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SELENIUM NANOPARTICLE IN CHRONIC WOUND MANAGEMENT: MECHANISM AND ITS BIOMEDICAL APPLICATIONS

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ABSTRACT

For the intended delivery, selenium nanoparticles (SeNPs) may be a desirable delivery method. The potential for selenium nanoparticles to treat a variety of conditions, including rheumatoid arthritis (RA), inflammatory bowel disease (IBD), asthma, liver, and other autoimmune disorders like psoriasis, cancer, diabetes, and numerous infectious diseases, is what has drawn them to the world. However, there is currently no recent literature that summarizes the therapeutic applications of SeNPs. The identification of SeNP targets in various diseases and the various functionalization techniques used to guarantee that SeNPs remain stable, can be readily transported to the tumor regions, and prevent undesirableIn order to comprehend the science underlying off-target effects, it is important to learn more about the therapeutic features. With that in mind, we have focused on this gap and made an effort to summarize the vast array of functionalization techniques as well as all the recent noteworthy targeted therapies of SeNPs in cancer treatment. Additionally, we have focused on the latest advancements in biomedical application mechanisms and SeNP functionalization techniques, particularly with regard to anticancer, anti-inflammatory, and anti-infection therapies According to our observations, SeNPs may be used in addition to their antibacterial and antiparasitic properties to decrease viral epidemics like the current COVID-19 pandemic. SeNPs are noteworthy nanoplatforms with a variety of desired clinical translation characteristics.

KEYWORDS: Selenium nanoparticles,anti-inflammatory, cancer therapy, antiviral activity, antiparasitic activity.

INTRODUCTION

Nanotechnology deals with nanoparticles (1–100 nm), which have garnered interest because of their magnetic characteristics. Numerous favorable characteristics of nanoparticles include their small size, solubility, high surface area, surface energy, and ease of attachment, transported to therapeutic agents.[1,2] These special qualities of nanoparticles have a wide range of uses in biological and medical domains. Physical systems are monitored, diagnosed, treated, and controlled by Nanomaterials.[3] Additionally, nanoparticles can be used for gene therapy, biolabeling, biosensing, and antimicrobial treatments.[4] Numerous biological applications use a variety of nanostructures, including dendrimers, polymers, micelles, and nanoparticles like Au, Ag, Zn, Cu, Se, Fe, Ce, Ti, I, etc.[5,7] Selenium (Se), which is extensively researched, is one such nanoparticle with special qualities. Depending on the oxidation state, selenium is colorless and non-toxic. It serves as the redox center for a number of enzymes that are antioxidants.[1,8,9] There are two different oxidation states of selenium: selenate (+6) and selenite (+4). Due to its high toxicity, selenite is a latent composite for microbial activity among these selenium classes.[10]

According to reports, selenium nanoparticles have certain special qualities that make them essential in a variety of applications (Figure 1). According to reports, selenium nanoparticles have low toxicity and high biological activity.[11] Although selenium is a necessary nutrient for all living things, its use is restricted because it becomes toxic at higher concentrations. Compared to other forms of selenium, selenium nanoparticles have been shown to have lower toxicity and sub-chronic toxicities.[12] This claim has also been validated: Nanoparticles of selenium are less harmful than selenomethionine.[13] Se nanoparticles have demonstrated superior selectivity between normal and cancer cells when compared to Se (IV) nanoparticles at comparable concentrations.[14] Compared to selenium species, Se nanoparticles have a strong antioxidant characteristic, making them a powerful substance.[15]

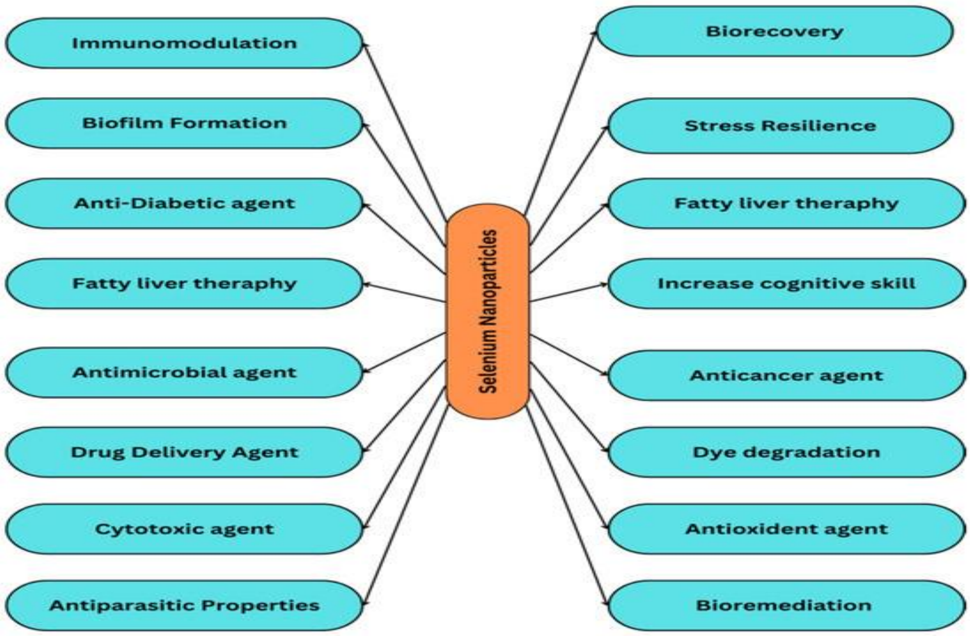

Figure 1: Advantages of using selenium nanoparticles in medicine and biology.[16]

Nanoparticles of selenium So far, reviews have mostly concentrated on their features, manufacture, and uses. The biological synthesis of selenium nanoparticles by bacteria, plants, and fungus has been covered in this review. The numerous biological uses of SeNPs, such as their antioxidant, antibacterial, anticancer, wound-healing, scolicidal, and antiviral properties, are covered in great detail in this article. The limits of earlier studies and upcoming advancements in selenium are also covered in this study. Since there aren't many reports on SeNPs, the review will serve as a starting point for anyone who deals with them.

1.1 Techniques for Producing Selenium Nanoparticles

Since the size, shape, and other properties of nanoparticles determine their usefulness, it is wise to choose the synthesis method based on the study. There are numerous methods of creating nanoparticles, which can be roughly divided into three categories: chemical, biological, and physical. In order to comprehend the properties of SeNPs, we describe the synthesis process in detail.

a. Physical Method

Techniques like hydrothermal, solvothermal, vapor deposition, and pulsed laser ablation were employed in the physical approach of SeNPs. Pulsed laser ablation is better than other techniques because it is simple to gather NPs by centrifugation and because they are highly stable.[17] A Variety of physical techniques for creating Se nanoparticle are listed.

The chosen target was sodium selenite (SeO3) which is not water soluble and placed in a cell containing de-mineralized H2O, as described by *Overschelde et al.*[18] After that, an excimer laser with a wavelength of 248 nm and a frequency of 50 Hz was used to expose the sodium selenite in the cell for 50 minutes. To avoid beam interaction during the experiment, a magnetic stirrer was affixed to the cell wall. The mixture was then centrifuged for 25 minutes at 600 rpm. The centrifuge separated the nanoparticles produced from the sodium selenite, which confirmed the nanoparticles were 60 nm in size.[18] Additionally, it was confirmed that the sodium selenite nanoparticles (SeNPs) had no leftover chemicals and were created by pulsed laser ablation in liquids. The samples were exposed to a titanium sapphire pulsed laser with a frequency of 80 MHz and a pulse duration of 100 fs. The laser beams were focused through a square cuvette that contained two milliliters of deionizer water and multiple selenium pellets at the bottom. It was confirmed that the spherical-shaped nanoparticles made with this method ranged in size from 50 to 400 nm, with an average size of about 128 ± 30 nm after 60 minutes. The synthesized nanoparticles were utilized for the biofilm inhibition studies against Candida albicans.[19] Tzeng and They have reported the production of both crystalline and amorphous selenium nanoparticles as a result of the interaction of a femtosecond laser with a Bl2 Se3 single crystal (using an 800 nm wavelength and a pulse energy of 49 nJ) to generate a laser-driven shock wave to create nanoparticles that are spherical in shape with diameters between 100 and 900 nm.[20] They also reported a method for synthesizing selenium nanoparticles that involved dissolving SeCl4 in distilled water containing sodium dodecyl sulphate (SDS) surfactant and adding it to a beaker containing 2 mL. of hydrazine while stirring at room temperature, to be irradiated with 750W light. After irradiation, the resulting solution changed colour, indicating the presence of Se2+. Upon continued irradiation, the colour of the solution became dark red, and the resultant precipitate was allowed to cool, filtered, dried at 70 ◦C in a vacuum, and characterized by TEM as being spherical and measuring between 5 and 25 nm in diameter. The resulting selenium nanoparticles have been incorporated into the development of solar cells.[21] Quintana et al. described their use of Nd:YAG lasers to fabricate Se nanoparticles from amorphous selenium by ablating a portion of the material onto three substrates. Silicon wafers, gold-coated glass, and glass slides in a vacuum formed using a diffusion pump to supply pressure are substrates used to produce selenium nanoparticles. In order to create the nanoparticles, a solution of encapsulated selenium was first exposed to a laser. A pulsed Nd:YAG laser with a 10 ns pulse width, 20 mJ of energy per pulse, and a 10 Hz frequency was utilized. After the laser had focused, it was directed onto the column of the solution, after which the resulting nanoparticles were examined with transmission electron microscopy (TEM) and found to be approximately 3 nm in diameter.[21] In conclusion, both methods of producing selenium nanoparticles produced nanoparticles that were confirmed to be in the nanometer size range.

b. Chemical Methods

The most popular technique for producing SeNPs is chemical reduction of inorganic selenium to create precursors. SeNPs are produced by chemically reducing inorganic selenium with ascorbic acid or any other reducing agent (glutathione, cysteine, etc.). Glucose, fructose, sodium metabisulfite, and ionic liquid 1-ethyl-3-methylimidazolium thiocyanate were among the reducing agents. BSA, carboxymethylcellulose, and water-soluble polymers served as stabilizing agents by stopping the aggregation of nanoparticles. Inorganic selenium is chemically reduced with ascorbic acid or any other reducing agent (glutathione, cysteine, etc.) to generate SeNPs. Because some of these are still present in the finished product, their potential pharmacological or therapeutic utility for generated SeNPs is restricted.[17]

c. Biomedical Applications

Many researchers around the world are concentrating on the possible biomedical applications of SeNP because of their significance for cellular and tissue levels. It is well-established that when there are abiotic stresses, there is an overproduction of toxic reactive oxygen species (ROS), resulting in numerous diseases due to damage to the body as a result of the loss of critical nutrients (carbohydrates, proteins, and lipids) that are caused by these ROS.[22] The increasing prevalence of diseases such as cancer, diabetes, and bacterial infections puts a tremendous strain on healthcare systems around the world, and thus finding effective treatments for these diseases are extremely important. Today, treatments for various types of cancer require several different forms of treatment (chemotherapy, radiotherapy, or a combination of both) to lower the worldwide death toll from cancer.[23,24] However, there is much concern regarding the adverse effects associated with these types of treatments.[25]

- **Anticancer Activity**

Recent studies have indicated that selenium nanoparticles have been the focus of multiple studies for anticancer activity against breast and lung cancer, kidney cancer and osteosarcoma as demonstrated by in vivo and in vitro testing.[26-30] Elemental selenium and naturally occurring selenium (selenocysteine and selenomethionine) cannot currently be administered as anticancer treatments due to toxicity and low bioavailability of these natural sources.[31]

Compared to other natural sources of selenium, which may have a lower toxicity, selenium nanoparticles are Due to their size, porosity and bio-dispersion characteristics; Porous polysaccharides produced by Polyporus umbellatus (PUP) were evaluated for their effect on tissue proliferation of cancerous tissues using MTT assays.

Polyporus umbellatus polysaccharides SeNPs demonstrated the ability to inhibit the growth of 4 types of human cancerous tissues, including:
a) MDA-MB-231 (breast)
b) HepG2 (liver);
c) HeLa (cervical);
d) HT29 (colon)

Researchers have demonstrated that using nano-selenium that is capped with the specified polysaccharide produces no toxicity to normal human cells such as LO2 liver cells, 293T (embryonic kidney cells) and NIH3T3 (mouse embryonic fibroblast cells).[32]

Multiple analyses validate that consumption of insufficient selenium leads to an increased risk of several lethal conditions and uses selenium as an anticarcinogen, when given in adequate doses.[33,34] Therefore, selenium is considered an adjunct to disease treatment with chemotherapy and radiation.[35] Reports indicate that the greatest anticarcinogenic effect of selenium is when given early in the disease process.[36,37] The presence of arsenic in drinking water can lead to an increased risk of cancer in humans; however, it has been suggested that the utilization of selenium nanoparticles encapsulated within Terminalia arjuna leaf extracts can reduce the generation of the reactive oxygen species As(III) active; thus, enhancing As(III) induced cell death and DNA damage.[38,39] Mouse model studies have indicated that oral administration of Lactobacillus brevis combined with Se nanoparticles results in enhanced production of interferon and delayed hypersensitivity responses.[30] promoting an immune response to metastatic breast cancer.

- **Antioxidant properties**

As a byproduct of several physicochemical and metabolic processes that take place within the human body, ROS and RNS (free radicals) are commonly produced. The likelihood of cellular damage and eventually fatal diseases increases with the number of intermediate complexes (such as superoxide and hydrogen peroxide) that occur from these kinds of interactions. As such, Antioxidant compounds are utilized for both the inhibiting formation and scavenging of these free radicals.[40,42] The surface of selenium (Se) nanoparticles, modified with various organic and/or plant extract materials, can act as both an antioxidant and an oxidizing agent to various cells in the body; however, there is a difference between.

Battin et a.[43] demonstrated that the use of selenium nanoparticles to reduce the concentration of free radicals is an effective method to protect against oxidative damage to DNA both in vivo and in vitro. It has also been subsequently demonstrated that a selenoprotein is a significant source of selenium and yields important antioxidant molecules (deiodinase, thioredoxin reductase, and glutathione peroxidase).[44] *Zhang et al*.[45] showed through their investigation that sodium selenium inhibited Candida utilis growth by enhancing glutathione excretion and biosynthesis. Similarly, chitosan functionalized SeNPs showed enhanced glutathione peroxidase and anticipated lipofuscin development in mice.[46] Additionally, ABTS°+ and superoxide anion radical can be scavenged by utilizing SeNPs in combination with *Cordyceps sinensis exopolysaccharide*.[32] The plant-based synthesis of selenium nanoparticles demonstrated antioxidative activity through ABTS and DPPH assays.[46]

Further, the Kong group[47] presented the enhanced antioxidative activity of *gum-arabic* functionalized SeNPs (GA-SeNPs) for scavenging hydroxyl radicals and the DPPH assay test. Selenium Nanoparticles were found to be hepatoprotective against acetaminophen-induced toxicity via improvement of liver function and reduction of oxidative stress In a study, by *Kokila et a*.[48] had an experimental approach to the investigate the antioxidative characteristics of SeNPs.

There are many material characteristics for Nanoparticles that are important to their function within the body, such as size and shape. For example, hollow spherical SeNPs Have Demonstrated an Antioxidative Effect.[49,51] There fore, it has been discovered that plant-based SeNPs are more effective than any Other source in preventing diseases linked to oxidative stress.

- **Antiparasitic action**

Various researchers have instituted multiple avenues of research over recent years exploring the antiparasitic activity of selenium nanoparticles.[52,54] Numerous types of parasitic disease and their effects on various human organs are illustrated. Bacillus sp. Msh-1 produced SeNPs have the potential to treat Leishmania major parasites (such as amastigote and promastigote), according to a combination of in vitro and in vivo research.[55] Furthermore, based on in vitro experimentation, Bacillus sp. Msh-1 SeNPs have been found to exhibit in vitro Leishmanicidal activity against Leishmania infantum.[56] and Leishmania tropica.[57] The application of gel electrophoresis has permitted the investigation of the time-dependent reduction of promastigote proliferation mediated by selenium nanoparticles; this has been related to the fragmentation of DNA through time.[58] In vitro experimentation using biosynthesized SeNPs (sized from 80-220 nm) revealed strong scolicidal activity against parasitic infections (cystic echinococcus).[59] Additionally, in this study it was found that there was a similar time-dependent cytotoxicity against the intracellular amastigote form of Leishmania major in BALB/c male mice, where administered selenium nano shells caused a significant anti-leishmanial effect by reducing the progression of the lesion at the injection site after the mice became infected with Leishmania major. The effectiveness of selenium nanoparticles at killing Leishmania infantum compared with selenium dioxide was examined in both the promastigote and the amastigote stages of the parasite using methods described by *Soflaei et al*.[54] SeNPs were shown to have greater anti-leishmanial performance with lower cytotoxicity in comparison with the same concentrations of SeO2. Soflaei et al. came to the conclusion that the greater anti-Leishmanial activity of SeNPs over SeO2 on L. infantum was due to the time and dose-dependent activity of SeNPs, and that the use of SeNPs offers substantial benefits in the treatment and prevention of leishmaniasis. In another study by Mahmoudvand and colleagues.[55] SeNPs in a specific size range were also determined to have an effect on the resistance of Meglumine antimoniate (MA) and the MA-sensitive L. tropica strain when tested in vitro. These results show that the effects of SeNPs on the promastigote are dose-dependent, prevent the growth of the two strains of amastigotes within macrophages, and are very effective in preventing infection. Additionally, when combined with MA, SeNPs produced greater anti-leishmanicidal activity than either SeNPs alone or MA alone.[60]

- **Antidiabetic Activity**

Insufficient secretion or utilization of insulin results in hyperglycemia, which leads to chronic diseases, including diabetes. The hormone insulin is responsible for control of glucose levels in the blood. Diabetes has a significant impact on individuals at all ages. There are many studies that show that selenium nanoparticles can be used for treatment of diabetes, as these will regulate the glucose level effectively. According to *Ellis et al*.[61] Diabetes can cause damage to organs by affecting both small and large blood vessels over time due to long-term complications associated with diabetes. All organs may develop complications that are related to the same disease, including the heart, legs, brain, eyes, kidneys, skin, digestive system, and mouth/immune system The Liu group[62]studied the increased ability to control blood sugars through the use of selenium nanoparticles, finding that they can be used to augment or enhance the antidiabetic activity of insulin by being able to provide greater amounts of insulin to the blood stream. The Antidiabetic activity of Carothelasma Ventricose polysaccharides Coating with SeNPs (Se Nanoparticles) in Strepzotozin(STZ)-induced diabetic mice and the possible synergistic effect of Se Nanoparticles in conjunction with insulin on the actions of insulin in STZ-induced diabetic mice.[63] The use of chitosan coated Se Nanoparticles at 2.0mg/kg body weight demonstrated increased antidiabetic activity[64], Phytomedicines are candidates with proven efficacy against diabetes.[65] thus, watery extract of mulberry leaf (Morus nigra) and Pueraria lobata extract (MPE) were demonstrated to have hypoglycemic properties and the ability to treat diabetes mellitus in diabetic mice when combined with coated Se Nanoparticles.[66] Selenium as an associated plasma biomarker has a positive role in developing and progressional diabetes through redox regulation and insulin signaling pathways.[67] Due to the presence of diverse functional moieties in the preparation of Se Nanoparticles, these types of preparations may one day be used as a treatment option for a variety of diabetes types.

- **Antifungal Activity**

It's properties are obtained by the use of selenium nanoparticles (SeNPs) in various biologically-based therapies. The following are some examples: SeNPs may be used in patients who have an impaired immune system to treat fungal infections, to improve probiotic numbers in a person's gut and to create antimicrobial and antifungal cloths to protect the skin from S. aureus (Staphylococcus aureus) and Tinea pedis (foot fungus) infections.[68] To prove these antifungal abilities, *Yip et al*.[69] showed that the nano-Se particles, which were created by using biogenic polysaccharide-protein (PSP) complexes from Pleurotus tuber-regium deposited onto fabric, effectively impeded the growth of both S. aureus and Trichophyton rubrum (a fungus). In a similar study, *Shakibaie et al*.[70] demonstrated that Bacillus sp., Msh-1 functionalized SeNPs had antifungal activity against Aspergillus fumigatus (which causes pulmonary infections) and Candida albicans (which causes skin infections). The study indicated that SeNPs produced using Klebsiella pneumoniae demonstrated antifungal effects against Malasseziasympodialis, Malassezia furfur, and Aspergillus terreus in concentrations within 10-260 µg/mL. SeNPs were specifically effective against Candida species that are resistant to nystatin.[71] and can be a substantial treatment option for patients with invasive aspergillosis when compared to amphotericin B.Conversely, conflicting data on the antifungal capabilities of SeNPs synthesized from Klebsiella pneumoniae were reported by the Kazempour group. SeNPs were ineffective at creating an antifungal post-antifungal effect on A. niger and C. albicans; additionally, they found a low concentration of Se stimulated A. niger growth. It was hypothesized that selenium has a physiological effect on selected proteins of A. niger which explains this action. The results may directly impact the occurrence of skin problems associated with A. niger and/or C. albicans. Thus, introducing SeNPs into people's surroundings will promote the regrowth of these pathogenic organisms onto their skin again. The concept of "post-antifungal effect (PAE)" is highly interdisciplinary from a pharmacodynamic standpoint of view, as it delineates the criteria for quantifying the antifungal action of an antifungal agent by documenting that, following its administration to a microorganism, the organism will once again begin proliferating after being initially exposed to the antifungal agent for a given time period.[72,74]

- **Antibacterial Effects on Selenium Nanoparticles**

1. Selenium nanoparticles (SeNPs) degrade proteins through their bactericidal properties.[75]
2. Selenium ions are released slowly from the surface of SeNPs and may interact with protein/enzyme functional groups such as -SH, -NH, or -COOH. This interaction may cause loss of tertiary/quaternary structure and function.[76]
3. SeNPs also inhibit the activity of the dehydrogenase enzyme, which is essential for maintaining the integrity of the bacterial cell membrane.[76]
4. Hyperproduction of reactive oxygen species (ROS), cellular membrane potential disturbance, and depletion of internal adenosine triphosphate (ATP) may all result from exposure to SeNPs.[77]
5. SeNPs also inhibit the ability of bacteria to attach to surfaces, and therefore, prevent the formation of bacterial biofilms.[78]
6. SeNPs have photocatalytic properties, which allow them to kill bacteria when exposed to light.[79]
7. SeNPs inactivate the natural mechanisms that allow for the transport of ions and nutrients across the bacterial cell membrane (thus blocking the ability of the bacteria to grow and multiply).[81]

In general, it appears that selenium nanoparticles have potential applications as alternative and/or additive materials for controlling populations of antibiotic resistant bacteria. It has also been shown that antimicrobial nanoparticles can disrupt bacterial cell structure by different means (i.e., having more than one way to affect bacterial cells) which creates difficulty for bacteria to develop a resistance to the multiple mechanisms of action of a particular nanoparticle.[80] In addition to antibacterial activity against prokaryotic (bacterial) cells, some researchers have reported that bacterial cells are not adversely affected when treated by selenium nanoparticles.[77]

There are two primary actions by which selenium nanoparticles exert their bacteriostatic activity, both of which involve inhibition of the enzyme, dehydrogenase, and destruction of the cell membrane's integrity. The bacteriostatic activity of selenium nanoparticles was explored using the arabinogalactan polysaccharide stabilized selenium nanoparticles.[76] It is feasible that there are different mechanisms by which selenium nanoparticles will exert their antimicrobial activity, and these mechanisms may arise from the interactions that occur at the surface of the nanoparticle with the living cell. Reactive oxygen species (ROS) overproduction on the surface of nanoparticles and lipid peroxidation (LPO) brought on by ROS overproduction on the surface of nanoparticles cause serious damage to cellular membranes and organelles, start transcriptional gene deactivation, trigger apoptotic genes, and impede the production of several proteins and enzymes within cells. In addition, it is possible that nanoparticles at the surface of cells will cause depolarization of the cellular membrane, destroy the integrity of the cell membrane and lead to loss of cellular life.[76] Silver has created what is referred to as an enhancer of the anti-adherence activity of pathogenic bacterium creating a stable adhesive structure. This has been shown in an experiment where the combination of silver nanoparticles and selenium nanoparticles exhibited an increase in adhesive strength to biofilm structures. There were also supporting data concerning this phenomenon.[78] The antifungal mechanisms include antibiofilm activity.[82,83] generation of ROS and causing oxidative stress (by adding the antifungal drug ketoconazole).[84] and its ability to induce expression of multiple drug resistance (MDR) genes.[85] SeNPs exhibit antiviral activity through different means including: interruption of the operation of viral capsid proteins (especially, hemagglutinin and neuramidase activities of the influenza virus); interference with the viral induced activation of the AKT-p52-Caspase3 dependent pro-apoptotic pathway; inhibition of viral replication in host cells; and potentiation of antiviral drug activity.[85,87]

- **CONCLUSION**

SeNPs (Nanoparticles Selenium) can be used to treat many disease processes associated with bacterial, fungal and viral infections; inflammatory and autoimmune disease and neurological disorders; diabetes and drug-induced toxicity. SeNPs can offer many benefits related to these areas of research; therefore they were included in nearly every study cited prior to writing this review. Furthermore, some Additional Characteristics of SeNPs are described in more detail based on differences between elemental forms of selenium.In hyperglycemia, colitis, and autoimmune diseases, results have shown efficacy of SeNPs compared to other forms of Se. Drug-induced toxicities and genotoxicity have been reduced significantly through the use of SeNPs.

It has been discovered that SeNPs block a number of the same regulatory mechanisms that lead to diabetes and inflammation. Establishing a therapeutic index for SeNPs is still a long way off because, as was previously indicated, the toxicity potential of Se is far larger than that of the other elemental selenides. However, SeNPs' characteristics make them appropriate for a variety of biological uses. The relationship between Se Selenium nanoparticles (SeNPs) have been shown in numerous trials to be effective against a number of deadly diseases, such as cancer, diabetes, Alzheimer's disease, and other drug-related toxicities. However, the potential toxicity of selenium nanoparticles remains a key concern for researchersThe authors found in the literature search of the publications that NPs composed of selenium have been the focus of several investigations as potential cancer treatments that act as both antioxidants and antibacterial agents. To fully understand the biochemical interactions between different biological molecules and selenium NPs, more research is needed. The bulk of the selenium NPs under evaluation had an average size between 50 and 200 nm.

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