Review Article

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A Systematic Review on Green Synthesized Selenium Nanoparticles as Antioxidant and Antidiabetic Agents: Mechanistic Insights and Therapeutic Potential

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Abstract

Nanotechnology has introduced revolutionary progress in medical sciences, providing unparalleled prospects for diagnosing and treating diseases. Notably, Nanomedicine enables targeted drug delivery, maximizes therapeutic effects, limits undesirable effects, and enhances therapeutic precision, which was unattainable with conventional methods. Furthermore, integrating natural biomolecules in nanoparticle synthesis has evolved as a sustainable approach, combining ecological safety with improved biocompatibility and pharmacological performance. This review aims to systematically scrutinize the literature on the beneficial effects of green Selenium Nanoparticles (SeNPs) on antioxidant and antidiabetic potential. For this study, the literature was meticulously searched, and data were collected from preferred sources, including PubMed, ScienceDirect, ScienceOpen, DOAJ, Google Scholar, ResearchGate, and Scilit. The literature search was restricted to English-language works published between 2014 and 2024. Data collection focused on the antioxidant and anti-diabetic properties of green-synthesized SeNPs, which were reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) approach. Methods like DPPH, ABTS, and FRAP assays were used to assess the antioxidant activity. This review finds that *Aloe vera*, *Annona muricata (A. muricata)*, *Waltheria indica (W. indica)* (IC_{50} 0.00692), *Millettia pinnata* (IC_{50} 0.0077), *Camellia sinensis*, *Citrus sinensis* (IC_{50} 0.00849) mediated NPs in DPPH and *W. indica* (IC_{50} 0.01685), *A. muricata*, *Calluna vulgaris* (IC_{50} 0.01687), *Echinacea purpurea*, *Aloe vera*, *Blighia sapida* NPs in ABTS (in *mg/ml* concentration) exhibited a very promising antioxidant effect. The plant *Fagonia critica (F. cretica)* (IC_{50} 0.1), *Cassica auriculata (C. auriculata)*, *Moringa oleifera (M. oleifera)*, *Caralluma tuberculate (C. tuberculate)* in α-glucosidase and *F. cretica*, *C. auriculata*, *M. oleifera*, *Broccoli florets*, *C. tuberculata* mediated NPs, in α-amylase assay (*mg/ml* concentration) showed the most prominent antidiabetic effects. Therefore, the green-synthesized SeNPs could be considered as distinct antioxidant and antidiabetic agents, potentially contributing to both antidiabetic and antioxidant therapy.

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Introduction

Oxidative stress is a state when there is a contrast between the generation of Reactive Oxygen Species (ROS) and the body's capability to detoxify these detrimental consequences. ROS are extremely reactive molecules that can result in cellular injury, leading to serious health issues. These highly reactive free radicals, produced by oxidative stress, cause damage to cells or interrupt cellular functions [1]. These also interfere with pro-

tein or DNA, leading to several chronic diseases, including cancer, cardiovascular, neurodegenerative, respire tory diseases, chronic kidney diseases, rheumatoid arthritis, and diseases like diabetes, which is called the mother of all diseases which is a major systemic metabolic disorder that significantly increases the risk of multiple chronic complications [2]. Antioxidants are compounds that detoxify or neutralize free radicals and broadly prevent oxidation, thus preventing thousands of serious health issues.

In this context, diabetes is a condition in which the pancreas cannot produce enough insulin or the body is incapable of using insulin to process blood sugar. It has been a major health issue in recent epochs. It can lead to numerous health issues. Diabetic conditions create a lot of complications in the body. It can affect every organ system of our body. It amplifies the risk of heart disease, the leading cause of chronic kidney disease and kidney failure, and causes retinopathy, which means eye damage that can lead to blindness. It damages nerves, leading to pain, numbness, and other issues, and it can also cause a stroke. Nerve damage and poor circulation can lead to severe foot infections and amputations [3,4]. There are a lot of such health complications leading to diabetes. Diabetes is a chronic condition and a name of common threat of this century. Recent valuation shows that relatively 537 million adults (aged 20-79 *yr*) worldwide are living with diabetes. This figure is anticipated to increase to 643 million by 2030 and 783 million by 2045 [5]. The prevalence of diabetes has been increasing rapidly. Globally, the number of diabetes mellitus patients was 11.3 million in 1990, while it increased to 22.9 million in 2017. The new case rate is almost 103%, Age-Standardized Incidence Rate (ASIR) rose from 234 *per* 100,000 persons in 1990 to 285 per 100,000 persons in 2017 [6]. In the United States, about 38.4 million people of all ages, or 11.6% of the U.S. population estimated to have diabetes in 2021, and diabetes was directly mentioned as a cause of death on 399,401 certificates [7]. The rate of global death is approximately 6.7 million, accounting for 12.2% of all deaths globally in 2021, which looks like a pandemic, and the way diabetic conditions are gradually increasing [8].

Both oxidative stress and diabetes are hazardous to health. They are interconnected and contribute to one another in a cycle. Oxidative stress acts as a factor for diabetes by damaging the pancreatic β-cell that produces insulin, and diabetes generates more free radicals and increases oxidative stress [9]. Both conditions collectively create menacing complications. It is difficult to combat either of the conditions through conventional medication. In this circumstance, an effective antioxidant and antidiabetic medication is a matter of basic need to counter this challenging situation. Therefore, nanomedicine could be a promising approach for managing diabetes and oxidative stress due to its precise control over drug release, target specificity, increased penetration capability, improved drug accessibility in hard-to-reach areas, increased absorption, enhanced bioavailability, higher efficacy, and fewer side effects [10]. Nanoparticles possess remarkable versatility in applications across various sectors owing to their distinctive features. Among them, it is extensively used in the medical and pharmaceutical sectors. Nano-medication has gained significant attention due to its potential to revolutionize the way of diagnosing and treating. It involves the use of nanoparticles and nanoscale materials to deliver the drugs. It is designed to specify target disease locations, which means medication can be sent precisely to diseased cells or tissues [11]. Nanoparticles are small enough to penetrate biological barriers and can enhance drug absorption at the cellular level. Drugs that are poorly soluble in water can be effectively delivered by nanoparticles. All the above criteria make nano-medication an effective form of medication. Especially for the diseases that were tough to tackle in a conventional way, such as oxidative stress, diabetes, cancer, *etc*.

Nanoparticles can be different types, some are organic, such as polymeric nanoparticles, liposomes, and dendrimers, and some are metallic, such as silver nanoparticles (AgNPs), gold nanoparticles (AuNPs), zinc oxide nanoparticles (ZnONPs), selenium nanoparticles (SeNPs), cerium oxide nanoparticles (CeO2NPs), *etc*. Among them, inorganic nanoparticles have promising antidiabetic and antioxidant effects [12]. The nanoparticles can be fabricated by diverse methods such as physical methods, chemical methods, biological methods, green synthesized methods, or different kinds of hybrid methods like physicochemical and mechanochemical methods, *etc*. [13]. Among all those methods, green synthesis is one of the sustainable approaches to synthesizing nanoparticles, which is eco-friendly, more biocompatible, suitable for medical and pharmaceutical applications, scalable as well as cost-effective [14]. Selenium and SeNPs themselves act as antioxidants, and when they are synthesized in combination with the plant components, they synergistically enhance their range of antioxidant and antidiabetic activity [15].

Green synthesized SeNPs can neutralize free radicals, lessen oxidative stress, and enhance glucose metabolism and insulin sensitivity more efficiently [16]. This synergistic interaction is undoubtedly a unique approach to therapeutic remediation, enabling the development of a pharmacologically active therapeutic strategy capable of delivering targeted therapy simultaneously with reduced side effects and enhanced potency. Recently, SeNPs have been extensively investigated to scrutinize their antioxidant and antidiabetic potentials; many research articles have been published, but there is a lack of systematic reviews on green synthesis of SeNPs with antioxidant and antidiabetic exploration. Therefore, this systematic review aims to discuss the green synthesis process of SeNPs, as well as explore and conjugate their antioxidant and antidiabetic potentials.

Materials and Methods

Search strategy

To find the desired full-text article concerning the antioxidant and antidiabetic effect of green-synthesized SeNPs for this review, a systematic literature search was carried out in various sources and databases. These are PubMed, Science Direct, Science Open, DOAJ, Scilit, and Google Scholar, Research Gate, as supplementary search tools to identify potentially relevant peer-reviewed articles. A combination of controlled vocabulary terms and free-text keywords was used. Search terms were adapted for each database to ensure sensitivity and relevance. The research article search had been confined to the English language, published from 2014 to 2024. The following keywords were searched for this study: Green synthesis of SeNPs, Phytochemical mediated SeNPs synthesis, Eco-friendly synthesis of SeNPs, Biomedical applications of SeNPs, Selenium nanoparticle and its antioxidant properties, SeNPs function as antioxidant, Greener SeNPs activity for Scavenging ROS, Greener SeNPs for scavenging free radicals, Green synthesized SeNPs and antioxidants activity, SeNPs activity on DPPH assay, SeNPs activity on ABTS assay, Antidiabetic potential of green mediated SeNPs, Biogenic SeNPs and their antidiabetic & antioxidant effects, SeNPs phytochemical synthesis & use in diabetic prevention, SeNPs from medicinal plants diabetic & antioxidant activity, SeNPs for therapeutic use, SeNPs and insulin sensitivity, SeNPs and glucose regulation, SeNPs in α-amylase and α-glucosidase enzymatic activity, Sustainable biosynthesis of SeNPs and its antioxidant & antidiabetic activity, SeNPs and health benefits, SeNPs, and bioactivity.

Inclusion criteria

The inclusion of published research articles for this study followed the following criteria; only full-text research articles were included that have sufficient and specific information regarding this study, papers were collected that were published in Scopus index journals and Q1, Q2, and Q3 journals, articles written in English language and published between 2014 to 2024, articles with *in vitro* and *in vivo* evaluation of green synthesized SeNPs for antioxidant and antidiabetic properties were included.

Exclusion criteria

The research articles with the following characteristics were excluded; Duplicated research articles, not containing predetermined specific information, non-related papers, review papers, thesis papers, project reports, case reports, conference proceedings, articles written other than in English language, articles without full text, computational research articles, articles published beyond the time limit, activity evaluation of SeNPs except antioxidant and antidiabetic properties and the articles published in predatory journals. To avoid the inclusion of predatory journals, explicit criteria were applied during the literature selection process. Only studies published in journals indexed in Scopus and listed in the Directory of Open Access Journals (DOAJ) were included. In addition, journal websites were screened for peer-review policies, editorial board transparency, and publication ethics when required. Title/abstract and full-text screening and data extraction were conducted independently against the eligibility criteria by two reviewers to avoid potential sources of bias, including selection, measurement, and reporting bias. Any disagreements were resolved through discussion and consensus with the third author.

Data screening and selection process

Following the aforementioned search strategy, exclusion, and inclusion criteria, a total of 413 publications were collected through literature searches. After excluding duplicate records, 347 records were eligible for screening. Based on the principle of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), approximately 267 reports were excluded. Finally, 78 full-text research articles were selected and included in the study. Although protocol registration was not performed, the review was conducted following the established systematic review principles, including a predefined research question, structured search strategy, and explicit inclusion and exclusion criteria. The entire data collection, screening, and selection process is given in a PRISMA flow diagram (Figure 1).

Green synthesis and characterization of selenium nanoparticles

Green synthesis process of SeNPs: The green synthesis of Selenium Nanoparticles (SeNPs) implicates an eco-friendly and cost-effective approach using biological or plant-based materials instead of chemical substances as reducing and stabilizing agents [17]. Green synthesis of selenium nanoparticles typically follows the bottom-up approach, where small particles, atoms, or molecules act as building blocks that cluster together to form larger nanoscale structures by processes like self-assembly and nucleation [18] (Figure 2).

The first step of green synthesis is to select a biological source, such as plant extracts, microorganisms (such as bacteria, fungi), algae, *etc*., which act as reducing and stabilizing or capping agents. If the selected source is a plant, then wash the plant material, dry it, and grind it if desired. Boil or macerate in distilled water to prepare the extract, then filter it to get rid of debris. If it is microorganisms, then cultivate it in an appropriate culture medium and harvest the biomass or cell-free supernatant [19]. The second step of the synthesis is the preparation of the selenium precursor solution. It is done by dissolving a selenium salt (commonly sodium selenite or sodium selenate) in distilled water to form an aqueous solution at the desired concentration. The concentration depends on the desired size and shape of the nanoparticles. After preparing the precursor solution, the biological extract needs to be mixed with the selenium precursor solution in a specific ratio under controlled conditions, such as pH, temperature, time, stirring speed, *etc*. [20].

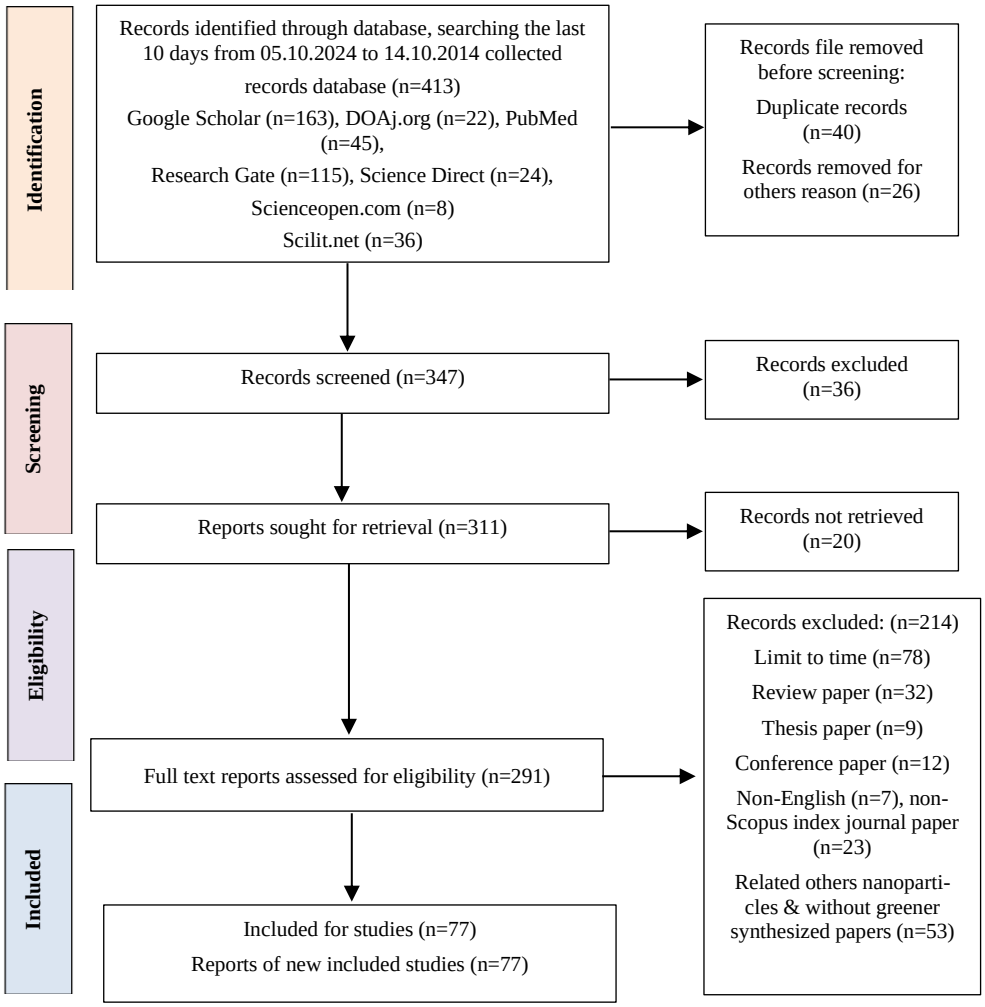

Figure 1. PRISMA flow diagram describing the data collection, screening, and selection process.

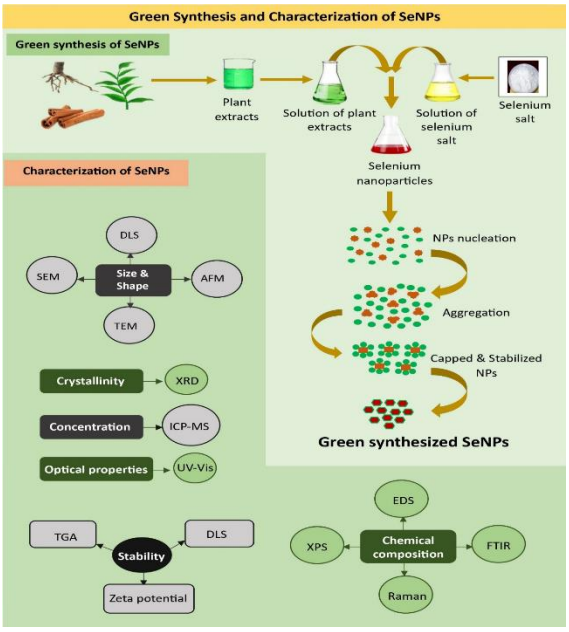

Figure 2. Green synthesis and characterization of SeNPs.

The bioactive compounds in the extract (such as polyphenols, flavonoids, proteins, alkaloids, *etc*.) act as reducing agents and convert selenium ions (Se^{4+} or Se^{6+}) into elemental selenium (Se^{0}) [21]. Bacteria, fungi, algae, and yeast can enzymatically reduce selenium salts. The bioactive compounds in the mixture also act as stabilizing agents and prevent the aggregation of nanoparticles, thus ensuring stability and uniformity [22]. Then the nanoparticles are purified through centrifugation to remove unreacted materials, by-products, or impurities. The purified SeNPs are washed with deionized water or ethanol, then dried, or redispersed the purified nanoparticles in distilled water or buffer for further use [23,24].

Characterization of green-synthesized SeNPs: The prepared solution of SeNPs is kept standing for a sufficient time for visual characterization through the color change phenomenon. After getting the color changed, it is widely believed that the nanoparticles are formed. Then, these green-synthesized SeNPs are characterized to evaluate their physicochemical properties, biological activity, and stability. Characterization of these SeNPs is

important to determine whether the required particles have evolved or not. Furthermore, the characterization is also crucial to guarantee that the NPs might produce the intended results. For analyzing optical properties, UV-visible Spectroscopy is generally used. The UV-Vis spectroscopy technique is used to confirm the formation of nanoparticles by identifying the characteristics of Surface Plasmon Resonance (SRP) peaks [25]. To measure the size and shape of synthesized NPs, Transmission Electron Microscopy (TEM), Scanning Electron Microscopy (SEM), Atomic Force Microscopy (AFM), and Dynamic Light Scattering (DLS) techniques are used [26]. These methods can determine the size (commonly 10-100 *nm*) and morphology (spherical, hexagonal, *etc*.) of nanoparticles. TEM provides high-resolution images for detailed morphology and size (Figure 2) [27]. Generally, green-synthesized SeNPs are partially crystalline. To identify the crystalline nature of SeNPs, X-ray Diffraction (XRD) is used. It identifies the crystalline or amorphous nature of NPs [28].

Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) is an excellent tool for the characterization of SeNPs in terms of elemental concentration (Figure 2) [29]. To analyze chemical and functional groups, Fourier Transform Infrared Spectroscopy (FTIR) is a good analytical tool. It identifies functional groups of biomolecules capping or stabilizing SeNPs. Peaks correspond to proteins, polysaccharides, or polyphenols from plant or microbial extracts used in synthesis [30]. To analyze the stability of SeNPs, Thermogravimetric Analysis (TGA), Dynamic Light Scattering (DLS), or zeta potential are good methods. They can assess the thermal stability and degradation potential of SeNPs and organic components (Figure 2) [31]. Ensuring the chemical compounds required several analytical techniques, among them Energy Dispersive X-ray Spectroscopy (EDS) that identifies elemental composition and confirms the presence of selenium in nanoparticles, X-ray Photoelectron Spectroscopy (XPS) analyses the oxidation states and chemical bonding of SeNPs, Fourier Transform Infrared Spectroscopy (FTIR) detects functional groups on the surface of the nanoparticle, Raman spectroscopy identify molecular vibrations with structural properties & different selenium allotropes *etc*. provides complementary information for ensuring a comprehensive understanding of SeNPs chemical compounds [32].

Results

This section summarizes the key findings derived from the systematic analysis of the included studies, focusing on green synthesis approaches, characterization techniques, and observed trends of selenium nanoparticle research in oxidative stress and diabetes.

The study selection process is illustrated in the PRISMA flow diagram. Records identified through database searching were screened, and full-text articles were assessed for eligibility according to predefined inclusion and exclusion criteria. The studies that met the criteria were included in the final qualitative synthesis.

Antioxidant activity of green-synthesized SeNPs

The Green-synthesized SeNPs exhibit antioxidant activity fundamentally by neutralizing Reactive Oxygen Species (ROS) and preventing oxidative stress that can damage cellular components like lipids, proteins, and DNA [33]. SeNPs are well-acting antioxidant components for their scavenging activity of free radicals. It can donate electrons to neutralize free radicals, such as hydroxyl, peroxyl, superoxide radicals, *etc*., and convert them into less harmful molecules like water or hydrogen peroxide *etc*. [34,35]. Also, SeNPs can mimic the activity of antioxidant enzymes such as glutathione peroxidase, superoxide dismutase, catalase, *etc*. [36]. Nanoparticles modulate endogenous antioxidant defense pathways by regulating key antioxidant enzymes such as Superoxide Dismutase (SOD), Catalase (CAT), and Glutathione peroxidase (GPx). This regulation is largely mediated through activation of the Nrf2-Keap1 signaling pathway, where nanoparticles promote nuclear translocation of Nrf2, leading to increased expression of antioxidant response element-driven genes [37]. SeNPs can chelate transition metal ions like iron and copper, thus reducing their participation in Fenton and Haber-Weiss reactions that produce harmful hydroxyl radicals and therefore prevent free radical production [38,39]. The bioactive compounds used in green synthesis (*e.g*., polyphenols, flavonoids) frequently remain on the surface of SeNPs and enhance their ROS scavenging activity by directly interacting and counteracting oxidizing agents. These several antioxidant mechanisms make green-synthesized SeNPs highly effective in reducing oxidative stress and defending biological systems [40]. These antioxidant methods for evaluating green-mediated SeNPs generally involve their ability to neutralize ROS and free radicals. The commonly used methods for the evaluation are the DPPH assay, which measures the ability of SeNPs to donate electrons or hydrogen to neutralize DPPH radicals, which are confirmed by a color change that indicates antioxidant activity ABTS assay [41], which estimates the ability of SeNPs to eradicate ABTS radicals [42], Ferric Reducing Antioxidant Power (FRAP) determines the reducing potential of SeNPs by converting ferric ions (Fe^{3+}) to ferrous ions (Fe^{2+}) in a reaction that produces a colored complex [43]. Superoxide Radical Scavenging assay tests the ability of SeNPs to neutralize superoxide anions that are generated in a specific chemical reaction, and the Hydroxyl Radical Scavenging assay evaluates the ability of SeNPs to scavenge highly reactive hydroxyl radicals. Hydrogen peroxide Scavenging measures the ability of SeNPs to decompose hydrogen peroxide into water and oxygen, and reduce oxidative stress [44], a lipid peroxidation inhibition assay that helps to test the ability to prevent lipid peroxidation in the cell membrane by neutralizing free radicals [45]. The above method defines the antioxidant potential of SeNPs and their effectiveness in alleviating oxidative stress (Figure 3).

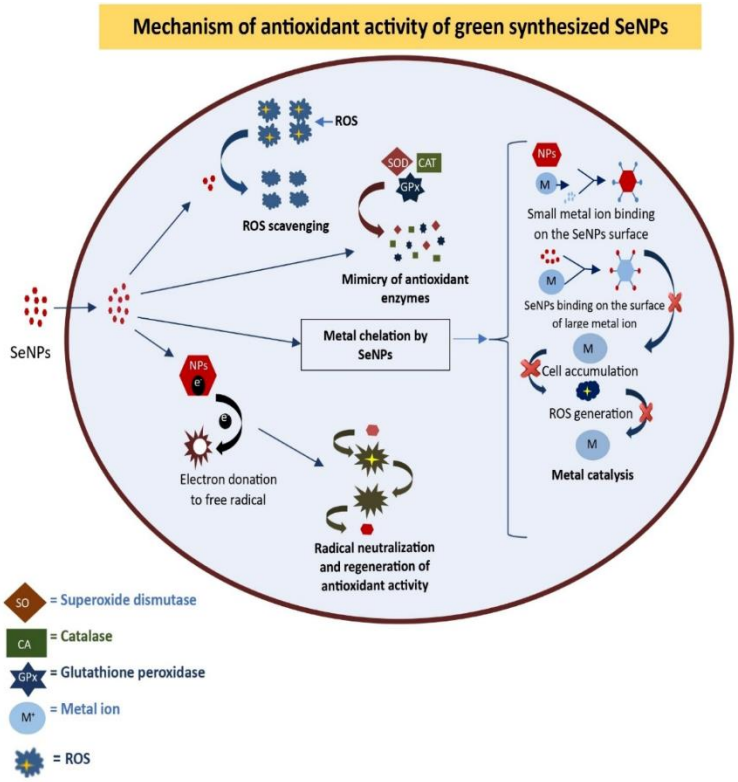

Figure 3. Mechanism of antioxidant activity of green-synthesized SeNPs.

Green-synthesized SeNPs cross the cell membrane and show their antioxidant activity by directly donating electrons to free radicals, mimicking antioxidant enzymes, and chelating metals. Antioxidant activities of different plant mediated SeNPs are descriptively represented in table 1. Among the various plants, some plant mediated SeNPs showed remarkable antioxidant activities. The most promising anti-oxidant activities of few plants mediated SeNPs in DPPH and ABTS assays are represented in the below diagram (Figures 4 and 5).

This summary represents the more potent plant-based greener SeNPs, which exhibited excellent antioxidant activity in the DPPH assay. The potentiality of antioxidant activity was evaluated by analyzing their IC_{50} values. Here, we can observe a gradual growth of the IC_{50} value, which represents the gradual decrease in antioxidant activity. The first three plants mediated SeNPs; *Waltheria indica (W. indica) (*0.00692) to *Citrus sinensis (C. sinensis)* (0.00849) exhibited the most potent effect, as their IC_{50} values are lower than others. It shows a little increase for *Withania somnifera (W. somnifera)* (0.014181). On the next plants, it shows a little variation with growing IC_{50} value from *Azadirachta indica* (*A. indica)* (0.02393) to *Tinospora cordifolia* (0.02862). Then it shows a gradual, rapid increase from *Terminalia arjuna* (0.04518) to *Goniothalamus wightii (G. wightii)* (0.07562). In this rapidly growing stage, the plants *Acai Berry* and *Cymbopogon citratus (C. citratus)* with *Syzgium aromaticum* give the same IC_{50} value of 0.05. Here, in the DPPH assay, the plant *W. indica* (IC_{50} value 0.00692) has the lowest IC_{50} value, which represents the highest antioxidant capacity, and *G. wightii* (IC_{50} value 0.07562) has the highest IC_{50} value among these plants based SeNPs, which indicates its lowest antioxidant capacity (Figure 4 and Table 1).

In this review, it was found that four plant-mediated green SeNPs showed more potent antioxidant activity in the ABTS assay. The potentiality of the SeNPs was also evaluated by their IC_{50} values. Here, *W. indica* (0.01685) and *Calluna vulgaris (C. vulgaris)* (0.01687) exhibited more promising activities as their IC_{50} value are the lowest. The *Annona muricata (A. muricata)* (0.0661) and *G. wightii* (0.07412) have had decreasing activities than the first couple, as their IC_{50} value is comparatively higher (Figure 5 and Table 1).

Meta-analysis of Antioxidant Activity of SeNPs

Forest Plot and Funnel Plot Analysis of IC_{50} Values for Different Plant-Based SeNPs

DPPH Assay: In this analysis, the forest plot represents IC_{50} values of plant-mediated SeNPs, which are used in biological research. The IC_{50} value is a critical parameter, representing the concentration of a substance required to inhibit 50% of scavenging activity. Lower IC_{50} values indicate higher potency, as smaller concentrations are needed for inhibition, whereas higher IC_{50} values suggest weaker activity. The accompanying error bars represent the Standard Deviation (SD) for each IC_{50}

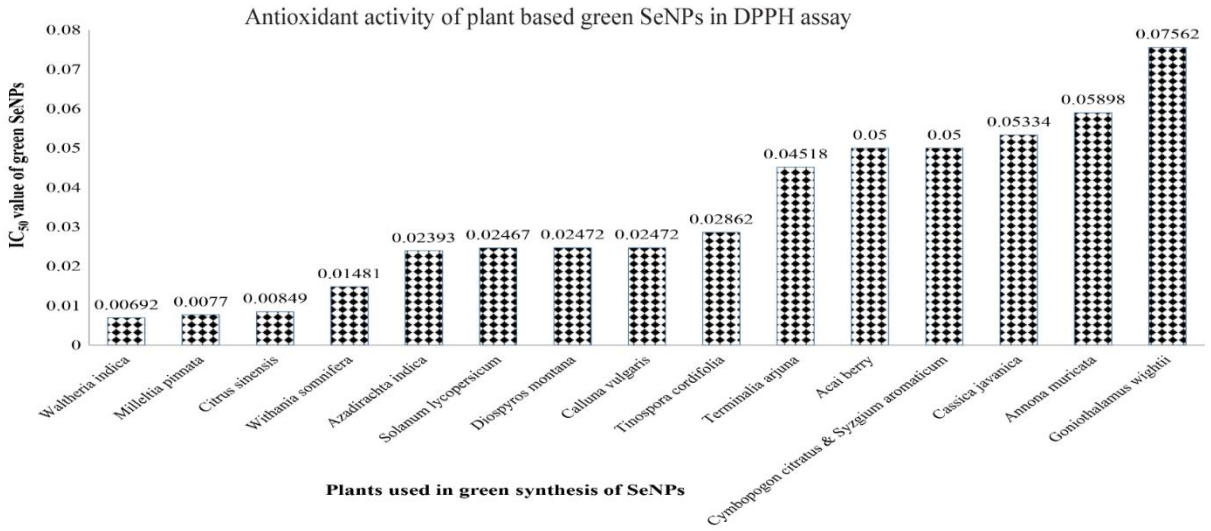

Figure 4. Antioxidant activity of plant based green synthesized SeNPs in DPPH assay

value, indicating the variability or precision of the IC_{50} measurement for each plant-mediated SeNPs. For example, *Bixa orellana (B. orellana)* mediated SeNPs have a low SD of 0.006, indicating high precision in their IC_{50} measurement. In contrast, *Holarrhena antidysenterica* has a higher SD of 0.022, reflecting more variability in its inhibitory activity. *B. orellana* (IC_{50} =0.00538) exhibited extremely strong inhibitory activity, requiring a very low concentration to achieve 50% inhibition. This suggests that *B. orellana* could be a highly effective candidate for further research in medicinal applications. *Acai Berry* (IC_{50}=0.05) and *Allium sativum (A. sativum)* (IC_{50}=0.05898) also exhibit strong potency, as their IC_{50} values are well below the threshold of 1, indicating that these plant-based SeNPs have significant inhibitory effects at relatively low concentrations. *C. citratus* (IC_{50}= 0.23) and *Cassia siamea (C. siamea)* (IC_{50}=0.1239) exhibited moderate inhibitory effects, with IC_{50} values above 0.1, yet still demonstrating potential for effective inhibition in certain contexts. The logarithmic scale on the x-axis enhances the clarity of the plot by compressing a wide range of IC_{50} values, making it easier to compare plants with both low and high values on the same plot. The scale spans from 0.01 to 100, with values greater than 1 showing a shift towards weaker potency (to the right of the vertical reference line at IC_{50}=1) (Figure 6 and Table 2).

A funnel plot is made of selected plant extracts-based SeNPs, approximately 13 plants, with IC_{50} values ranging from 0.12 *mg/ml* (*Aloe vera*) to 2.37 *mg/ml* [*Polygala tenuifolia (P. tenuifolia)*]. The overall mean IC_{50} was approximately 0.47 *mg/ml*. Most SeNPs clustered around this mean with relatively small variability, for example, *A. sativum* (IC_{50}=0.16±0.007) and *C. siamea* (IC_{50}=1.50±0.011). More precise estimates with lower SD values (*e.g.*, *A. sativum*, *A. indica*) feel closer to the mean, while SeNPs with larger IC_{50} values [*e.g.*, *Moringa oleifera (M. oleifera)*, IC_{50}= 0.46±0.010, and *P. tenuifolia*, IC_{50}=2.37±0.012] lie toward the edges of the funnel. Most points were located within the 95%CI boundaries, with no extreme outliers observed. The funnel plot (Table 2) demonstrated a generally symmetrical distribution of IC_{50} values around the pooled mean of 0.47 *mg/ml*. Lower IC_{50} values, such as *Aloe vera* (0.12± 0.020 *mg/ml*) and *A. indica* (0.124± 0.014 *mg/ml*), were balanced by higher IC_{50} values, including *C. siamea* (1.50±0.011 *mg/ml*) and *P. tenuifolia* (2.37±0.012 *mg/ml*). The absence of strong asymmetry suggests limited evidence of publication bias. As expected, studies with smaller SDs (more precise estimates, *e.g.*, *A. sativum* at 0.16±0.007 *mg/ml*) appear near the top of the funnel and cluster closely around the mean, while those with higher variability spread more widely. Although the plot is consistent with unbiased reporting, it should be noted that the use of SD instead of SE may underestimate or overestimate the actual confidence intervals. Moreover, the relatively small number of included SeNPs (n=13) reduces the sensitivity of the funnel plot to detect subtle asymmetries.

ABTS assay: The forest plot generated using the provided data shows the IC_{50} values for different plant-based green SeNPs and their SDs. The IC_{50} values are plotted on a logarithmic scale with error bars representing the 95% Confidence Intervals (CIs). The confidence intervals are calculated as the range within which the true IC_{50} value lies with 95% certainty. IC_{50} denotes the concentration at which 50% of the free radicals are inhibited. Standard Deviation (SD): Represents the variability of the IC_{50} value for each plant. 95%CI: The confidence interval for the IC_{50}, typically calculated as IC_{50} ±(1.96×SD), where 1.96 is the Z-value for a 95% confidence level.

SeNPs with smaller IC_{50} values (indicating stronger inhibitory capacity) tend to have higher precision, as indicated by the tight clustering of data points at the top

Table 1. Antioxidant activity of green-synthesized SeNPs

Author (Year), Ref.	Scientific name of plants (common name)	Extraction method and plant parts	Acting concentration of green SeNPs (*mg/ml*)	Assay type	IC_{50} value (*mg/ml*)	Size (*nm*) of NPs	Shape of NPs	Antioxidant activity (%)
Suresh *et al* 2023 [46]	*Acai Berry* (Acai)	Aqueous whole plant extract	0.010-0.050	DPPH	0.050	<100	Spherical	Scavenging capacity 80%
Vyas *et al* 2017 [47]	*Allium sativum* (Garlic)	Aqueous buds extract	0.3-0.6 0.10-0.6 0.50-0.6	ABTS DPPH FRAP	- - -	7- 45	Spherical	Inhibits more than 80% Inhibits more than 80% Inhibits more than 80%
Vyas *et al* 2017 [48]	*Aloe vera* (Aloe)	Aqueous leaf extract	0.100-0.600 0.1-0.6 0.1-0.5	ABTS DPPH FRAP	- - -	7-48	Spherical and hollow	Inhibits almost 90% Scavenging activity is 90% Scavenging capacity 90%
Garza-García *et al* 2023 [49]	*Amphipterygium glaucum*	Methanolic leaf extract	0.05-0.1 0.05-0.1 0.05-0.1	ABTS DPPH FRAP	- - -	40–60	Spherical and needle-shaped	Shows concentration-dependent scavenging activity Demonstrate scavenging activity that is reliant on concentration Shows concentration-dependent scavenging activity
Chitti Kondal Rao *et al* 2022 [50]	*Annona muricata*	Aqueous fruit extract	0.005-0.1 0.005-0.1 0.005-0.1	ABTS DPPH FRAP	0.0661 0.05898 -	SEM: 120–160	Spherical	Shows scavenging activity around 90% at the higher level of acting concentration 0.1 *mg/ml*) Scavenging activity is 90% Shows concentration-dependent scavenging activity
Hawsah *et al* 2023 [51]	*Azadirachta indica* (Neem)	Methanolic leaf extract	-	DPPH	0.02393	62.1-77.6	Spherical	Demonstrate scavenging activity that is reliant on concentration
O. Ibraheem *et al* 2024 [52]	*Blighia sapida*	Methanolic leaf extract	10 10 10	ABTS DPPH FRAP	- - -	-	Amorphous and granular	Scavenging capacity 570.2% Scavenging capacity 5.8% Scavenging capacity 200.5%
Dhanraj *et al* 2021 [53]	*Brassica juncea* (Mustard Greens)	Aqueous broccoli extract	10-50	DPPH	0.160	-	Spherical	Scavenging capacity increases with concentration
Shanmugam *et al* 2023 [54]	*Cymbopogon citratus* and *Syzygium aromaticum*	Aqueous leaf and bud extract	0.010-0.050	DPPH	0.050	78	Spherical	92.26% and increase antioxidant capacity with concentration
Erdem *et al*, 2024 [55]	*Calluna vulgaris* (Heather)	Aqueous whole plant extract	0.00146-1.5 0.00146-1.5	ABTS DPPH	0.016.87 0.02472	42.91-66.93	Spherical	Scavenging capacity 99.7% Scavenging capacity 86.6%
Sentkowska *et al* 2023 [56]	*Camellia sinensis* (green tea)	Aqueous leaf extracts	0.091	DPPH	-	108	Spherical	Scavenging capacity close to 100%
Ali *et al* 2024 [57]	*Caralluma tuberculata*	Aqueous root extract	0.050-0.4	ABTS	-	-	Spherical	Scavenging capacity 82% (at 0.4 *mg/ml*)
S. R. Vundela *et al* 2022 [58]	*Carica papaya* (Papaya)	Aqueous fruit extract	0.005-0.080 0.005-0.080	DPPH ABTS	- -	101-137	Spherical	Scavenging capacity 45.65±2.01% Scavenging capacity 43.06±3.80%
Soliman *et al* 2024 [59]	*Cassia javanica* (Pink Cassia)	Aqueous flower extract	0.00195-1.000	DPPH	0.05334	-	Spherical	Scavenging capacity showed less than 20% to greater than 80% within this acting concentration range
Deepa *et al* 2022 [60]	*Cassica auriculata* (Tanner's Cassia)	Aqueous flower extract	0.020–0.160	DPPH	-	-	Spherical	Scavenging capacity increases with concentration

of the funnel. For example, *A. sativum* (IC_{50}=0.0661) and *Aloe vera* (IC^{50}=0.01687) are located near the top, suggesting strong inhibitory effects with low variability in the estimates. SeNPs with larger IC_{50} values (indicating weaker inhibitory capacity) show a wider spread on the funnel plot, representing lower precision and larger uncertainty in their inhibitory effects. For instance, *G. wightii* (IC_{50}= 0.07412) and *Morinda citrifolia* (IC_{50}= 0.01) show increased variability in their IC_{50} measurements, as evidenced by the larger spread toward the bottom. The symmetry of the funnel plot is important. A symmetric funnel indicates that the data is reliable and

Contd. Table 1. Antioxidant activity of green-synthesized SeNPs

Author (Year), Ref.	Scientific name of plants (common name)	Extraction method and plant parts	Acting concentration of green SeNPs (*mg/ml*)	Assay type	IC_{50} value (*mg/ml*)	Size (*nm*) of NPs	Shape of NPs	Antioxidant activity (%)
Choudhari *et al* 2020 [61]	*Chrysanthemum indicum* (Indian Chrysanthemum)	Aqueous whole plant extract	0.010-0.050	DPPH	28.7	-	Spherical	Scavenging capacity 87% at high acting concentration
	Cinnamomum verum (Cinnamon)	Aqueous bark extract	0.010-0.050	DPPH	-	10-50	Spherical	Greater than 70% at high acting concentration
			0.010-0.050	ABTS	-			Scavenging capacity 82% At high concentration
Shin *et al* 2022 [62]	*Cirsium setidens* (Korean thistle or Gondeure)	Aqueous whole plant extracts	0.00625-0.010	DPPH	-	117.8	Spherical	Scavenging capacity 85%
			0.00625-0.010	ABTS	-			Scavenging capacity 60% (at 0.010 *mg/ml*)
Behera, *et al* 2024 [63]	*Citrus sinensis* (Orange)	Aqueous peel extract	0.010-0.050	DPPH	0.008.49	272	Spherical	Scavenging capacity 83.7% at high acting concentration
Barma *et al* 2022 [64]	*Clitoria ternatea* (Butterfly Pea)	Ethanolic leaf and flowers extract	0.01-0.05	DPPH	-	50-150	Spherical	Inhibition 89.1% at higher level acting concentration
Alafeef. *et al* 2020 [65]	*Coffea arabica* (Coffee)	Aqueous seed extract	0.100-0.400	FRAP	-	30-60	Spherical	Showed 85.8% of scavenging capacity
			0.100-0.400	DPPH	-			Scavenging capacity 83.6%
Alizadeh *et al* 2023 [66]	*Crocus caspius* (Caspian Saffron)	Aqueous whole plant extract	0.01706–0.273	DPPH	0.1239±0.0025	23.47	Spherical	Showed an excellent IC_{50} value
Shalaby *et al* 2021 [67]	*Cucumis sativus* (Cucumber)	Aqueous fruit extract	0.010-0.200	DPPH	-	50-100	Spherical	Showed good antioxidant capacity at 0.200 *mg/ml*
Shanmugam *et al* 2023 [54]	*Cymbopogon citratus* (Lemongrass)	Aqueous leaf extract	0.010-0.050	DPPH	-	20-70	Spherical	Exhibit concentration-dependent actions
Zhai *et al* 2023 [68]	*Cyperus esculentus*	Ethanolic whole plant extract	0.40977	DPPH	-	138.3±0.569	Spherical	Showed scavenging capacity 61.03±0.757%
			0.40977	ABTS	-			Showed scavenging capacity 52.47±0.848%
			0.40977	Hydroxyl Radicals	-			Scavenging capacity 57.31±0.466%
Puri *et al* 2022 [69]	*Diospyros montana* (mountain persimmon)	Aqueous bark extract	0.010-0.100	DPPH	0.02472±0.00063	100-150	Spherical	scavenging capacity 73.19% at higher acting concentration
			0.02-0.1	FRAP	-			Demonstrated concentration-dependent actions
Sarı *et al* 2024 [70]	*Echinacea purpurea* (purple coneflower)	Aqueous whole plant extract	0.100-5.000	DPPH	0.26478	33.38	Spherical	93.40% scavenged at higher acting concentration
			0.100-5.000	ABTS	0.34419			Scavenging capacity 97.92%
Dhabian *et al* 2023 [71]	*Elettaria cardamomum* (Cardamom)	Aqueous seed extract	0.00156-0100	DPPH	0.124	20-60	Spherical	Scavenging activity increases with acting concentration
Gunti *et al* 2019 [72]	*Emblica officinalis* (amla/indian gooseberry)	Aqueous fruits extract	0-0.25	DPPH	-	15–40	Spherical	Scavenging activity and EC_{50}: 0.01567±0.00141*mg/ml*
			0-0.25	ABTS	-			Demonstrate concentration-dependent scavenging action and EC_{50} value is 0.01884±0.00102 *mg/ml*
El-Zayat *et al* 2021 [73]	*Ephedra aphylla stems* (leafless ephedra)	Aqueous stem extract	-	DPPH	0.296	13.95-26.26	Spherical	Activity increased with increasing concentration

unbiased. As seen in this plot, the data follow a symmetrical funnel shape, suggesting that there is no significant publication bias or distortion in the data. This indicates that the IC_{50} estimates for plant extracts are generally consistent across studies. The funnel plot appears symmetric, which suggests that the IC_{50} values for these plant-based SeNPs are reliable and consistent for antioxidant activity in the ABTS assay, with no significant bias or outliers in the data (Table 2).

Antidiabetic effect of SeNPs

Diabetes is a rapidly growing global health concern, and diabetic patients has been rapidly increasing in recent times. Most synthetic conventional medicines are about to be botched to treat this condition. Moreover,

Contd. Table 1. Antioxidant activity of green-synthesized SeNPs

Author (Year), Ref.	Scientific name of plants (common name)	Extraction method and plant parts	Acting concentration of green SeNPs (*mg/ml*)	Assay type	IC_{50} value (*mg/ml*)	Size (*nm*) of NPs	Shape of NPs	Antioxidant activity (%)
González-Lemus *et al* 2022 [74]	*Festuca arundinacea* schreb (tall fescue)	Aqueous whole plant extract	0- 0.0045 0- 0.0045	ABTS DPPH	- -	-	Spherical	Shows concentration-dependent scavenging activity Demonstrate scavenging activity that is reliant on concentration
Benitha *et al* 2021 [75]	*Garcinia mangostana* (Mangosteen)	Aqueous whole plant extract	0.010-0.050	DPPH	-	300-600	Spherical	Scavenging capacity 75% at 0.010 *mg/ml* and close to 75% at 0.050 *mg/ml*
Menon *et al* 2019 [76]	*Zingiber officinale* (ginger)	Aqueous root extract	0.03125-0.5	DPPH	0.125	100-150	Spherical	Close to 50%
C. Santhosh *et al* 2022 [77]	*Goniothalamus wightii* (malamthelli)	Aqueous leaf extract	0.005- 0.1 0.005- 0.1	DPPH ABTS	0.07562 0.07412	20-110	Spherical	Showed concentration-dependent actions Demonstrate concentration-dependent scavenging action
	Hohenbuehelia serotina (oyster mushroom)	Aqueous whole plant extract	0-16	DPPH	18.73±1.32	35–106	Spherical	At high acting concentration, the inhibition capacity was 87.29±1.50%
Cai *et al* 2018 [78]	*Lignosus rhinocerotis* (tiger milk mushroom)	Aqueous whole plant extract	0.25–1.25 0.25-1.75	DPPH ABTS	- -	50	Spherical	Scavenging capacity 83.18% Scavenging capacity 81.54% at higher acting concentration
Zhang *et al* 2018 [79]	*Lycium barbarum* (Goji berry)	Aqueous whole plant extract	0.005-0.025 0.005-0.025	DPPH ABTS	- -	83–160	Spherical and triangular	Scavenging capacity 52.5% at EC_{50} concentration Showed 99% activity at high acting concentration
Shahbaz *et al* 2022 [80]	*Melia azedarach and acorus calamusas* (chinaberry tree)	Aqueous leaves and rhizomes extract	0.025-0.400 0.025-0.400	DPPH ABTS	- -	281	Spherical	Scavenging capacity 83.33% Scavenging capacity 74.84%
Behera *et al* 2024 [63]	*Millettia pinnata* (seashore mempari)	Aqueous leaf extract	0.030-0.060	DPPH	0.0077	266	Spherical	Increase scavenging activity with Concentration
Sheikhalipour *et al* 2021 [81]	*Momordica charantia* (bitter melon)	Aqueous fruit extract	0.010-0.020	DPPH	-	30-80	Spherical	Scavenging capacity close to 50%
Nagalingam et al 2022 [82]	*Morinda citrifolia* (noni)	Aqueous leaf extract	0.010-0.05	ABTS	-	12-160	Spherical	Inhibit free radicals 66.7 to 83.7%
Ahamad Tarmizi *et al* 2023 [83]	*Moringa oleifera* (moringa or drumstick tree)	Aqueous leaf extract	0.01582-1 0.01582-1	DPPH ABTS	45.41 -	20–250	Spherical	Scavenging capacity 84% at 1.00 *mg/ml* Exhibited concentration-dependent actions
Satpathy *et al* 2024 [84]	*Nyctanthes arbortristis L* (parijat)	Aqueous leaf extract	0.05-0.25 0.05-0.25	DPPH Hydroxyl Radicals	- -	60–80	Spherical	At higher concentrations, the inhibition capacity is more than 50% Inhibition capacity 65%

this conventional medicine has a lot of side effects like hypoglycemia, weight gain, gastrointestinal issues (nausea, diarrhea, abdominal pain, bloating), vitamin B12 deficiency, lactic acidosis, urinary tract infections, fluid retention (edema), *etc*. [111]. In this condition, nanomedicines could be a promising option as it has some extraordinary capabilities of enhancing drug delivery, drug solubility, stability, selective targeting, and the ability to reduce side effects [112].

As a part of nanomedicine therapy, green-synthesized SeNPs can be a good choice. The antidiabetic effects of green-synthesized SeNPs are mostly owing to their capacity to improve insulin sensitivity. SeNPs enhance glucose uptake by cells and improve insulin signaling pathways [113]. It protects pancreatic β-cells from oxidative damage and conserves their activity of insulin production and secretion [114]. It inhibits the enzymes α-Glucosidase and α-Amylase, which help in breaking

Contd. Table 1. Antioxidant activity of green-synthesized SeNPs

Author (Year), Ref.	Scientific name of plants (common name)	Extraction method and plant parts	Acting concentration of green SeNPs (*mg/ml*)	Assay type	IC_{50} value (*mg/ml*)	Size (*nm*) of NPs	Shape of NPs	Antioxidant activity (%)
Hassan *et al* 2022 [85]	*Olea ferruginea* (indian olive)	Methanolic fruit extract	0.025-0.40	DPPH	-	60-80	Spherical	Scavenging activity 85.2±0.009%
			0.025-0.40	ABTS	-			Scavenging activity 81.12± 0.007% at a higher level of acting concentration
Miao *et al* 2023 [86]	*Prunus persica L. (olecranon peach)*	Aqueous *fruit* extract	0.005-0.010	DPPH	-	-	Spherical	Scavenging capacity 24.1% to 41.7%, and increasing with concentration
Skrypnik *et al* 2024 [87]	*Origanum vulgare* L. (oregano)	Aqueous leaf extract	0–0.004	DPPH	-	50-100	Spherical	Scavenging activity 120.2±10.8 at 0.005 *mg/ml* concentration.
			0–0.004	ABTS	-			Scavenging activity 178.8±12.6% at 0.010 *mg/ml*
			0–0.004	FRAP	-			Scavenging activity 155.1±21 at 0.040 *mg/ml*
Abid *et al* 2021 [88]	*Panax ginseng* (ginseng)	Aqueous root extract	0.005-0.020	Hydroxyl Radicals	-	20-80	Spherical	Scavenging capacity depends on the acting concentration
Chen *et al* 2022 [89]	*Polygonatum sibiricum* (siberian solomon 's-seal)	Aqueous whole plant extract	0.25–1.0	ABTS	-	105	Spherical	Scavenging activity was 89% at 1 *mg/ml* concentration
			0.25–1.0	DPPH	-			Scavenging activity is less than 60%
Lee *et al* 2023 [90]	*Psidium guajava* (guava)	Ethanolic leaf and fruit extract	0.00625-0.200	DPPH	0.46056	20-70	Spherical	Showed concentration dependent activity
El-Amier *et al* 2023 [91]	*Pulicaria undulata (gethgath)*	Aqueous whole plant extract	0.004 - 0.034	DPPH	0.125	78.16-89.64	Spherical	Scavenging capacity 85.38±3.88% at a higher level of acting concentration
Shnoudeh *et al* 2022 [92]	*Punica granatum* (pomegranate)	Aqueous fruit and seed extract	0.010-0.02	DPPH	-	47.35	Spherical	Scavenging capacity 30% to 40% with increased concentration
Hernández-Fuentes, *et al* 2023 [93]	*Pyrus communis L* (Pear)	Aqueous fruits extract	0.05	DPPH	-	-	Spherical	Scavenging capacity 20.44 % at higher acting concentration
			0.05	ABTS	-			Scavenging capacity 25.32±1.50% at higher acting concentration
Jha *et al* 2022 [94]	*Rhizophora mucronata (Bhara or Bhora)*	Aqueous leaf extract	0.010-0.200	DPPH	-	31.82	Spherical	75.45% at a higher acting concentration
			0.010-0.200	ABTS	-			Scavenging capacity 82.36%.
Nirmala *et al* 2023 [95]	*Waltheria indica (Khar Dudhi)*	Methanolic root extract	0.010-0.050	DPPH	0.00692±0.0010	10–20	Rod-shaped	Scavenging capacity 81.12±0.76%
			0.010-0.050	ABTS	0.01685±0.00139			Scavenging capacity 89.57±1.06% at higher concentration (0.050 *mg/ml*)
Wang *et al* 2021 [96]	*Sargassum fusiforme* (Brown Seaweed)	Ethanolic whole plant extract	0.1-1.5	DPPH	1.5	60	Spherical	Scavenging capacity 80% at 1.5 *mg/ml*
			0.1-1.5	ABTS	-			Scavenging capacity 80% at 1.5 *mg/ml*

down carbohydrates to glucose. SeNPs can inhibit these enzymes and reduce blood glucose levels [115]. Their suppression contributes to lower postprandial blood glucose levels [116]. It can also control oxidative stress and inflammation, lowering the levels of ROS and inflammatory cytokines, which are elevated in diabetes [113]. Moreover, green SeNPs were reported to lower fasting blood glucose by decreasing albumin and creatinine in the liver and kidneys. It helps to restore blood glucose, as glycogen consequently reduces the glucose level in the blood (Figure 6) [117].

Contd. Table 1. Antioxidant activity of green-synthesized SeNPs

Author (Year), Ref.	Scientific name of plants (common name)	Extraction method and plant parts	Acting concentration of green SeNPs (*mg/ml*)	Assay type	IC_{50} value (*mg/ml*)	Size (*nm*) of NPs	Shape of NPs	Antioxidant activity (%)
Tritean *et al* 2024 [97]	*Hippophae rhamnoides* (Sea Buckthorn)	Aqueous leaf extract	0.1-0.5	DPPH	-	-	Spherical	Scavenging capacity increases with concentration
			0.1-0.5	FRAP	-			Exhibited concentration-dependent actions
			0.1-0.5	CUPRAC	-			Showed concentration-dependent actions
Sani-e-Zahra *et al* 2022 [98]	*Solanum lycopersicum* (tomato)	Aqueous fruit, juice, and seed extract	0.010-0.100	DPPH	0.02476	Seed:115.5 Fruits:102	Spherical	Inhibition capacity 30.535% at 0.010 *mg/ml* and 61.6666% at 0.100 *mg/ml*
Abdel-Moneim *et al* 2022 [99]	*Spirulina platensis* (Spirulina)	Aqueous whole plant extract	0.1-0.5	ABTS	-	136 to 190	Spherical	Radical inhibition is 93% at higher levels of acting concentrations
			0.1-0.5	DPPH	-			Scavenging capacity 90% at higher levels of acting concentrations
Zan *et al* 2023 [100]	*Camellia sinensis* (Tea)	Aqueous and Alkali (NaOH) leaves extract	2-10	DPPH	2.37	98	Spherical	Scavenging capacity 46.5% at higher concentration
			2-10	ABTS	10.56			Almost 50% scavenged
Puri *et al* 2023 [101]	*Terminalia arjuna* (Arjuna)	Aqueous bark extract	0.010–0.100	DPPH	0.04518 ± 0.11	100- 150	Spherical	Showed scavenging capacity from 66.51% to 78.1±2.9%
Mellinas *et al* 2019 [102]	*Theobroma cacao L.* (koko or Chocolate Nut Tree)	Aqueous bean shell extract	28.6	ABTS	-	1–3	Spherical	Scavenging activity 28.6±0.1%
			12.4	FRAP	-			Scavenging activity 12.4±0.2%
Puri *et al* 2022 [103]	*Tinospora cordifolia* (Guduchi or Giloy)	Aqueous stems extract	0.1-1	DPPH	0.02862±0.00063	100-200	Spherical	78.03% scavenging at 1*mg/ml*
Kora *et al* 2018 [104]	*Commiphora wightii* (Tree gum/ Gum resin)	Aqueous gum extract	0.0025–0.025	DPPH	-	105.6	Spherical	Scavenging activity 73.2% at 0.025 *mg/ml*
			0.0025–0.025	ABTS	-			Scavenging activity 92.2%
Al-Shammeryi *et al* 2024 [105]	*Trigonella foenum-graecum* (Fenugreek)	Aqueous seed extract	0- 0.08	DPPH	-	20-50	Spherical	29.801% inhibition capacity at 0.020 *mg/ml* and 27.691% scavenged, 35.181% at 0.08 *mg/ml*
Daler *et al* 2024 [106]	*Vitis vinifera* (Grape)	Aqueous seed extract	0.001-0.10	DPPH	-	20-70	Spherical	Scavenging capacity is high at high concentrations
Saivarshine *et al* 2021 [107]	*White Pepper* (Piper nigrum)	Aqueous seed extract	0.010-0.050	DPPH	-	30-60	Spherical/ rod	Scavenging activity 60% - 85% at acting concentration
Alagesan *et al* 2019 [108]	*Withania somnifera* (Ashwagandha)	Aqueous leaf extract	20-100	DPPH	0.01481	45-90	Spherical	Activity rises to 80% with increased concentration
Lashin *et al* 2023 [109]	*Ziziphus spina-christi* (Christ's Thorn Jujube)	Aqueous callus extract	0.00061588–0.078	DPPH	-	20 and 45	Crystalline/ spherical	Antioxidant activity is around 95% at 0.078 *mg/ml*
Lungu *et al* 2024 [110]	*Acacia catechu* (Cutch Tree)	Methanolic whole plant extract	0.15-2.4	DPPH	-	-	Spherical	Scavenging capacity 3.99-22.55%
			0.039-10	Hydroxyl Radicals	-			Antioxidant capacity 2.86-53.89%

Green SeNPs show their antidiabetic potentials by pancreatic beta cells reformation, scavenging beta cell's reactive oxygen species, blocking the breakdown of complex carbohydrates in GIT and, and regulating glucose metabolism.

In this review, various studies were scrutinized to identify anti-diabetic potentials of green synthesized SeNPs in both α-glucosidase and α-amylase inhibition assays. Antidiabetic effects were measured based on the IC_{50} value in both assays. Different plant-based SeNPs

Table 2. Antidiabetic activity of green-synthesized SeNPs

Author name (Year), Ref	Scientific name of plants (common name)	Extraction method and plant parts	Size of SeNPs (*nm*)	Shape	Assay type	IC_{50} value (*mg/ml*)	Acting concentration (*mg/ml*)	Antidiabetic activity (%)
Gutiérrez *et al* 2022 [118]	*Cinnamomum verum*, *Origanum majorana*, and *Origanum vulgare* (COO) (Daruchini, sweet marjoram, and Jongli Maruya)	Ethanolic leaf extract	65.76	Spherical	*In vivo* α-*amylase*	-	10-20	Inhibit 69±3.19 to 54±4.61% depending on higher acting concentration
Deepa *et al* 2022 [60]	*Cassica auriculata (Avaram or Ranawara)*	Aqueous flower extract	-	Spherical	*In vitro*: α-amylase	-	0.020–0.100	Inhibition capacity greater than 95% at higher acting concentration
					In vitro: α-glucosidase			Inhibition capacity is 97% at higher acting concentration
Olaoye *et al* 2024 [119]	*Moringa oleifera (Sojina)*	Aqueous leaf and bark extract	Leaf:17.2, Bark:20.1	Spherical	*In vitro*: α-glucosidase	-	0.020-0.100	Exhibited 66.2% inhibition capacity at higher acting concentration
					In vitro: α-amylase	-	0.020-0.100	Inhibition activity 82.8 % at 0.025 *mg/ml*
Ali *et al* 2024 [120]	*Caralluma tuberculata* (Chunga)	Aqueous whole plant extract	40−100	Spherical	*In vitro*: α-glucosidase	-	0.200- 0.800	Inhibit 71.55% at higher acting concentration
					In vitro: α-amylase	-	0.200- 0.800	Inhibits 78.24% at higher acting concentration
Lungu *et al* 2024 [121]	*Acacia catechu* (Khair or Khair Babul)	Methanolic whole plant extract	-	Spherical	*In vitro*: α-glucosidase	-	0.039-10	Inhibition rate was 5.87% to 72.55%
					In vitro: α-amylase	-	0.039-10	Inhibition rate was 2.67% to 50.74%
Wang *et al* 2024 [122]	*Zea mays* (convar. saccharata var. rugosa)	Aqueous extract of corncob polysaccharide	127.82	Spherical	*In vitro*: α-amylase	0.5-4	1.80	α-amylase inhibition depends on the acting concentration
Sani-e-Zahra *et al* 2022 [98]	*Solanum lycopersicum* (tomato)	Aqueous fruits and seeds extract	-	Spherical	*In vitro*: α-amylase	0.0244642	0.010-0.100	Inhibition activity 30.4464% at higher acting concentration
Ibraheem *et al* 2024 [52]	*Blighia sapida (Akee apple)*	Methanolic leaf extract	-	Amorphous and granular shape	*In vitro*: α-glucosidase	-	0.100-0.500	Inhibition ranging from 20% to 60%, depending on concentration
					In vitro: α-amylase	-	0.100-0.500	Inhibit 20% to less than 60%
Rajeshkumar *et al* 2021 [123]	*Broccoli florets* (Broccol)	Aqueous whole plant extract	-	Spherical	*In vitro*: α-amylase	-	0.010-0.050	78.4% inhibition capacity at higher acting concentration
Zhao *et al* 2023 [124]	*Ribes nigrum L* (Black Currant)	Aqueous whole plants extract	164.2	Spherical	*In vitro*: α-glucosidase	4.484	0.4-6.0	Inhibition activity increases with concentration

exhibited different extents of activities, where some plantmediated SeNPs showed more promising activities.

Here, among the various plants, two plants were found those mediate SeNPs exhibited potent antidiabetic effects in the α-glucosidase inhibition assay. One of them is *Fagonia cretica (F. cretica)* (0.1) and the other is *Ribes nigrum L*. (4.484). *F. cretica* gives the most promising antidiabetic effects when used to mediate SeNPs, as it has exhibited the lowest IC_{50} value. *Ribes nigrum L*. also showed encouraging activities, but comparatively less than *F. cretica* (Table 1).

In the α-amylase inhibition assay, the effects of the plant-based SeNPs were also evaluated by their IC_{50} value. Two plants that mediate the SeNPs showed the most propitious antidiabetic effects among all the plants reviewed. The SeNPs fabricated using *Solanum lyco-*

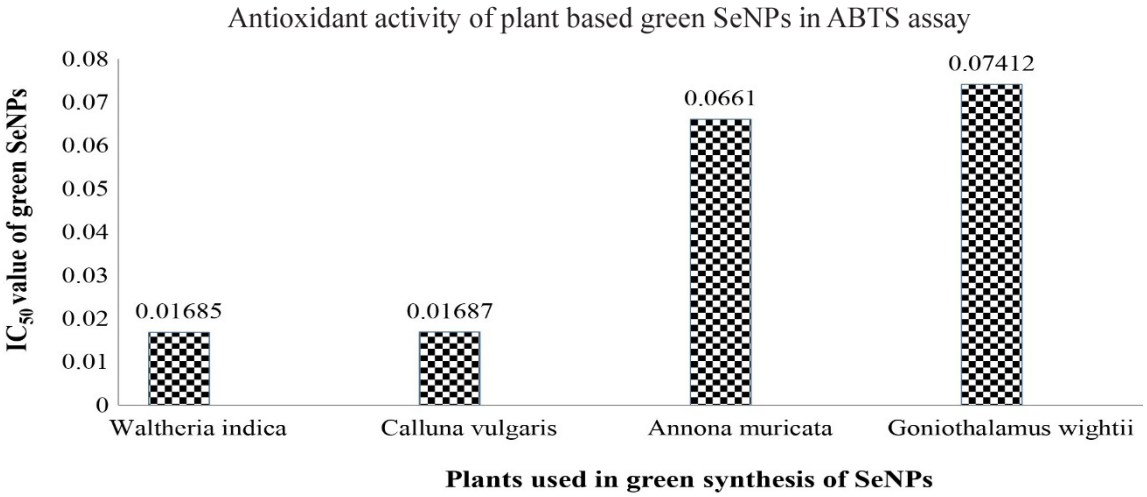

Figure 5. Antioxidant activity of plant based green synthesized SeNPs in ABTS assay.

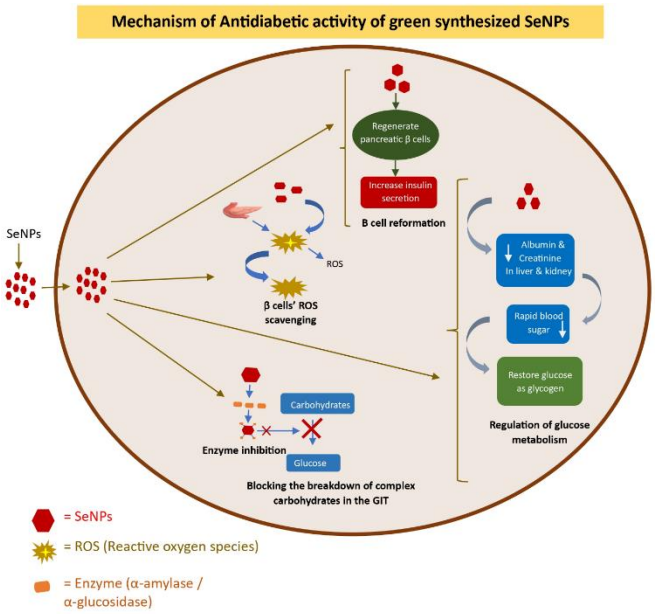

Figure 6. The Forest plot of the effect size and 95% confidence interval of IC_{50} values in the DPPH assay of various plant extract-mediated SeNPs.

persicum (*S. lycopersicum*) (IC_{50} 0.0244642) showed the lowest IC_{50} value in the inhibition assay, and showed the most promising antidiabetic activity. The second one, which mediated the SeNPs, is *F. cretica* (0.092), having a slightly increased IC_{50} value between the two plants, indicating its decreased activity in the α-amylase inhibition assay (Table 1).

Meta-analysis of Antidiabetic Activity of SeNPs

Forest Plot and Funnel Plot Analysis of IC_{50} Values for Different Plant-Based SeNPs

Alpha amylase assay: The forest plot highlights marked variability in α-amylase inhibitory activity among the tested plant extract-mediated SeNPs. The most potent inhibitors, *S. lycopersicum* and *F. cretica*, have IC_{50} values well below 1 *mg/ml*, indicating strong enzyme inhibition. *Zea mays* shows intermediate inhibition, while *Ribes nigrum* L is comparatively weak. The 95% confidence intervals are narrow for the most potent extracts mediated SeNPs, reflecting relatively precise estimates, whereas they widen with higher IC_{50} values. Overall, the plot demonstrates a clear gradient of inhibitory potency, with *S. lycopersicum* and *F. cretica* being the most promising candidates for α-amylase inhibition.

The funnel plot presented below visualizes the relationship between the log-transformed IC_{50} values (on the x-axis) and the standard deviations (SDs) (on the y-axis) for various plant extract-mediated SeNPs. This log transformation is typically used in meta-analysis to compress the wide range of IC_{50} values and allow for more meaningful comparisons. The log-transformed IC_{50} values give insight into the inhibitory potency of the SeNPs. A lower IC_{50} corresponds to stronger inhibitory activity (requiring lower concentrations), while a higher IC_{50} indicates weaker activity (requiring higher concentrations). The SDs on the y-axis represent the uncertainty or variability in the IC_{50} estimates. Larger SD values correspond to less precision in the IC_{50} estimates, while smaller SD values reflect more reliable and precise measurements. Data points at the top of the funnel indicate high precision, while those at the bottom reflect low precision.

Discussion

The present study provides a comprehensive synthesis of existing evidence on the antioxidant potential of nanoparticles and their relevance in oxidative stress-mediated pathologies. The findings indicate that nanoparticle-based systems consistently exhibit significant antioxidant and antidiabetic activity, primarily through modulation of intracellular redox balance and related

cellular pathways. In this study authors found some plant mediated SeNPs those give promising antioxidant and antidiabetic activities. In DPPH assay, *Aloe vera* mediated SeNPs show scavenging activity near to 90% at 0.6 *mg/ml* concentration. *Annona muricata* NPs exhibit 90% scavenging at 0.1 *mg/ml* concentration. *Camellia sinensis* NPs show close to 100% scavenging at 0.091 *mg/ml* concentration. *W. indica* NPs show the lowest IC_{50} value (IC_{50}-0.00692) and scavenging capacity 81.12±0.76% at 0.010-0.050 *mg/ml* concentration represent its promising activity. *Citrus sinensis* NPs (IC_{50}-0.00849) exhibit scavenging capacity 83.7% at 0.050 *mg/ml* concentration. The plant *W. somnifera* NPs (IC_{50}-0.014181) activity rises to 80% at 100 *mg/ml* concentration. In ABTS assay *Annona muricata* NPs (IC_{50}-0.0661) show almost 90% scavenging at 0.1 *mg/ml* concentration. *C. vulgaris* NPs (IC_{50}-0.016.87) exhibit 99.7% scavenging activity at 1.5 *mg/ml* concentration. *Echinacea purpurea* NPs exhibit 93.40% scavenging activity at 5 *mg/ml* concentration. In the FRAP assay, *A. sativum* NPs exhibit more than 80% inhibition at 0.5-0.6 *mg/ml* concentration. *Aloe vera* NPs scavenge nearly 90% at 0.5 *mg/ml* concentration. *Blighia sapida* NPs, scavenging capacity 200% at 10 *mg/ml* concentration and its ABTS scavenging capacity is 570.2%.

Greener SeNPs, which exhibited potent antidiabetic effects in α-glucosidase inhibition assay are, *F. cretica* NPs (IC_{50}-0.1) showed inhibitory activity of 79.56% at 1 *mg/ml* concentration, *Cassica auriculata (C. auriculata*) NPs inhibition capacity greater than 97% at 0.1 *mg/ml* concentration, *M. oleifera* NPs show 66.2% inhibition at 0.1 *mg/ml* concentration, *Caralluma tuberculate (C. tuberculate)* NPs show 71.55% inhibition at 0.8 *mg/ml* concentration. In the α-amylase inhibition assay, *F. cretica* NPs show 79.56% inhibition at 1 *mg/ml* concentration. *C. auriculata* NPs display 95% inhibition at 0.1 *mg/ml* concentration, *M. oleifera* NPs show 82.8% inhibition at 0.025 *mg/ml* concentration, *C. tuberculata* NPs exhibit 78.24% inhibition at 0.8 *mg/ml* concentration and *Broccoli florets* NPs exhibit 78.4% inhibition at 0.05 *mg/ml* concentration.

The effects of the plant-based SeNPs were also evaluated by their IC_{50} value. Two plants that mediate the SeNPs showed the most propitious antidiabetic effects among all the plants reviewed. The SeNPs fabricated using *S. lycopersicum* (IC_{50} 0.0244642) showed the lowest IC_{50} value in the inhibition assay, and showed the most promising antidiabetic activity. The second one, which mediated the SeNPs, is *F. cretica* (0.092) 78.13±0.69%, having a slightly increased IC_{50} value between the two plants, indicating its decreased activity in the α-amylase inhibition assay.

Greener SeNPs exhibit some potential activity both as antioxidant and antidiabetic agents. *M. oleifera*-mediated SeNPs (MO-SeNPs) suggestively increased the activities of hepatic antioxidant enzymes such as GSH-Px, CAT, and SOD in diabetic rat models, while reducing malondialdehyde levels, a marker of lipid peroxidation and oxidative damage. Thus, it works as both an antioxidant and an antidiabetic agent [125]. Additionally, SeNPs modulated inflammatory responses by lowering pro-inflammatory cytokines and reducing the accumulation of advanced glycation end products, thereby lessening oxidative stress-induced tissue damage. These findings suggest that SeNPs provide a dual protective mechanism by scavenging ROS and enhancing endogenous antioxidant defenses. Beyond this antioxidant role, SeNPs directly influence glucose homeostasis. In an *in vivo* study, MO-SeNPs reduced fasting blood glucose levels, enhanced insulin sensitivity, and restored pancreatic β-cell function [126]. Furthermore, SeNPs improve glucose uptake by increasing the expression of glucose transporter-4 in muscle cells and facilitate efficient glucose utilization. All this evidence suggests that SeNPs may act as a remarkable antioxidant and antidiabetic candidate.

The green biosynthesis method is an environmentally benign process using natural and biological resources like plant parts to synthesize NPs and evaluate biological (antioxidants and antidiabetic) activities. The green NPs are more suitable for antioxidant and enzymatic functions in diabetes. A lot of free radicals are generated in the body by biological mechanisms. These free radicals (oxygen free radical, methyl or ethyl free radical, and chlorine free radical) are more reactive and interfere with normal body mechanisms as well. Green synthesized SeNPs can scavenge these free radicals by their natural antioxidant potentials and functionally reduce oxidative stress. Various methods and assays like DPPH, ABTS, FRAP, *etc*., are used to estimate the scavenging capacity of free radicals. The measure of scavenging free radicals represents the high neutralization capacity of an antioxidant agent.

In this review, it was observed that the biogenic SeNPs showed concentration-dependent free radical scavenging activity. The green SeNPs with high concentration have a better scavenging capacity of free radicals. For example, among 10, 100, 200, and 400 *mg/ml*, the 400 *mg/ml* concentration showed better antioxidant capacity than the others. The free radical scavenging capacity is simply represented by the IC_{50} values. The agents with lower IC_{50} values represented the higher neutralizing capacity.

This study also scrutinized and conjugated the antidiabetic capacity of green-synthesized SeNPs. Diabetes is a metabolic disorder that raises blood glucose levels due to low insulin production in the Islets of Langerhans of the pancreas, specifically in the β-cell. Green SeNPs are more effective for diabetic treatment. Green-mediated SeNPs exhibit a concentration-dependent antidiabetic action. The overall functions of SeNPs have been shown on insulin hormone and blood glucose levels. Some enzymes are interrelated to maintain blood glucose levels by controlling carbohydrate digestion. Various *in vitro* and *in vivo* models suggested that the green synthesized SeNPs dose-dependently induce insulin

sensitivity and inhibit the α-amylase and α-glucosidase enzymes (enzymes responsible for carbohydrate digestion), thus aiding in maintaining the blood glucose level and showing antidiabetic potential.

The biological effects of SeNPs depend significantly on their size and shape. Smaller and rod-shaped SeNPs are more reactive and potentially more toxic, but larger and spherical SeNPs are more stable and less toxic. High doses or prolonged exposure to SeNPs can lead to organ-specific toxicity, especially in the liver, kidneys, heart, and lungs, while low doses are generally safe and beneficial. SeNPs exhibit various side effects beyond their well-known antioxidant and antidiabetic properties. At high doses, it induces oxidative stress instead of reducing, leading to DNA damage, lipid peroxidation, mitochondrial dysfunction, cell apoptosis, *etc*. It can cause neurotoxicity, hepatotoxicity, and immunotoxicity at high doses [127,128]. So, the uses of nanoparticles for specific conditions require careful consideration to avoid toxicities.

Future perspective & limitations

Green synthesis is an eco-friendly process that presently reduces the need for toxic chemicals during nanoparticle synthesis, and shortly it will limit the large-scale use of hazardous chemicals in synthetic chemistry. Thus, this is an innocuous process both for environmental and biological health. Green-mediated SeNPs have been promisingly used in medical fields, and recently, nanotechnology has expanded its dimensions of use in the medical detection and care of diseases through treatment [129,130]. It enables targeted drug delivery, increases bioavailability by enhancing the solubility of poorly water-soluble drugs, enables sustained and controlled drug release, and reduces the side effects of drugs [131]. Due to its comprehensive benefits, it may serve as an ideal antioxidant and antidiabetic agent. Except for their antioxidants and antidiabetic potentials, SeNPs exhibit strong antibacterial, antifungal, and antiviral properties, which makes them ideal for treating microbial infections [132]. Their unique mechanisms can encounter drug-resistant pathogens. SeNPs are also good for cancer therapy because of their targeted drug delivery and for decreasing the side effects of cancer therapy. As SeNPs have potent antioxidant properties that can help in managing oxidative stress-related diseases like neurodegenerative disorders [133]. They show promise in modulating immune responses, which could aid in therapies for autoimmune diseases and inflammatory conditions. It can also be used for the diagnosis of disease [134]. These particles may produce other better effects of Integration with Other Technologies. Combining SeNPs with other nanomaterials (like graphene or gold nanoparticles) could enhance their properties for medical use, or SeNPs might assist in delivering CRISPR/Cas9 systems for targeted gene therapy [135].

Although this systematic review offers a comprehensive outline of the antioxidant and antidiabetic potential of green-synthesized selenium nanoparticles (SeNPs), but the main limitation of this review was the protocol non-registration. There are some other limitations should be considered when interpreting the findings as review was mostly carried out based on *in vitro* assays. Thus, the translational relevance of these findings to human populations remains uncertain. Another significant limitation is the degree of heterogeneity among the included studies in terms of plant sources, synthesis methods, characterization techniques, particle size, and assay protocols. This variability makes direct comparisons perplexing and challenging; it also complicates the performance of a robust quantitative meta-analysis. In addition, the probability of publication bias cannot be omitted, as studies reporting optimistic outcomes are more likely to be published compared to those with undesirable or inconclusive results. Future research should focus on well-designed, standardized preclinical and clinical studies that will investigate the optimal dosing, safety profiles, and mechanistic pathways of SeNPs as antioxidants and in diabetes management. Multi-center randomized controlled trials and meta-analyses will be necessary to confirm the therapeutic potential observed in preclinical studies and to establish clear clinical guidelines for the use of green-synthesized SeNPs. By addressing these gaps, future studies can strengthen the evidence, facilitate clinical translation, and pave the way for the potential development of SeNPs-based therapeutic agents for oxidative stress and diabetes management.

Conclusion

The remarkable potential of green-synthesized SeNPs as a sustainable and eco-friendly nanotechnology approach for biomedical applications is highlighted by this study. Nowadays, nanomedicines are better known for their effectiveness than conventional drugs. The use of nanoparticles in conjunction with biological extracts to improve disease management is a relatively recent breakthrough in modern research. It is impactful than any other conventional idea. Green synthesis is non-toxic, cost-effective, and environmentally amicable, in contrast to conventional chemical and physical processes causes which use biological elements such as plant extracts, microorganisms, and biomolecules. In this review, it was noticed that SeNPs may be used as a viable alternative to conventional medications, exhibiting enhanced therapeutic efficacy with reduced toxicity in antioxidant and antidiabetic assays, as well as reducing environmental impact. Their effectiveness will be promising in treating conditions like oxidative stress or diabetes. Now, further studies should focus on optimizing synthesis protocols to enhance SeNPs stability and scalability, and it's a need to conduct in-depth pre-clinical and clinical trials to validate their safety and efficacy, and ascertain the synergistic effects with other bioactive compounds to extend their therapeutic applications. SeNPs themselves have antioxidant properties. When it is synthesized with another biological extract that also has antioxidant properties, hypothetically, the

result will be better than the previous one. These SeNPs, made with environmentally safe approaches, also have excellent antidiabetic properties due to their high surface reactivity and bioavailability. Additionally, SeNPs can transport medications with precision, release them in a controlled manner, and produce minimal side effects. Due to these attributes, green-synthesized SeNPs may act as promising therapeutic candidates, particularly for the treatment of diabetes and oxidative stress-related ailments. Thus, the green-synthesized selenium nanoparticles have acquired the potential to revolutionize the medical field due to their affordable and multifunctional nature.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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