, cavity plasmon resonances and their coupling, emerges in the near-field propagating domain, in reality, Scanning Near-field Optical Microscopy (SNOM) is used to observe the increased transmission phenomenon and surface plasmon-mediated mechanism through specifically designed structures, outside of the range of diffraction [99]. Thermogravimetric Analysis (TGA) is performed to detect and determine the presence and quantity of organic components from the used extract in the synthesized NPs product using the thermal decomposition step [100]. Differential Scanning Calorimetry (DSC) is used in order to evaluate the stability of organic compounds present on the surface of biosynthesized NPs in terms of heating behavior, within a range of temperatures and in order to measure the melting behavior of MNPs at a specified heating rate [101, 102]. The X-Ray Photoelectron Spectroscopy (XPS) becomes one of the most adopted methods for the surfaces study of NPs. This technique uses X-rays bombarding on sample surface and measuring the reflected electrons and it is extremely effective due to surface sensitivity and capacity to offer chemical data frames from the analyzed sample, practically all minerals and elements can be used with this approach [103]. Static Light Scattering (SLS) is known as laser diffraction, used for the determination of particle size distributions; the intensity of the light refracted, diffracted, reflected, and absorbed by the NPs as well as the scattering angle depends on and chemical composition, structure, and particle size of the sample to be analyzed [104]. The Small-Angle X-Ray Scattering (SAXS) approach can give more information about the average thickness of NPs and average sizes of cylinders, which is not available in SEM images, also SAXS data provide an average of a far larger number of particles than those seen in the TEM images [105]. In addition, the SAXS technique permits to monitor the change in particle size during the catalyst operation [106]. The X-Ray Fluorescence (XRF) technique is performed for the elemental analysis of the NPs sample using an X-ray micro analyzer, that is presented as strong signals in the XRF spectrum to confirm the existence of elemental Se in the sample [107].

2.14. Antioxidant Activity

The in vitro antioxidant activity can be evaluated by different assays as presented in the study of Kumar *et al.* who determined the activity of SeNPs synthesized by cell-free extract of *Geobacillus* sp strain ARB04 by ABTS "2, 2′-azino-bis (3-ethylbenzthiazoline-6-sulfonic acid)", DDPH "1, 1-diphenyl-2-picrylhydrazyl" and FRAP "ferric reducing antioxidant power" assays when they found the higher antioxidant power of SeNPs compared to its salt (sodium selenite) and the cell-free extract due to its synergic effect through the biomolecules which involved in its formation [108]. Khurana *et al.* indicate in their research paper, even though it's unexpected, the fundamental question is: How can SeNPs mitigate the toxicological effects of Se? Understanding Se's redox state is crucial for providing an answer because Se's oxidation state is what drives both the observed biological impacts and the harm it causes. selenocysteine, Selenomethionine, and methyl selenocysteine are the most prominent organic forms of Se, whereas selenite and selenate are the most prominent inorganic forms. Se can be found in different oxidation states, including selenite (SeO_3^{2-}, +4), selenate (SeO_4^{2-}, +6), selenide (Se^{2-}, +2), and Se (Se°). The controlled interplay of different oxidation states of Se may provide a plausible reason for the reduction of toxicity upon nanosizing. The toxic effect of Se is determined by its bioavailability and aqueous solubility in different oxidation states. However, there is still no strong evidence for what exactly causes the apparent low toxicity of SeNP. However, there is still no sound evidence for what exactly causes the apparent low toxicity of SeNP [109]. Another study demonstrated the potential effect of ultrasound technique in increasing the potency of SeNPs prepared with a polysaccharide of *Lignosus rhinocerotis* compared to non-ultrasonic approaches through DPPH and ATBS assays [110]. The Quercetin-loaded selenium nanoparticles modified by a combination of acacia and polysorbate 80 exhibit an excellent scavenging of radical (DPPH) activity and this nanocomposite reduces the effect of H_2O_2 and protect the PC12 cells from death through in vitro Cell Counting Kit (CCK)-8 analysis [111]. Wang *et al.* conclude that nanoparticles of selenium modified by polysaccharide from *Sargassum fusiforme* exhibit a stronger stability and antioxidant activity, which allows for the potential application of SeNPs in the food and medicine fields [112]. In vivo study manifest the attractive antioxidant ability of SeNPs biosynthesized using *Lactobacillus casei* ATCC 393 orally administrated against intestinal barrier dysfunction induced by diquat in mice through elevation of total Superoxide Dismutase (SOD), Glutathione Peroxidase (GPx) and Thioredoxin Reductase (TrxR) activities in blood serum; due to the importance of Se containing in structure of selenoproteins and crucial part of antioxidant enzymes participate in regulation of redox state [113]. Kojouri *et al.* informed that there is a significant and positive correlation between the activities of SOD and catalase, which indicates the advantageous role of SeNPs in antioxidant defense and increases the capacity of the immune system to prevent the cells against free radical attack [114]. The growth rate and well-being of *Dicentrarchus labrax* is enhanced by the diet of SeNPs through its anti-inflammatory effect and antioxidant responses, which activate the mechanism of antioxidant defense in fish and involve in the selenocysteine and glutathione peroxidase builds [115]. Furthermore, SeNPs synthesized using chitosan or/and chitooligosaccharide were found to be extremely safer and protect the cells from the destruction of oxidative stress induced by ethanol based on their potential to down-regulate the lipid and protein oxidation and up-regulate the SOD, GP-x and catalase levels [116]. El-Sayed *et al.* informed the effective antioxidant use of SeNPs prepared by the bacterium *P. agglomerans* to combat the oxidative stress generated in broiler chickens due to its neutralization and reduction of the effect of produced free radicals [117]. Table 3 presents the antioxidant activity of SeNPs in some previous studies.

2.15. Anti-Inflammatory Activity

The now focus of researchers is the revelation and development of new strategies to fight inflammation as what are present in several recent either in vitro or in vivo studies. The anti-inflammatory activity of biologically synthesized SeNPs using arrowroot and *Coriander oleoresin* extract was presented by a potential inhibitory effect against denaturation of protein (Bovine serum albumin (BSA)) through the albumin denaturation assay [122, 123]. In RAW264.7 inflammatory macrophages induced by lipopolysaccharide (LPS), SeNPs exhibit a potential anti-inflammatory activity by down-regulating the mRNA expression of inducible nitric oxide synthase (iNOS) enzyme, interleukin 1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) with reducing the Nitric Oxide (NO) production [124]. The SeNPs synthesized by *Lactococcus lactis* NZ9000 did not exhibit

Table 3. Antioxidant activity of biosynthesized selenium nanoparticles

Method	Standard	IC_{50} of SeNPs	IC_{50} of Standard	Reducing agent	Reference
FRAP assay	Ascorbic acid	46.30 ± 0.21 µg/mL	28.46±34µg/mL	*Diospyros montana*	[56]
SOR assay	Ascorbic acid	80.55±1.14 µg/ml	74.95 ± 0.95 µg/mL	*Anabaena variabilis* NCCU-441	[118]
RP assay	Ascorbic acid	81.60±0.20 µg/mL	43.84±1.20 µg/mL	*Tinospora cordifolia*	[119]
ABTS assay	Ascorbic acid	43.06±3.80 µg/mL	36.39 ± 2.47 µg/mL	*Carica papaya*	[120]
DPPH assay	Ascorbic acid	24.72±0.63 µg/mL	12.51± 0.16 µg/mL	*Diospyros montana*	[56]
ABTS assay	Ascorbic acid	66.10±1.01 µg/mL	61.92 ± 2.47 µg/mL	*Annona muricata*	[121]

Inhibition concentration 50% (IC_{50}); Ferric reducing ability power (FRAP); Superoxide anion radical (SOR); reducing power (RP); 2,2′-diphenylhydrazyl (DPPH); 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS)

immunotoxicity on porcine jejunal epithelial cell line (IPEC-J2 cells) and had an anti-inflammatory impact on IPEC-J2 cells challenged to Enterotoxigenic Escherichia coli K88 (ETEC K88), which lead to conclude that this biosynthesized SeNPs might be a promising supplementation with antioxidant and anti-inflammatory activities [125]. The paper by Nayak *et al*. demonstrated that the suppression of expression of TNF-α m-RNA through the inhibition of production of LPS-stimulated nitric oxide was carried out by the selenium nanoparticles which were surface functionalized by water-soluble derivatives of *Ganoderma lucidum* [126]. Another investigation showed that the protective effect of SeNPs prepared with *Ulva lactuca* polysaccharide on acute colitis induced by Dextran Sulphate Sodium (DSS) in mice was performed by their anti-inflammatory activity, when SeNPs were characterized by low toxicity, in particular when they are decorated with natural biological compound, through their effect of improving macrophage infiltration as evidence by the reduction of a cluster of differentiation 68 (CD68) levels in colon tissue sections and their modulation of interleukin 6 (IL-6) and TNF-α secretion by suppressing the nuclear translocation of nuclear factor kappa B (NF-κB) which leads to transcription of these pro-inflammatory cytokines [127]. From the study by El-Ghazaly *et al.*, the SeNPs gave a potential anti-inflammatory against paw edema induced by carrageenan in rats where the anti-inflammatory activity of Se was related to the inhibition of eicosanoid synthesis including that of Prostaglandin (PG) and Leukotrienes (LT), in addition to the inhibition of infiltration of neutrophils [128]. The anti-inflammatory activity of SeNPs exerts by reduced macrophage infiltration and immunomodulatory as shown in several references [129]. The effects of selenium and other metal nanoparticles have anti-diabetic effects which are related to the regulation of biochemical markers, oxidative stress markers, the reduction of inflammation, and apoptosis of the pancreas as reported in the previous literature [130]. Rheumatoid Arthritis (RA) is accompanied by oxidative stress which has a direct contribution to the destruction or proliferation of synovium; the Reactive Oxygen Species (ROS) acts as a second messenger to activate NF-κB that regulate the expression of different genes related to inflammatory response and is under their control such as TNF-α and IL-1β. Glutathione peroxidase (GPx) reduces the production of inflaming prostaglandins and leukotrienes because it is the first selenoenzyme to have an essential role in the protection of cells against oxidative damage of ROS through the degradation of hydroperoxide intermediates in the lipoxygenase and cyclooxygenase pathways; in addition to selenoproteins W, P and K which might implicate in this process. Also, the transmembrane selenoproteins S and K of endoplasmic reticulum are linked to immune regulation and inflammation. So, the anti-inflammatory activity of Se is related to its anti-oxidant activity [131]. Ren *et al.* revealed that treatment by SeNPs significantly decreased the IL-6, IL-1β, TNF-α, and MCP-1 in ankle joint tissues of Complete Freund's Adjuvant (CFA) induced Rheumatoid Arthritis (RA) in rats; also, they demonstrated that the therapeutic effect of standard drugs of RA such as celecoxib and SeNPs was similar through alteration of pro-inflammatory cytokines in different condition of oxidative stress [132]. The anti-

inflammatory mechanism can be explain by the presence of bioactive compounds that coat the surface of biosynthesized SeNPs, including different secondary metabolites such as terpenoids which prevent diseases like cancer, modulate the immune system, and enhance anti-inflammation activity [122]. In addition, NPs are more effective at blocking inflammation-enhancers like inflammation-assisting enzymes and cytokines because they have a higher surface area-to-volume ratio [133]. Table 4 presents the anti-inflammatory activity of SeNPs in some previous studies.

3. Discussion

Cancer is one of the most devastating disorders of the 21st century, creating a major concern among clinicians and researchers. Many different treatment strategies are being tried to fight the war against cancer and a plethora of strategies have been attempted [138]. Nanotechnology has significantly improved our approach to personalized medicine whereby the targeting has improved. Various inorganic nanoparticles have been investigated to induce cytotoxicity in cancer cells and one of the successfully tried nanoparticles is SeNPs. SeNPs-based approaches have shown hope in fighting the drug resistance problem and in mitigating toxicities associated with chemotherapeutic agents [139]. Initial studies have demonstrated that SeNPs have better antiproliferative properties for the MCF-7 cells line (inhibition concentration 50 (IC50) value of 25 µg mL^{-1}) than the MDA-MB-231 cells line, reflecting their antitumor potential for early-stage breast cancer (estrogen receptor α (ERα) positive) than late-stage breast (ERα negative) cancer treatment. In vivo assays

showed that the administration of 0.4 mg/kg/day significantly reduced tumor growth, which suggests that the antiproliferative activity of SeNPs in breast cancer is related to ERα levels [140]. The anticancerous property of SeNPs is due to the induction of Glutathione S-Transferase (GST) by selenium. Cancer cells selectively incorporate SeNPs via endo¬cytosis, and then these SeNPs induces the apoptosis of cancer cell by triggering apoptotic signal transduction pathways [141]. More recently, Liao *et al.* also studied the anticancer application of biogenic SeNPs prepared using E. coli towards several cancer cell lines. These SeNPs displayed antiproliferative potential against colon, liver, cervical, breast, melanoma, and prostate cancer cells, both androgen-dependent and androgen-independent prostate cancer cells, by increasing the expression of p21 and Bax mRNA and enhancing caspase-3 activity [142]. SeNPs are believed to internalize via receptor-mediated endocytosis. The malignant cells have an acidic pH state with redox imbalance. This microenvironment of malignant cells leads to prooxidant conversion of SeNPs triggering the further formation of free radicals which on one side causes mitochondrial membrane disruption causing leakage of Mitochondrial (Mt) proteins and on the other side leads to Endoplasmic Reticulum (ER) stress [143]. Damage to the Mt membrane leads to the leakage of various proteins and triggers apoptosis via the activation of caspases. In addition, SeNPs have been shown to slow down the angiogenic signaling in cancer cells which further checks the growth and proliferation. Amalgamation of these disruptive cellular events initiates DNA damage causing cell cycle arrest ultimately culminating in cell death [129] (Figure 11).

SeNPs also show antitumor potential towards Dalton's lymphoma, by enhancing ROS stress and decreasing mitochondria membrane potential, which ultimately leads to Deoxyribonucleic Acid (DNA) fragmentation, cell cycle arrest at G0/G1, and apoptosis [144]. SeNPs have been observed to inhibit the growth of prostate LNCaP cancer cells moderately

Table 4. Anti-inflammatory activity of biosynthesized selenium nanoparticles

Method	Standard	Parameter	SeNPs	Standard	Reducing agent	Reference
Albumin denaturation assay	diclofenac sodium	Inhibition percentage	92.6 %	84 %	*Thymus vulgaris*	[134]
Hemolysis assay	SDS	Hemolysis percentage	11.5 %	>11.5%	*Pseudomonas stutzeri* (MH191156)	[135]
Albumin denaturation assay	diclofenac sodium	Inhibition concentration 50 %	22.9 µg/mL	17.8 µg/mL	*Spermacoce hispida*	[136]
Hemolysis assay	*Elettaria cardamomum*	Hemolysis percentage	4.4 %	9.9 %	*Elettaria cardamomum*	[137]

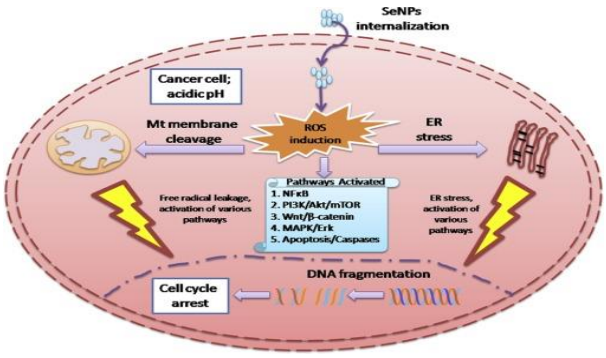

Figure 11. Mechanism of anticancer activity of selenium nanoparticles [126]

via caspases-mediated apoptosis in vitro [145]. Sonkusre *et al.* have shown that the introduction of biologically synthesized SeNPs (concentration as low as 2 µg $Se.mL^{-1}$) is competent enough to suppress the proliferation and induce caspase-independent necrosis in human prostate adenocarcinoma cells (PC3) [146]. SeNPs also demonstrated suppressive effects against androgen-dependent prostate cancer cell lines. SeNPs reduced the levels of androgen receptor, a protein associated with cancer cell survival, at both a transcriptional and translational level. On the one hand, mRNA levels of both androgen receptor and Prostate-Specific Antigen (PSA) were downregulated [147]. On the other hand, SeNPs induced androgen receptor and Mdm2 phosphorylation by AKT, which led to the ubiquitination and proteolysis of the androgen receptor by proteasomes, increased levels of caspase-3, caspase-8, and caspase-9 levels, as well as their substrate PARP, which result in the inhibition of prostate cancer cells growth and apoptosis [148]. Widely studies have been investigated on in vitro and in vivo anti-cancer activity of selenium nanoparticles against lung, breast, osteosarcoma, and kidney cancers [137]. Rajasekar and Kuppusamy studied the *in-vivo* effect of SeNPs on breast cancer cell line and found that MDA-MB-231 human breast cells were severely impacted by SeNPs green synthesized using Carica papaya latex with IC_{50} values of 34 lg/mL [149]. Another study tested the anti-cancer activity of SeNPs against a lung cancer cell line (A549), and the results showed a decrease in the cell growth by almost 80% at 40µg/ml concentration and almost 50% cell death at 20µg/ml concentration [150]. The SeNPs synthesized using Kaempferia parviflora demonstrated significant cytotoxicity in human gastric adenocarcinoma cells (AGS cells) but not in normal cells due to its effect on intracellular signaling pathways, including the upregulation of intrinsic apoptotic signaling markers such as B-cell lymphoma 2, Bcl-associated X protein, and caspase 3 in AGS cells. SeNPs also caused autophagy of AGS by increasing the autophagic flux-marker protein, LC3B-II, whilst inhibiting autophagic cargo protein, p62 [151]. It emerged that coating metal NPs improved their stability and decreased their toxicity, particularly when it came to the green synthesis method. The different substances that coat the surface of NPs usually prevent the ionization of MNPs, the shape and size changes of the NPs. It has been confirmed that uncoated and chemically produced MNPs have a higher cytotoxic and genotoxic effect than coated and green synthesized MNPs, which makes their biocompatibility typical. Despite the coating's primary role in stabilizing the nanoparticle and preventing agglomeration, green-synthesized MNPs are suitable for a range of biological applications due to their biocompatibility [18]. Until now, there have not been studies investigating the toxic effect and disadvantages of SeNP in the physiological systems; SeNPs attracted attention due to their extensive use in the therapeutics field. In comparison to inorganic selenium, SeNPs have lower toxicity, acceptable bioavailability, and higher efficiency to attack free radical species. Additionally, based on the experimental results, SeNPs' toxicity is rated as being lower than that of other inorganic and organic compounds including selenite, selenite, and selenomethionine. SeNPs play important physiological and metabolic roles, including the control of the antioxidant defense system and the immune system [152].

4. Conclusion

Selenium nanoparticles synthesized by green materials like plant, microbial, fungi, and algal extracts as reducing agents have different applications as an antioxidant and anti-inflammatory agents. Furthermore, this study brings new insights into the cytotoxic actions of SeNPs against cancer cells. Metal nano-therapies such as SeNPs are granted research consideration for many cancers, including breast, and prostate treatment. SeNPs attracted attention due to their extensive use in the therapeutics field. Such therapeutic approaches may then be found useful not only in these specific cancer conditions, but also in other types of proliferative diseases. The biocompatibility achieved through green

synthesis suggests its possible use in varying fields of biomedical application with low risk of toxicity of these molecules.

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