

Review Article

Phytoantioxidant Functionalized Nanoparticles: A Green Approach to Combat Nanoparticle-Induced Oxidative Stress

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Nanotechnology is gaining significant attention, with numerous biomedical applications. Silver in wound dressings, copper oxide and silver in antibacterial preparations, and zinc oxide nanoparticles as a food and cosmetic ingredient are common examples. However, adverse effects of nanoparticles in humans and the environment from extended exposure at varied concentrations have yet to be established. One of the drawbacks of employing nanoparticles is their tendency to cause oxidative stress, a significant public health concern with life-threatening consequences. Cardiovascular, renal, and respiratory problems and diabetes are among the oxidative stress-related disorders. In this context, phytoantioxidant functionalized nanoparticles could be a novel and effective alternative. In addition to performing their intended function, they can protect against oxidative damage. This review was designed by searching through various websites, books, and articles found in PubMed, Science Direct, and Google Scholar. To begin with, oxidative stress, its related diseases, and the mechanistic basis of oxidative damage caused by nanoparticles are discussed. One of the main mechanisms of action of nanoparticles was unearthed to be oxidative stress, which limits their use in humans. Secondly, the role of phytoantioxidant functionalized nanoparticles in oxidative damage prevention is critically discussed. The parameters for the characterization of nanoparticles were also discussed. The majority of silver, gold, iron, zinc oxide, and copper nanoparticles produced utilizing various plant extracts were active free radical scavengers. This potential is linked to several surface fabricated phytoconstituents, such as flavonoids and phenols. These phytoantioxidant functionalized nanoparticles could be a better alternative to nanoparticles prepared by other existing approaches.

1. Introduction

Nanotechnology is being designated the “next industrial revolution” since it is rapidly developing with the introduction of nanomaterial-based consumer goods [1, 2]. Nanoparticles (10^{-9} m) are small objects that function as a whole unit in their transport and characteristics [3]. Nanoparticles (NPs) have diverse applications in disciplines like agriculture, healthcare, diagnosis, drug delivery, imaging, cosmetics, sunscreens, food, paints, catalysis, biolabeling, sensors, electronics, fiber optics, and other areas [2, 4–7]. Interestingly, most nanoparticles, such as Ag, Au, MgO, CuO, Al, CdS, and TiO₂, are potent antibacterial agents [3, 8–10]. Copper oxide (CuO) NPs are used in antimicrobial products, cosmetics, heat transfer liquids, and semiconductors [11–13]. On the other hand, iron nanoparticles are used in biological material labeling and magnetic separation, drug delivery, and anticancer hyperthermia therapy [14]. Zinc oxide nanoparticles (ZnO NPs) are used in sunscreens, cosmetics, food additives, and packaging purposes [15–17]. Silver nanoparticles (Ag NPs) are popular due to their broad-spectrum antibacterial action [18–20]. Their therapeutic application ranged from silver-impregnated catheters to wound dressings [21, 22]. The silver-Acticoat™ dressing containing Ag NPs is superior to silver nitrate and silver sulfadiazine in wound healing [23, 24]. Ferric oxide (Fe₂O₃) NPs are used as catalysts and in the manufacture of pigments [25]. TiO₂ NPs are believed to be the most valuable materials for cosmetics, food colorants, paper inks, pharmaceuticals, and protecting skin from UV rays [26–29]. Further, they have been used to prevent the spread of many infectious diseases [30, 31]. Furthermore, NPs including SiO₂, TiO₂, Bi₂O₃, Ag₂O, FeO, MnO₂, and Al₂O₃ play important roles in a variety of medicinal applications [32, 33]. In addition, AgS-, CuS-, FeS-, Zn-, and Cu-based metal organic frameworks are frequently utilized in drug delivery and antibacterial formulations [34].

Despite significant advances in nanomedicine, the long-term implications of NP exposure on human health and the environment are unknown [35]. When NPs enter the environment, they affect water, soil, and the air, where they might persist for a longer duration or be gobbled up by living organisms. They may biodegrade or bioaccumulate in the food chain, posing a hazardous risk [36–38]. The membrane injury, inflammatory response, DNA damage, and apoptosis have all been harmful consequences of ZnO NPs in mammalian cells [39–41]. Although Ag NPs are highly toxic to cancer cells, their use is limited since they are also hazardous to normal cells [35]. In continuation, when the toxicity of Ag NPs (10 μ g/mL) was investigated in human mesenchymal stem cells, DNA damage, impaired functioning, and cell death were observed [42]. Subsequently, ZnO NPs (300 mg/kg) caused oxidative stress in mice, which resulted in DNA damage [43]. Furthermore, intratracheal instillation of TiO₂ NPs in mice resulted in accumulation of ROS, lipid peroxidation, and decreased antioxidant capacity [44]. Metal-derived NPs (copper, iron, cadmium, and silver) produce reactive oxygen species (ROS), which causes oxidative stress, restricting their wide-ranging application [45–50].

As evidenced by several pieces of research, oxidative stress is the key factor ascribed to the biological potential of nanoparticles [2, 35, 51]. ROS-induced oxidative stress destroys lipids, proteins, and DNA, and long-term exposure leads to neurological disorders, diabetes, rheumatoid arthritis, cancer, cardiovascular problems, and other diseases [52–56]. In the current situation, one interesting possibility for combating nanoparticle-induced oxidative stress could be the phytoantioxidant functionalized nanoparticles synthesized using plant extract-mediated green approach. Since these NPs contain a variety of surface-attached bioactive compounds from plants, they are referred to as phytoantioxidant functionalized NPs. The sonochemical, thermal decomposition, microwave aided, electrochemical, chemical reduction, and green synthesis are some of the chemical and physical methods used to synthesize NPs [57–62]. Unfortunately, many of these technologies employ hazardous chemicals, necessitate much energy, and produce poisonous by-products [63]. Green synthesis, which encompasses synthesis using plants, bacteria, fungus, algae, actinomycetes, and other organisms, is environmentally friendly, cost-effective, biocompatible, and safe [64–70]. Furthermore, phyto-mediated synthesis is preferable to a microbial method, which necessitates time-consuming and expensive downstream processing [71, 72].

Keeping in view the problem of nanoparticle-induced oxidative stress, in this review, we attempted to put some light on the antioxidant potential of phytoantioxidant functionalized NPs. Firstly, we have compiled a brief overview of oxidative stress-associated disorders and oxidative stress-mediated toxicity of nanoparticles. Secondly, a brief overview of green synthesis using plant extracts and the protective role of phytoantioxidant functionalized NPs as a therapeutic for oxidative stress is highlighted along with its mechanistic approaches.

2. Search and Inclusion Criteria

Science Direct, PubMed, and Google Scholar databases have been searched in this review with various keywords like oxidative stress, its related disorders, reactive oxygen and nitrogen species, mechanism of action, the toxicity of nanoparticles, oxidative stress-induced toxicity of nanoparticles, green synthesis, and antioxidant activity of nanoparticles. The literature review took place between May 1, 2021, and July 2, 2021. This review only considered full-length, original, and English-language papers from Web of Science, Scopus-indexed, and peer-reviewed journals.

3. Oxidative Stress and Its Related Disorders: A Brief Overview

Free radicals are strongly reactive atoms or molecules with unpaired electrons in their exterior shell and can be generated when oxygen reacts with specific molecules [73]. Free radicals, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS), are produced continuously throughout cellular metabolism and play an important part in various cell signaling pathways [74–78]. Various endogenous

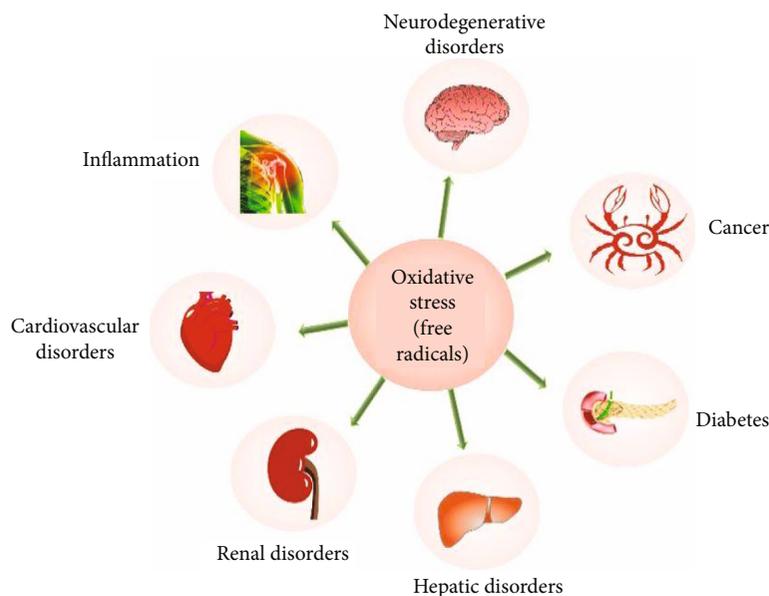


FIGURE 1: Various indications associated with the generation of oxidative stress.

and external activities generate ROS and RNS, and antioxidant defenses mitigate their harmful effects. Superoxide radicals ($O_2^{\cdot-}$), hydroxyl for ($\cdot OH$), hydrogen peroxide radicals (H_2O_2), and singlet oxygen are generally defined ROS [79–82]. RNS comprises nitric oxide, peroxynitrite ($ONOO^{\cdot}$), and their reaction products [83].

The protein phosphorylation, transcription factor activation, immunity, apoptosis, and differentiation are all reliant on adequate ROS production within cells, which must be maintained at a minimum level [84]. The ROS generation occurs mainly in the mitochondria, cell membranes, and cytoplasm. Even though these organelles have an inherent potential to scavenge ROS [85], it is noteworthy that this is insufficient to fulfill the cellular demand to eliminate the quantity of ROS generated by mitochondria [86].

The disparities between ROS and RNS generation and antioxidant defenses cause oxidative stress. Furthermore, when the formation of ROS rises, they begin to have adverse effects on essential cellular components (lipids, proteins, and nucleic acids) [77, 78, 87–89]. A substantial body of evidence suggests that oxidative stress has a role in the genesis and overall progress of various diseases, including diabetes; metabolic disorders; atherosclerosis; neurological, cardiovascular, and respiratory disorders; and cancer [90–92]. In Figure 1, several disorders linked to oxidative stress are presented.

Furthermore, as the level of antioxidant enzymes, glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD), diminishes with age, the age-related functional losses are attributed to ROS- and RNS-mediated lipid, protein, and DNA damage [93, 94]. Oxidative stress has a role in vascular endothelial dysfunction with age [95]. Several reports (both *in vivo* and *ex vivo*) shred the threads of evidence against oxidative stress-induced atherosclerosis, hypertension, ischemic heart disease, cardiomyopathy, and congestive heart failure [96–99]. Importantly, oxidative

stress causes cardiovascular complications in type 2 diabetes (T2D) subjects by promoting prothrombotic reactions [100]. ROS are also associated with cardiac arrest by cardiac hypertrophy development, ischemia-reperfusion injury, and myocyte apoptosis [101–103].

There are reports that asthma and chronic obstructive pulmonary disease (COPD) are linked to ROS-induced oxidative stress [104–106]. Choudhury and MacNee [107] reported increased levels of oxidative stress biomarkers (8-hydroxydeoxyguanosine, protein carbonyl, 3-nitrotyrosine, F2-isoprostanes, and advanced glycation end products) in COPD patients. Subsequently, oxidative stress contributes to chronic kidney disease (CKD) pathogenesis via glomerular damage, renal ischemia, inflammation, and endothelial dysfunction [97, 108, 109]. In CKD patients, polymorphonuclear leukocytes (PMNs) and monocytes are activated, resulting in increased release of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and myeloperoxidase (MPO), which promotes the formation of ROS [110].

On the other hand, oxidative stress disrupts neuronal and cellular processes and has been related to several neurological illnesses, including amyotrophic lateral sclerosis, depression, amnesia, and Parkinson's and Alzheimer's disease [56, 111, 112]. The lipid membrane is one of the most impacted structures in the brain due to redox imbalance [113]. Moreover, due to higher glucose, insulin blood levels, fatty acids, and impaired glutathione synthesis, diabetes individuals have substantial ROS levels [114]. Increased production of ROS causes a mutation in an oncogene, leading to cancer [115]. ROS disrupt the Akt/PI3K/ERK cell signaling pathway, diminishing proapoptotic proteins while boosting antiapoptotic genes [116, 117]. Subsequently, ROS has been linked to acute liver injury pathogenesis for a long time [118]. Similarly, multiple reports have shown that oxidative stress has a role in the etiology of inflammatory disorders like rheumatoid arthritis [119–121].

4. Oxidative Stress-Mediated Toxicity of Nanoparticles

Nanotechnology has found applications in a range of fields, including the environment, energy, food, and medicine. Nanoparticles are employed in biomedical applications because they have several advantages over bulk materials, including a higher surface-to-volume ratio, improved magnetic characteristics, thermal stability, and improved optical and mechanical properties. Despite the widespread use of NPs stated in Introduction, there is still a lack of ample knowledge about NP-mediated toxicity. However, there are reports that NPs induce toxicity via increasing intracellular ROS levels. Nanoparticle toxicity due to oxidative stress is well documented, restricting their usage in human patients.

In this context, using carboxy-2',7'-dichlorofluorescein diacetate (H₂DCFDDA) assay, the function of oxidative stress in the toxicity of iron oxide NPs against murine macrophage (J774) cells was examined. It was shown that exposing cells to a higher concentration of NPs (500 µg/mL) enhanced the generation of ROS, resulting in cellular damage and death [122]. Subsequently, when human microvascular endothelial cells were exposed to iron NPs, they showed an increase in permeability, ascribed to ROS generation. Furthermore, when cells are exposed to iron NPs, ROS is proven to be a significant factor in modulating Akt/GSK-3-mediated cell permeability [123].

Ahamed et al. [51] investigated the CuO NP-induced genotoxic reaction in human pulmonary epithelial cells (A549) via the p53 pathway. CuO NPs increased the cell cycle checkpoint protein p53 and the DNA damage repair proteins Rad51 and MSH2. In a dose-dependent manner, CuO NPs also triggered oxidative stress (10, 25, and 50 µg/mL), as evidenced by glutathione, CAT, and SOD depletion and the stimulation of lipid peroxidation. These findings show that CuO NPs exerted genotoxicity in A549 cells, which could be due to oxidative stress. Likewise, using the Alamar blue assay, the cytotoxicity of CuO, silicon oxide, and ferric oxide NPs against human laryngeal epithelial cells (HEp-2) was examined. CuO exhibited cytotoxicity; however, HEp-2 cells were unaffected by silicon oxide or ferric oxide even at high doses (400 µg/cm²). CuO-induced oxidative stress was suggested by a considerable rise in amount of 8-isoprostanes and the ratio of oxidized glutathione to total glutathione [124]. In human liver cells (HepG2), the apoptotic and genotoxic capacity of ZnO NPs was investigated. Their cellular toxicity was also examined at the molecular level. HepG2 viability was reduced on exposure to ZnO NPs (14–20 µg/mL) for 12 h, and the cell death that occurred was apoptosis. They also triggered DNA damage, as demonstrated by an upsurge in formamidopyrimidine DNA glycosylase- (Fpg-) sensitive regions mediated by oxidative stress. ROS led to a decline in mitochondria membrane capacity and a rise in the Bax/Bcl2 ratio, resulting in a mitochondria-mediated apoptosis pathway [2].

Similarly, the impact of oxidative stress in the toxicity of ZnO NPs against human skin melanoma (A375) cells was studied. ZnO NPs were reported to cause oxidative stress,

as evidenced by lipid peroxidation and the depletion of antioxidant enzymes. In cells exposed to the ZnO NPs, DNA damage was seen, which could be mediated by oxidative stress [125]. The occurrence of oxidative damage in lipids and proteins of MRC-5 human lung fibroblasts after exposure to Au NPs was investigated *in vitro* by Li et al. [126]. In addition, Au NP-treated cells produced considerably higher lipid hydroperoxides, indicating lipid peroxidation. Furthermore, oxidative damage was confirmed by verifying malondialdehyde (MDA) protein adducts using western blot study.

The impact of oxidative stress on the cytotoxic and genotoxic potential of Ag NPs was investigated against human lung fibroblasts (IMR-90) and the human glioma (U251) cell lines. The findings revealed mitochondrial malfunction and ROS generation by Ag NPs, which resulted in DNA damage and chromosomal abnormalities. The mitochondrial respiratory chain disruption by Ag NPs is thought to cause the generation of ROS and the cessation of ATP synthesis, which leads to DNA damage [35]. Chairuangkitti et al. [127] evaluated the *in vitro* mechanisms of Ag NP (<100 nm) toxicity in connection to the ROS generation in A549 cells. Surprisingly, both ROS-dependent (cytotoxicity) and ROS-independent (cell cycle arrest) mechanisms are involved in Ag NP toxicity in A549 cells. The oxidative stress-dependent activity of NPs is depicted in Figure 2.

Several investigations using various human cells have added to our understanding of the underlying mechanism of NPs concerning ROS production. To a large extent, ROS formation causes cytotoxicity, genotoxicity, and signaling and inflammatory response activation, revealing the mutagenic and carcinogenic properties of NPs [51, 128, 129]. Increased ROS production is highly linked to the size and shape of NPs [130, 131]. However, because research reports vary, it is difficult to draw broad conclusions about shape and size.

In the event of NP exposure to cells, ROS generation is enhanced and leads to hyperoxidation of cell organelles, disruption of mitochondrial activity, endoplasmic reticulum (ER) stress, and unfolded protein response [129, 132–137]. Mitochondrial and ER stresses have cumulative effects on cell ROS production and apoptotic cell death, referred to as cytotoxicity [35, 132]. Furthermore, NPs in the nucleus cause oxidative base damages (8-oxoguanine), strand breakage, and mutations in DNA, resulting in genotoxicity [138–141]. Furthermore, NPs can mediate oxidative-sensitive activation of signaling cascades such as mitogen-activated protein kinase (MAPK), epidermal growth factor receptor, transcription factor activator protein-1, and nuclear factor-kappa B (NF-κB), as well as activate the inflammatory response, which plays a role in mammalian growth and proliferative and developmental processes [97, 129, 142]. Subsequently, when phagocytes, such as neutrophils and macrophages, fail to phagocytose NPs completely, the NADPH-oxidase enzyme system produces ROS. The stimulation of cell signaling pathways such as MAPK, NF-κB, Akt, and RTK by NP-induced ROS promotes an inflammatory cascade of chemokine and cytokine expression. The majority of the subsequent adverse effects elicited by NPs are due to ROS [129].

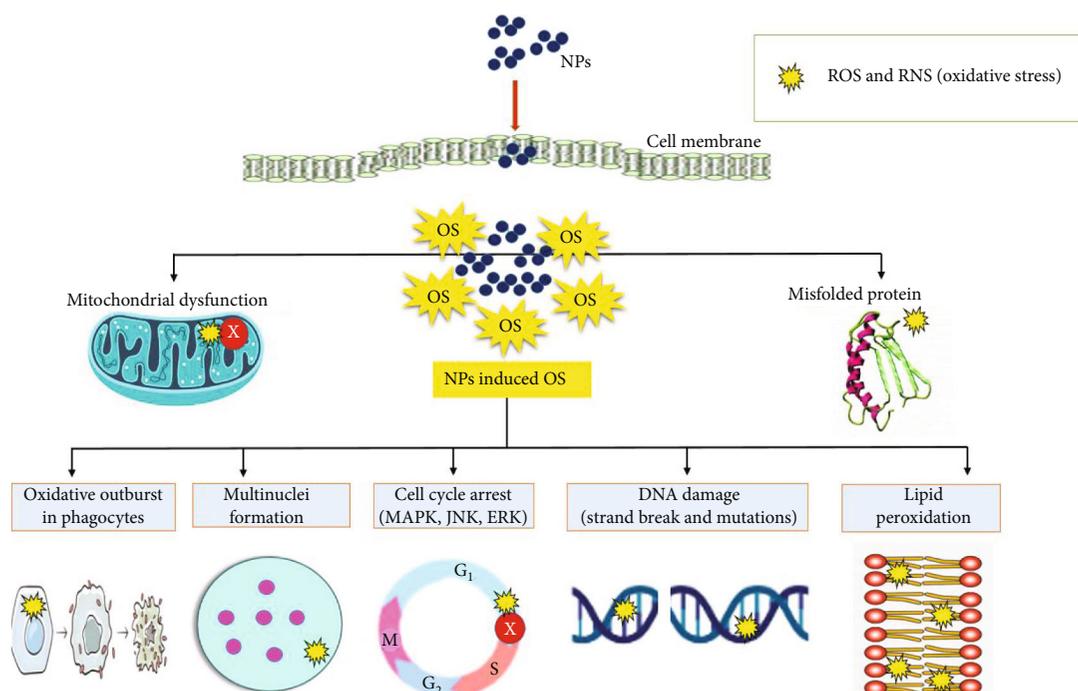


FIGURE 2: Mechanistic aspects of oxidative stress-mediated nanoparticle-induced toxicity. NPs: nanoparticles; ROS: reactive oxygen species; OS: oxidative stress; RNS: reactive nitrogen species.

For instance, Chen and Schluesener [143] demonstrated that, to the human primary organ system, silver is relatively nontoxic and nonmutagenic. In contrast to antimicrobial metallic NPs (Au, Pt, Cu, Zn, Ti, and so on), silver is recognized to have the most potent antibacterial activity. Ag NPs' powerful antibacterial, antifungal, and antiviral properties are related to their potential to produce H_2O_2 , O_2^- , $\cdot\text{OH}$, and hypochlorous acid (HOCl) singlet oxygen [20, 144–147]. Furthermore, free radicals induced by Ag NPs reduce glutathione to glutathione disulfide that leads to oxidative stress, apoptosis, and stimulation of oxidative signaling pathways [51, 90, 128, 129, 148].

The cytotoxicity, genotoxicity, and inflammatory response of Ag NPs in cells have raised concerns about their unintended human exposure [149]. Ag NPs' cytotoxic, genotoxic, apoptotic, and antiproliferative effects, on the other hand, can be employed to treat glioblastoma [150, 151]. Dakal et al. [152] reported that Ag NP-induced ROS production and increased oxidative stress are linked to antimicrobial effects, with cytotoxic and genotoxic consequences. The most devastating and undeniable issue with using silver or any other nanoparticles in humans is their biosafety and biocompatibility.

5. Green Synthesis of NPs: A Brief Overview

Several methods for the synthesis of NPs have been developed, but their use in biomedical applications is limited due to the use of toxic compounds, the high energy requirements, and the formation of toxic by-products. The choice of a solvent medium, an environmentally friendly reducing agent, and a nontoxic substance for NP stabilization are all

important components to consider during the NP preparation process [153]. In this context, green synthesis, which encompasses synthesis through plants, bacteria, fungi, algae, and others, is an effective way for generating NPs [64, 154] as shown in Figure 3(a). The ability of numerous biological entities, such as those indicated above, to generate metal nanoparticles for diverse pharmacological applications has been extensively researched. In general, plant extracts and microorganisms are used in the green, environmentally acceptable synthesis of NPs [65, 66].

Plant-derived NPs overwhelm microorganism-derived NPs, owing to the former's single-step, nonhazardous fabricating process [72]. Furthermore, phyto-mediated synthesis is preferable to microbial synthesis, which requires time-consuming and expensive downstream processing [71]. The plant extract is combined with a metal salt solution in the green synthesis of metal nanoparticles. The electrochemical potential of a metal ion and the pH of the reaction mixture, temperature, concentration, and reaction time are all critical aspects to consider. The phytoconstituents promote metal ion reduction to zero-valent state, followed by nucleation and growth to generate metal NPs [72, 154, 155] as depicted in Figure 3(b).

The plant-mediated synthesis is attributed to protein, phenols, terpenoids, ascorbic acid, and flavonoids that are capable of reducing the ions to nanosize and capping of nanoparticles [156, 157]. This method has several advantages, including energy savings due to the lack of high energy and pressure, use of biological entities that work as both reducing and stabilizing agents, environmental friendliness, lower costs, and the capacity to be employed on a large scale [64, 68, 69, 154]. Several NPs such as TiO_2 using *Azadirachta indica* [9],

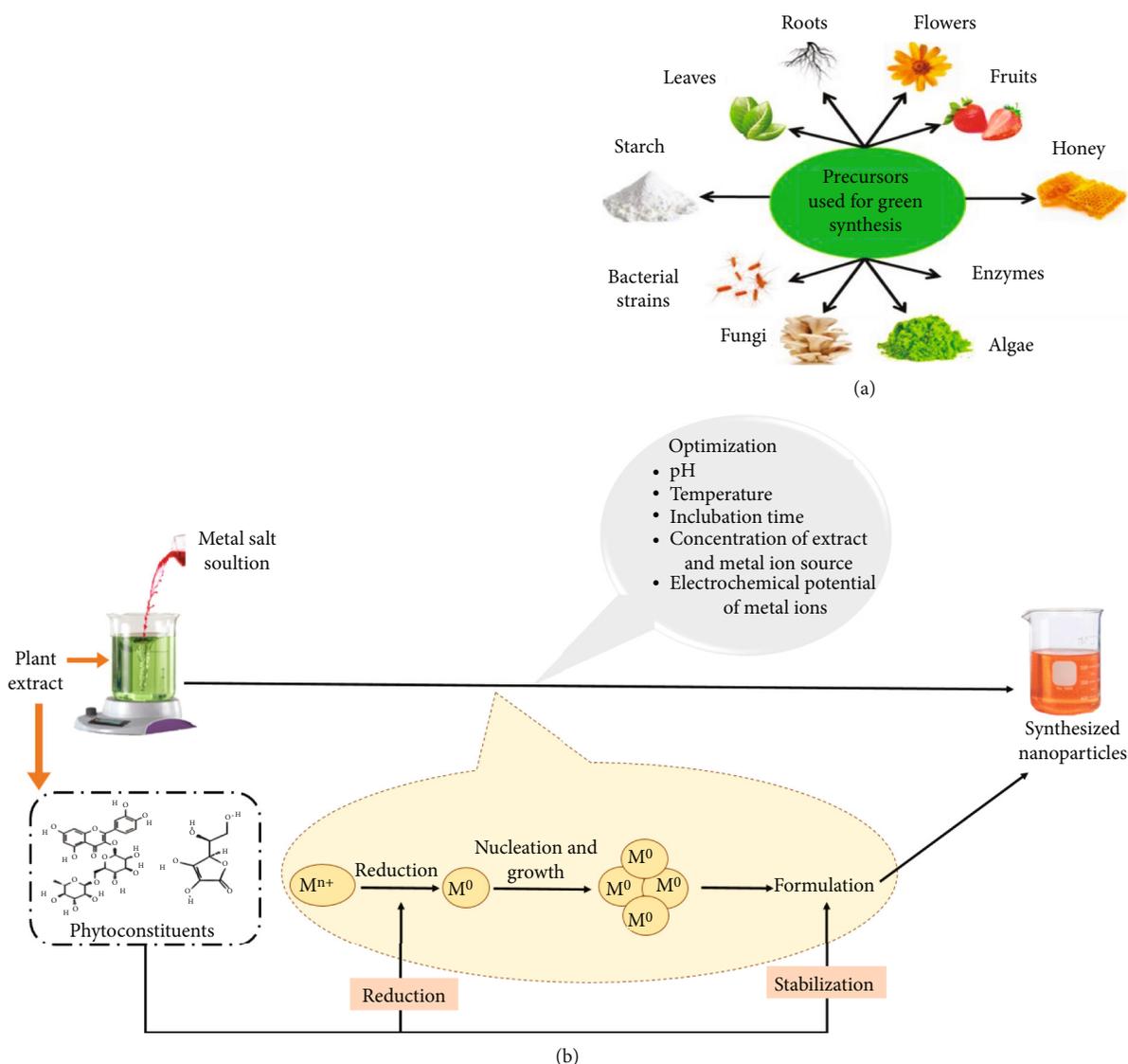


FIGURE 3: (a) Various precursors used for green synthesis of NPs; (b) mechanistic insight into plant-mediated green synthesis of metallic NPs. Reproduced from Kumar et al. [154] and Bhardwaj et al. [72] under Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).

ZnO using *Ocimum tenuiflorum*[158], CuO using *Ocimum tenuiflorum*[159], and ZnO using *Aloe vera*[160] have been successfully synthesized using the green approach.

6. Antioxidant Potential of Phytoantioxidant Functionalized Nanoparticles

Green synthesis is an innovative method of synthesizing phytoantioxidant functionalized NPs using plant extracts. It is gaining popularity as a result of its cost-effective, environmentally friendly, and large-scale production capabilities. As the importance of green synthesis using plant extracts is already highlighted in Section 5, in Table 1, the antioxidant potential of phytoantioxidant functionalized nanoparticles is shown. *Hibiscus rosa-sinensis* demonstrated excellent ability to synthesize copper NPs at optimal temperatures. These NPs showed good antioxidant potential in ferric-reducing

antioxidant power (FRAP) and hydrogen peroxide (H_2O_2) assays [161]. Cu NPs synthesized using *Dioscorea bulbifera* tubers (DBTE) showed 40.81 ± 1.44 , 79.06 ± 1.02 , and $48.39 \pm 1.46\%$ scavenging against 1,1-diphenyl-2-picrylhydrazyl (DPPH), nitric oxide (NO), and superoxide radicals ($O_2^{\cdot-}$), respectively; this demonstrated its role in the prevention of oxidative stress, which is a significant factor in the progression of a variety of diseases. The action of DBTE is believed to be due to its substantial ascorbic acid content [162].

The aqueous fruit extract of *Couroupita guianensis* (CG), a promising bioreductant for reducing Au^{3+} ions into their nanoscale analogs, was used to produce gold nanoparticles (Au NPs) in a smaller duration of time. Au NPs have exceptional antioxidant characteristics; DPPH radical scavenging at $100 \mu\text{g/mL}$ was 70.6%, compared to 96.28% for ascorbic acid. Further, they showed dose-dependent ferric ion

TABLE 1: Characterization and antioxidant profile of phytoantioxidant functionalized nanoparticles.

Nanoparticle type	Plant (part used)	Reaction time (temp.)	Characterization methods	Size (nm)	Shape	Storage stability	Antioxidant assay and major findings (IC ₅₀ /μg/mL)	Reference standard in antioxidant assay (IC ₅₀ /μg/mL)	Data source
Copper	<i>Hibiscus rosa-sinensis</i> (leaves)	48 h (RT)	TEM, FT-IR, UV-Vis	NM	NM	n.d.	H ₂ O ₂ : 68.5% at 500 μg/mL FRAP: OD: 1.2 at 1000 μg/mL (% at 100 μg/mL)	DNS	[161]
Copper	<i>Dioscorea bulbifera</i> (tubers)	5 h (40°C)	TEM, EDX, XRD, DLS, FT-IR, UV-Vis	86-126	Spherical	n.d.	DPPH: 40.81% NO: 79.06% O ₂ ⁻ : 48.39%	AA (100 μg/mL) 51.42% 68.37% 14.11%	[162]
Gold	<i>Couroupita guianensis</i> (fruits)	1 h (70°C)	TEM, EDX, XRD, DLS, FT-IR, UV-Vis, zeta potential	26	Spherical, triangular, and hexagonal	45 days (RT)	O ₂ ⁻ : 89.8% Reducing power: OD: 0.3 OH (IC ₅₀): 36	AA 96.28% 90% OD: >0.7 <20 μg/mL	[67]
Gold	<i>Rhus coriaria</i> (whole plant)	40 min (40°C) followed by 1 h (RT)	UV-Vis, XRD, TEM, FT-IR, zeta potential	15-25	Spherical	n.d.	(% at 800 μM) DPPH: 85.73% ABTS: 96.83%	Glutathione (100%)	[163]
Silver	<i>Hippophae rhamnoides</i> (leaves)	24 h (RT)	TEM, UV-Vis, EDX, FT-IR, DLS, zeta potential	10-40	Spherical	1 year	DPPH: >80% at 20 μg/mL	AA DNS	[164]
Silver	<i>Costus afer</i> (leaves)	2 h (90°C)	SEM, TEM, UV-Vis, EDX, FT-IR	20	Spherical	n.d.	DPPH (IC ₅₀): <50	Similar to AA	[165]
Silver	<i>Taraxacum officinale</i> (leaves)	15 min (RT)	TEM, XRD UV-Vis, FT-IR	5-30	Spherical	4 months (RT)	ABTS (IC ₅₀): 45.6 DPPH (IC ₅₀): 56.1 NO (IC ₅₀): 56.1	AA and catechol (IC ₅₀): 40-60	[166]
Silver	<i>Erythrina suberosa</i> (leaves)	Overnight (RT)	DLS, TEM, UV-Vis, FT-IR	12-115	Spherical	n.d.	DPPH (IC ₅₀): 30.04	BHT (DNS)	[167]
Silver	<i>Cestrum nocturnum</i> (leaves)	1 week (RT)	SEM, TEM, XRD, UV-Vis, FT-IR	20	Spherical	n.d.	DPPH: 29.55% H ₂ O ₂ : 45.41% OH: 20% O ₂ ⁻ : 8%	AA 24.28% 65.63% 9.47% 32%	[168]
Silver	<i>Cassia angustifolia</i> (flowers)	NM (27 ± 1°C)	UV-Vis, SEM, EDX, XRD, FT-IR, DLS, zeta potential	10-80	Spherical	n.d.	DPPH (IC ₅₀): 47.24 H ₂ O ₂ (IC ₅₀): 78.10 FRAP (IC ₅₀): 63.21	AA (IC ₅₀) >60 in all tested assays	[169]
Silver	<i>Camellia sinensis</i> (leaves), <i>Allium sativum</i> (bulb), <i>Curcuma longa</i> (rhizome)	2 h (60°C)	SEM, TEM, UV-Vis, EDX, FT-IR	8	Spherical	n.d.	IC ₅₀ between 5.02 and 22.93 (ABTS, DPPH, OH, O ₂ ⁻ , H ₂ O ₂)	AA and rutoside (IC ₅₀) 7.14 ± 1.02 to 14.17 ± 0.24	[170]

TABLE 1: Continued.

Nanoparticle type	Plant (part used)	Reaction time (temp.)	Characterization methods	Size (nm)	Shape	Storage stability	Antioxidant assay and major findings (IC ₅₀ /μg/mL)	Reference standard in antioxidant assay (IC ₅₀ /μg/mL)	Data source
Silver	Spice blend	24 h (NM)	UV-Vis, EDX, SEM, XRD, TEM, FT-IR	6-28	Spherical	n.d.	DPPH (IC ₅₀): <31.2 ABTS (IC ₅₀): 68.75	Comparable to rutin	[171]
Silver	<i>Psidium guajava</i> (leaves)	30 min (RT)	SEM, TEM, XRD, UV-Vis, EDX, FT-IR, zeta potential	20-35	Spherical	n.d.	DPPH (IC ₅₀): 52.53 ABTS (IC ₅₀): 55.10	AA (IC ₅₀) <40	[172]
Zinc oxide	<i>Berberis aristata</i> (leaves)	DNS	SEM, XRD, UV-Vis, FT-IR, EDX, DLS	5-40	Needle-like	n.d.	DPPH (IC ₅₀): 3.55	AA (IC ₅₀) 1.69	[173]
Silver	<i>Ananas comosus</i> (fruit peel)	20-30 min (100°C)	UV-Vis, SEM, EDX, XRD, FT-IR	NM	Spherical	n.d.	(% and OD at 100 μg/mL) ABTS: 10-20% DPPH: <50% NO: <30% Reducing power: OD < 0.1	BHT (100 μg/mL) >90% 80% >70% OD > 3.0	[174]
Silver	<i>Prosopis farcta</i> (fruits)	25-45 min (50-70°C)	UV-Vis, XRD, TEM	10-15	Spherical	n.d.	DPPH (IC ₅₀): 0.70 ± 0.08 FRAP: >25 mmol Fe(II)/mg extract	AA (IC ₅₀) (0.26 ± 0.09) NM	[175]
Gold	<i>Vitex negundo</i> (leaves)	Overnight (RT)	SEM, TEM, XRD, UV-Vis, FT-IR, EDX	20-70	Spherical	n.d.	DPPH (IC ₅₀): 62.18 NO (IC ₅₀): 70.45	DNS	[176]
Silver	<i>Morus alba</i> (leaves)	10 min (NM)	SEM, TEM, XRD, UV-Vis, EDX, DLS, FT-IR	12-39	Spherical	n.d.	IC ₅₀ between 25.9 and 97.2 (DPPH, ABTS, O ₂ ⁻ , NO, metal chelating)	AA (IC ₅₀) 10-50	[177]
Silver	<i>Lavandula stoechas</i> (aerial parts)	30 min (80°C)	UV-Vis, SEM, XRD, TEM, FT-IR	20-50	Spherical	n.d.	(% at 25 mg/mL) DPPH: 75%	AA (25 mg/mL) 100%	[178]
Silver	<i>Nothapodytes foetida</i> (leaves)	NM (80°C)	UV-Vis, TEM	20-50	Spherical	n.d.	DPPH (IC ₅₀): 22.56 ABTS (IC ₅₀): 41.47 (% at 200 μg/mL)	Comparable to BHT	[179]
Silver	<i>Brassica oleracea</i> (leaves)	10 min (RT)	TEM, EDX, FT-IR, UV-Vis, zeta potential	20	Spherical	n.d.	DPPH: 80% NO: 80% O ₂ ⁻ : 60-80% OH: 60-80%	AA (200 μg/mL) >80% in all tested assays	[180]
Silver	<i>Blighia sapida</i> (leaves)	2 h (30 ± 2°C)	UV-Vis, FT-IR, SEM	50-70	Spherical	n.d.	(% at 150 μg/mL) DPPH: 75.42% Reducing power: 53.52%	AA (150 μg/mL) >80% 70.19%	[181]
Iron	<i>Asphodelus aestivus</i> (aerial parts)	20 min (50-60°C)	SEM, TEM, XRD, UV-Vis, FT-IR, EDX, TGA, zeta potential	20-25	NM	n.d.	DPPH (IC ₅₀): 3.48	NM	[182]

TABLE 1: Continued.

Nanoparticle type	Plant (part used)	Reaction time (temp.)	Characterization methods	Size (nm)	Shape	Storage stability	Antioxidant assay and major findings (IC ₅₀ /μg/mL)	Reference standard in antioxidant assay (IC ₅₀ /μg/mL)	Data source
Silver	<i>Atropa acuminata</i> (leaves)	30 min (60°C)	TEM, XRD, EDX, DLS, zeta potential, UV-Vis, FT-IR	5-20	Spherical	n.d.	DPPH (IC ₅₀): 16.08 H ₂ O ₂ (IC ₅₀): 25.4 O ₂ ⁻ (IC ₅₀): 21.12 (% at 500 μg/mL) DPPH: >85% TAA: >90%	AA (IC ₅₀): 27.68 GA (IC ₅₀): 28.31 AA (IC ₅₀): 30.48 AA (500 μg/mL) >90% <50%	[183]
Titanium dioxide	<i>Psidium guajava</i> (leaves)	24 h (RT)	FT-IR, SEM, EDX, XRD	32.58	Spherical	n.d.	(% at 10-80 μg/mL) DPPH: 32.61-62.06% H ₂ O ₂ : 78.45-99.23 %	NM	[184]
Titanium dioxide	<i>Cola nitida</i> (leaves, pods, seeds, and seed shell)	1 h (RT)	UV-Vis, FT-IR, TEM, XRD, EDX	25-191	Spherical	n.d.		NM	[185]

Note: n.d.: not determined; NM: not mentioned; DNS: data not shown; AA: ascorbic acid; BHT: butylated hydroxytoluene; GA: gallic acid; IC₅₀: half-maximal inhibitory concentration; %: percent scavenging; RT: room temperature; nm: nanometer; O₂⁻: superoxide radical; DPPH: DPPH radical scavenging activity; H₂O₂: hydrogen peroxide radical scavenging activity; ABTS: ABTS radical scavenging activity; OH: hydroxyl radical scavenging activity; NO: nitric oxide radical scavenging activity; FRAP: ferric-reducing antioxidant power; UV-Vis: ultraviolet and visible absorption spectroscopy; SEM: scanning electron microscopy; TEM: transmission electron microscopy; FT-IR: Fourier transform infrared spectroscopy; XRD: X-ray diffraction analysis; EDX: energy-dispersive X-ray spectroscopy; DLS: dynamic light scattering; TGA: thermal gravimetric analysis; TAA: total antioxidant activity.

reduction activity and hydroxyl ($\cdot\text{OH}$) radical scavenging ability, which is primarily due to the presence of antioxidant residues, such as phenolics from the CG on its surface, which have been recognized, using various analytical techniques [67]. Subsequently, Au NPs were synthesized using *Rhus coriaria*, which is used as a reducing and capping agent. The plant polyphenols may play a role in reducing gold ions, as evident from FT-IR analysis. *In vitro*, antioxidant activity studies showed that DPPH (85.73% at 800 μM) and ABTS activities (96.83% at 800 μM) increased in a dose-dependent manner (25–800 μM) which is related to the adsorption of phytochemicals on the surface of the Au NPs [163].

Hippophae rhamnoides leaves were utilized by Kalaiyarasan et al. [164] for the biosynthesis of silver NPs (Ag NPs). As the sample concentrations (5–25 $\mu\text{g}/\text{mL}$) began to rise, the DPPH radical scavenging abilities increased, indicating that the antioxidant capabilities of the samples are dosage-dependent. The activity of Ag NPs has enhanced by more than tenfold when compared to that of the plant extract alone, which can be attributable to the presence of plant phytochemicals, including flavonoids. Due to these flavonoids and silver ions, antioxidant activity may occur via a single electron transfer mode [186, 187]. Similarly, Ag NPs developed using *Costus afer* leaves were more effective DPPH scavengers than the leaf extract alone, and their antioxidant activity was comparable to those of ascorbic acid with IC_{50} value < 50 $\mu\text{g}/\text{mL}$ [165]. Ag NPs fabricated using *Taraxacum officinale* leaves demonstrated substantial antioxidant capability against ABTS (IC_{50} 45.6 $\mu\text{g}/\text{mL}$), DPPH (IC_{50} 56.1 $\mu\text{g}/\text{mL}$), and NO (IC_{50} 55.2 $\mu\text{g}/\text{mL}$). Catechol and ascorbic acid were utilized as controls, with IC_{50} 40 to 60 $\mu\text{g}/\text{mL}$ [166]. Ag NPs synthesized using *Erythrina suberosa* leaves demonstrated significant antioxidant activity in a DPPH radical scavenging experiment, with IC_{50} 30.04 $\mu\text{g}/\text{mL}$. The BHT was used as a standard. The findings significantly support the use of Ag NPs as natural antioxidants against oxidative stress-linked degenerative disorders [167].

Ag NPs synthesized using *Cestrum nocturnum* leaves, when evaluated for antioxidant activity, were found more active scavengers of DPPH (29.55% at 100 $\mu\text{g}/\text{mL}$) as compared to ascorbic acid at a similar concentration (24.28%). Further, Ag NPs showed 45.41 and 20% scavenging of H_2O_2 and $\cdot\text{OH}$ as compared to ascorbic acid (65.63 and 9.47% at 250 $\mu\text{g}/\text{mL}$, respectively). However, negligible activity was reported in the $\text{O}_2^{\cdot-}$ scavenging assay [168].

Subsequently, DPPH, H_2O_2 , and FRAP assays were used to estimate the antioxidant activity of Ag NPs prepared using *Cassia angustifolia* flowers. Ag NPs were found to have FRAP and DPPH IC_{50} values of 63.21 ± 0.75 and 47.24 ± 0.5 $\mu\text{g}/\text{mL}$, respectively. On the other hand, in the H_2O_2 assay, the IC_{50} value was 78.10 ± 1.2 $\mu\text{g}/\text{mL}$ [169]. The H_2O_2 scavenging is well related to the presence of phenolic components in the samples [188]. A compound mixture containing *Camellia sinensis* leaves, *Allium sativum* bulbs, and *Curcuma longa* rhizome mediated Ag NPs which were found highly active scavengers of ABTS, DPPH, $\cdot\text{OH}$, $\text{O}_2^{\cdot-}$, and H_2O_2 radicals with IC_{50} ranging between 5.02 ± 1.11 and 22.93 ± 0.34 $\mu\text{g}/\text{mL}$ in comparison to rutoside and

ascorbic acid (IC_{50} between 7.14 ± 1.02 and 14.17 ± 0.24 $\mu\text{g}/\text{mL}$) [170]. Interestingly, Ag NPs synthesized using a spice blend exhibited IC_{50} < 31.25 and 68.75 $\mu\text{g}/\text{mL}$ against DPPH and ABTS, respectively, and the findings are comparable to standard rutoside. The different functional groups of spice blends present on the surface of Ag NPs could be responsible for the activity [171]. *Psidium guajava* leaves were utilized by Wang et al. [172] for the successful synthesis of Ag NPs, which were found to be highly active in scavenging free radicals with IC_{50} 52.53 ± 0.31 $\mu\text{g}/\text{mL}$ (DPPH) and 55.10 ± 0.29 $\mu\text{g}/\text{mL}$ (ABTS). In contrast, standard ascorbic acid showed IC_{50} < 40 $\mu\text{g}/\text{mL}$ against both DPPH and ABTS radicals. On the other hand, *Berberis aristata* leaf-mediated ZnO NPs, when evaluated for antioxidant activity using DPPH, showed 61.63% scavenging at 5 $\mu\text{g}/\text{mL}$, lower than ascorbic acid (87.76%) at the same concentration [173]. On the other hand, Ag NPs synthesized using *Ananas comosus* fruit peel exhibited a moderate ABTS and DPPH and reduced power and nitric oxide (NO) scavenging activity as compared to standard BHT [174]. The action is due to the involvement of numerous plant functional groups attached to the surface of Ag NPs [189].

The antioxidant activity of Ag NPs fabricated using *Prosopis farcta* (PF) fruits was evaluated using DPPH and FRAP assay. Ag NPs had a scavenging activity of 43 to 63% at doses of 0.2–1 mg/mL; however, the effect was lower (74% at 1 mg/mL) than that of standard ascorbic acid. Ag NPs were also found active with FRAP activity > 25 mmol Fe(II)/mg extract at 1 mg/mL [175]. The primary phytochemicals responsible for the antioxidant capacity are phenolics and flavonoids, abundant in PF [190]. Subsequently, *Vitex negundo* leaf-mediated Au NPs exhibited IC_{50} values of 62.18 and 70.45 $\mu\text{g}/\text{mL}$ in DPPH and nitric oxide assays, respectively [176]. Moreover, *Morus alba* leaves were utilized by Das et al. [177] for synthesizing Ag NPs. When compared to ascorbic acid (10–50 $\mu\text{g}/\text{mL}$), antioxidant activity of produced NPs against DPPH, ABTS, superoxide, and nitric oxide was dose-dependent with IC_{50} ranging between 25.9 and 97.2 $\mu\text{g}/\text{mL}$. The lowest IC_{50} (25.9 $\mu\text{g}/\text{mL}$) of Ag NPs was observed in the ABTS assay.

The DPPH radical scavenging activity of *Lavandula stoechas* aerial part-mediated Ag NPs (75% scavenging at 25 mg/mL) is attributed to phytochemical compounds such as phenol and terpenoid flavonoids that are involved in the reduction of Ag^+ to Ag^0 [178]. *Nothapodytes foetida* leaf-mediated Ag NPs (100 $\mu\text{g}/\text{mL}$) exhibited strong antioxidant potential with 93.80% inhibition of DPPH and comparatively lower ABTS radical scavenging activity (84.59% at the same conc.); however, results are comparable to standard BHT [179].

Likewise, Ansar et al. [180] utilized *Brassica oleracea* leaves for Ag NP synthesis. Ag NPs revealed a strong antioxidant potential against DPPH, NO, superoxide ($\text{O}_2^{\cdot-}$), and hydroxyl radical ($\cdot\text{OH}$) with percent scavenging ranged between 60 and 80% at 200 $\mu\text{g}/\text{mL}$ as compared to standard ascorbic acid (>80% at 200 $\mu\text{g}/\text{mL}$). The antioxidant capacity of these nanoparticles could be attributed to the abundance of surface fabricated flavonoids and phenolics as capping agents [180]. In another study, Akintola et al. [181]

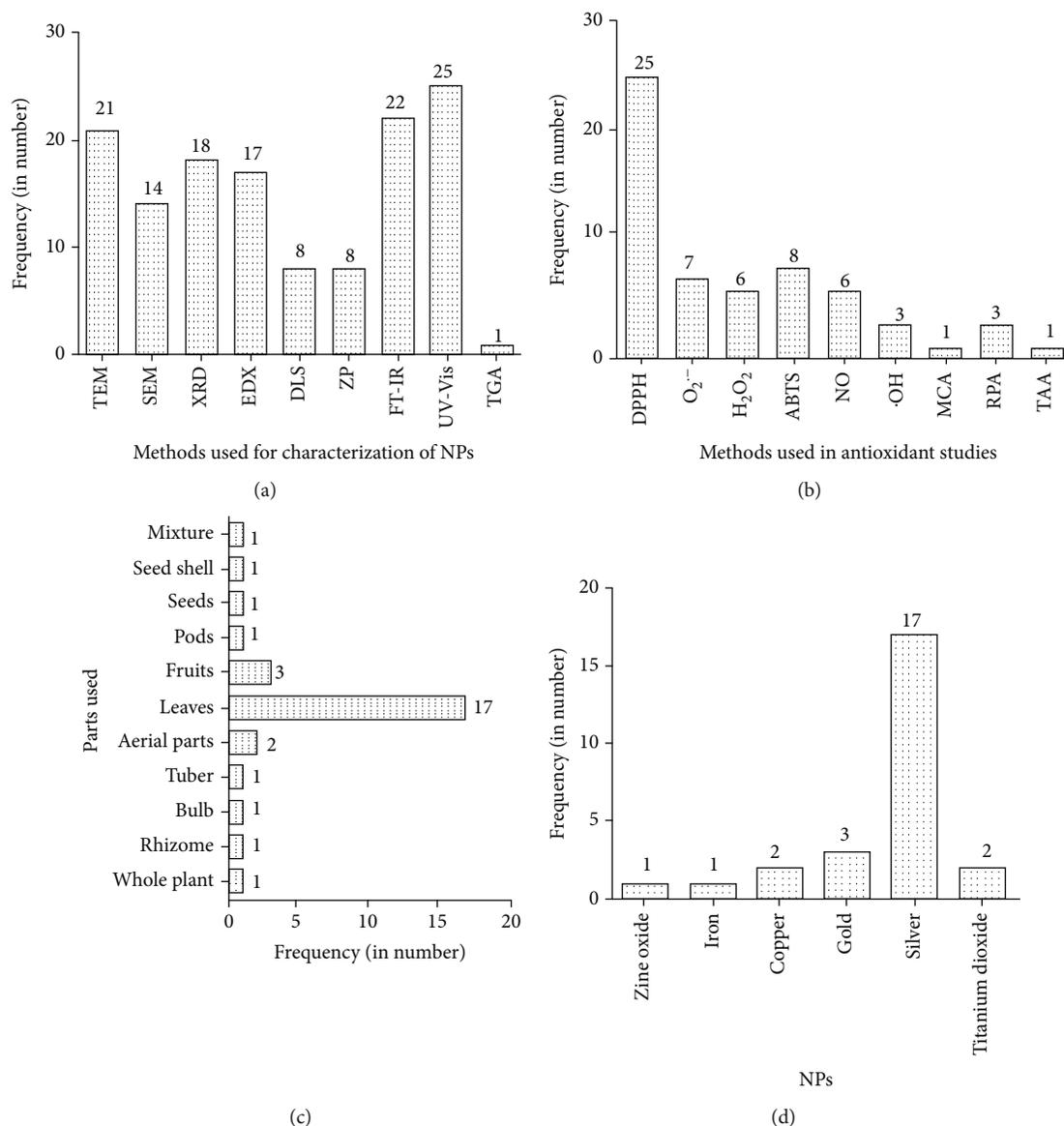


FIGURE 4: Frequency of methods used for (a) NP characterization, (b) antioxidant studies, (c) plant part used, and (d) types of NPs. Note: O₂⁻: superoxide radical; DPPH: DPPH radical scavenging activity; H₂O₂: hydrogen peroxide radical scavenging activity; ABTS: ABTS radical scavenging activity; ·OH: hydroxyl radical scavenging activity; NO: nitric oxide radical scavenging activity; FRAP: ferric-reducing antioxidant power; UV-Vis: ultraviolet and visible absorption spectroscopy; SEM: scanning electron microscopy; TEM: transmission electron microscopy; FT-IR: Fourier transform infrared spectroscopy; XRD: X-ray diffraction analysis; EDX: energy-dispersive X-ray spectroscopy; DLS: dynamic light scattering; TGA: thermal gravimetric analysis; TAA: total antioxidant activity.

investigated the antioxidant effects of Ag NPs (synthesized using *Blighia sapida* leaves) using DPPH and reducing power assay. Ag NPs at different concentrations (50, 75, 100, 125, and 150 µg/mL) scavenged DPPH by 58.10, 59.26, 62.33, 71.24, and 75.42%, respectively. These effects, however, are less pronounced than those of ascorbic acid (>80% at 150 µg/mL). Ag NPs had a maximum reduction capability of 53.52% at 150 µg/mL compared to ascorbic acid (70.19%).

Similarly, iron NPs produced using *Asphodelus aestivus* aerial parts scavenged DPPH with IC₅₀ 3.48 µg/mL [182]. In addition, Rajput et al. [183] evaluated the antioxidant potential of Ag NPs (*Atropa acuminata* leaf mediated) using DPPH, H₂O₂, and O₂⁻ assay with IC₅₀ 16.08, 25.4, and

21.12 µg/mL, which is lower than standard ascorbic and gallic acid (IC₅₀ 27.68–30.48 µg/mL). In the DPPH and total antioxidant activity (TAA) assays, TiO₂ NPs made from *Psidium guajava* leaves displayed strong antioxidant capability, with >85 and >90% scavenging at 500 µg/mL, respectively. When compared to standard ascorbic acid, the action of NPs in TAA is more prominent [184]. On the other hand, different parts (leaves, pods, seeds, and seed shell) of *Cola nitida* (10–80 µg/mL) exhibited 32.61–62.06% scavenging of DPPH. In addition, the scavenging ranged between 78.45 and 99.23% in H₂O₂ assay [185]. The antioxidant activity of phytoantioxidant functionalized NPs is related to the bioactive composition of the plant. The substantial body of

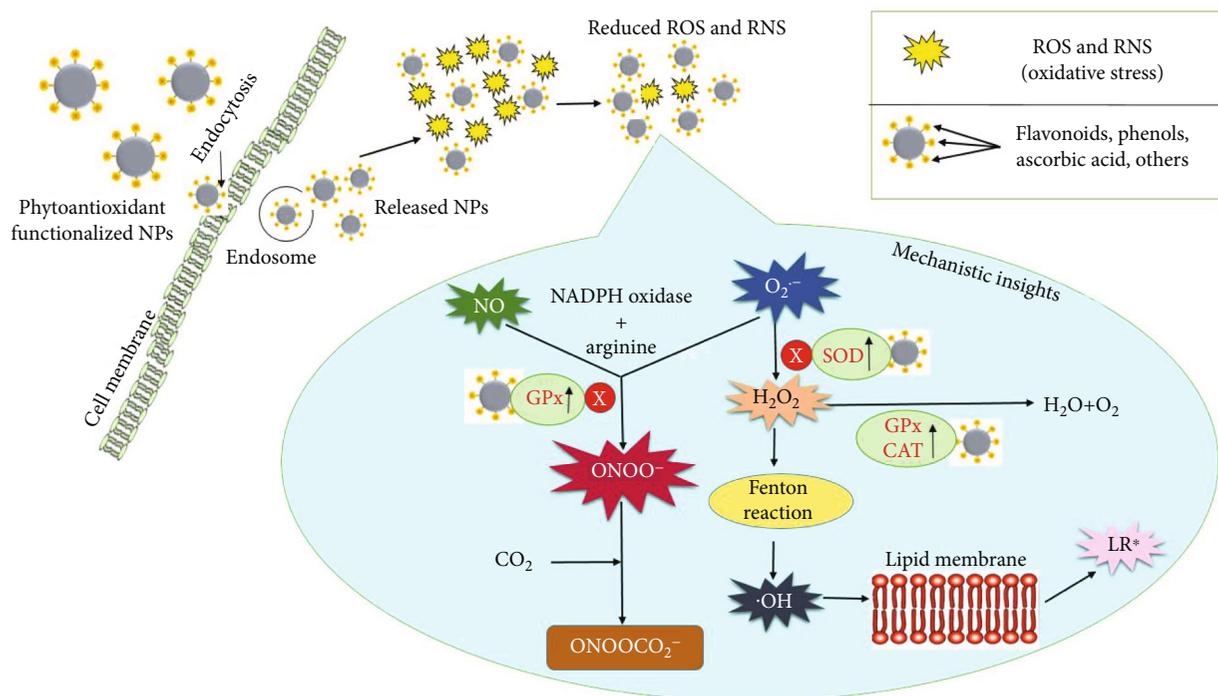


FIGURE 5: Role of phytoantioxidant functionalized nanoparticles in ameliorating oxidative stress. Note: GPx: glutathione peroxidase; CAT: catalase; $O_2^{\cdot-}$: superoxide radical; H_2O_2 : hydrogen peroxide; LR*: lipid radical; H_2O : water; O_2 : oxygen; SOD: superoxide dismutase; OH: hydroxyl radical; NO: nitric oxide; CO_2 : carbon dioxide; NADPH oxidase: nicotinamide adenine dinucleotide phosphate oxidase; $ONOOCO_2^-$: nitrosoperoxy carbonate; $ONOO^-$: peroxynitrate.

research, including those selected in this study, did not go into extensive depth about plant selection. However, the selection of antioxidant-rich plants is the most important factor in the activity of phytoantioxidant functionalized NPs.

The frequency of methodologies utilized for characterization of NPs, their significance, methods used for assessing antioxidant activity, plant parts used in green synthesis, and choice of NPs were all examined critically. The most commonly used strategy for antioxidant investigations was observed to be DPPH, followed by ABTS, superoxide, nitric oxide, and others. Surprisingly, all of the free radicals were successfully scavenged by the tested NPs. On the other hand, almost all plant parts have been used, but leaves are primarily harvested to synthesize NPs (Figure 4 and Table 1). Ag NPs are frequently employed in practice due to their inclusion in various formulations; the majority of researchers are currently focusing on these NPs, with silver topping the list of studies, followed by gold, copper, iron, and zinc oxide NPs.

The most common approach for measuring surface plasmon resonance and investigating the optical characteristics of produced NPs is UV-visible absorption spectroscopy, followed by FT-IR analysis to identify functional groups corresponding to surface-attached bioactive compounds responsible for reduction and stabilization. In 14, 21, and 18 investigations included in this study ($N = 26$), the shape and size of produced NPs were analyzed using scanning electron microscopy, transmission electron microscopy, and X-ray diffraction analysis. Dynamic light scattering analysis was also used to determine hydrodynamic size and

surface charge. Zeta potential measurements were carried out to assess NP stability; a relatively high zeta potential value shows that the surface has a substantial electric charge, demonstrating its stability. The thermal stability of NPs was evaluated using thermal gravimetric analysis (TGA) in a single study (Figure 4 and Table 1). Furthermore, elemental analysis was carried out using energy-dispersive X-ray analysis (EDX), which is used to detect impurities [67, 163, 166, 169, 177, 182, 183].

7. Mechanistic Basis of Oxidative Stress Management by Phytoantioxidant Functionalized NPs

Antioxidant defenses mitigate the detrimental effects of ROS and RNS, which are generated by a variety of endogenous and external mechanisms [88]. NADPH oxidase, lipoxygenase, angiotensin II, and myeloperoxidase (MPO) are all endogenous producers of ROS and RNS [191]. NADPH oxidase produces superoxide radical ($O_2^{\cdot-}$), which in turn is dissociated into the H_2O_2 by SOD [192]. Glutathione peroxidase (GPx), SOD, and CAT aid in the breakdown of free radicals into safe and less active molecules (H_2O_2 /alcohol, and O_2) [2, 193–198]. The phytoconstituents upregulate the level of antioxidant enzymes, and SOD is a significant force in radical neutralization [198]. As previously stated, SOD converts $O_2^{\cdot-}$ to H_2O_2 , which is then degraded by CAT and GPx into water and oxygen, preventing the formation of $\cdot OH$ [199, 200]. Glutathione-S-transferase and

glucose-6-phosphate dehydrogenase are two other antioxidant enzymes [200]. The inhibition of $\cdot\text{OH}$ generation contributed to lipid radical (LR^*) inhibition, which is generated due to the interplay between $\cdot\text{OH}$ and lipid membrane [198, 199]. GPx inhibits the peroxy nitrite anion produced by numerous interactions, such as when combined with carbon dioxide to make nitrosoperoxy carbonate, which disintegrates over time to form nitrogen dioxide and carbonate radicals [198, 201].

On the other hand, nonenzymatic antioxidants interact with ROS and RNS to stop the free radical chain. In continuation, blood contains α -tocopherol, bilirubin, and β -carotene whereas albumin and uric acid make about 85% of antioxidant defense in plasma [89]. The phytoconstituents on nanoparticle surfaces reduce oxidative stress [72]. In Figure 5, a mechanistic approach to the protective impact of phytoantioxidant functionalized nanoparticles in the regulation of oxidative stress is highlighted.

The abundance of terpenoids, ascorbic acid, flavonoids, phenols, and other bioactive phytoconstituents on the surface of NPs is strongly correlated with their antioxidant activity [178, 180]. The phytoantioxidant functionalized nanoparticles would upregulate the antioxidant enzymes, and nonenzymatic components such as ascorbic acid on the surface of these NPs would also neutralize the adverse effects of free radicals.

8. Conclusion and Perspectives

In conclusion, the evidence of oxidative stress caused by nanoparticle exposure raises concerns about their use in humans. Although the antioxidant potential of phytoantioxidant functionalized NPs is well documented, the majority of the researches have been conducted *in vitro*. The bioactive substances like flavonoids and phenols are correlated to the antioxidant action of these NPs. The stability of nanoparticles is an important aspect, but only three articles have investigated the storage stability of these NPs. Most studies lack a zeta potential measurement, which is an indicator of stability. The data compiled in this review is expected to serve as a roadmap for researchers to fulfill various gaps. Because of their widespread use in a variety of industries, Ag NPs are the most investigated NPs. It is suggested that the plant utilized for green synthesis should be selected carefully, as antioxidant action is linked to phytoconstituents. As an alternative to NPs, phytoantioxidant functionalized NPs could be employed; however, high-quality toxicity studies are necessary. Nanotechnology is rapidly expanding, but research into the nanoparticles' toxicological impacts on human health and the environment is still in its early stages.

Data Availability

All data are included in the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

Authors' Contributions

A.B. supervised the first draft. A.K. and V.A. wrote the first draft of the manuscript. A.R. and A.K. contributed in figures and in providing literature. R.V., D.K., N.T., E.N., O.K., and K.K. critically reviewed the first draft. A.K. and V.A. improved the first draft. The final submitted version of the manuscript has been seen and approved by all contributors.

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Supplementary Materials

Graphical abstract. (*Supplementary Materials*)

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