The Role of Diverse Nanoparticles in Oxidative Stress: In Vitro and In Vivo Studies

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Abstract

Nanoparticles are a very advanced area of nanotechnology and play an important role in medical sciences and technology. Nanoparticles such as polymer and metal nanoparticles are widely used in applications for antioxidant activity. Nonenzymatic antioxidant assays using free radical–scavenging activity of nanoparticles have been investigated using different methods such as 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) assays, nitric oxide radical inhibition assays, superoxide anion–scavenging activity, reducing power, determination of total phenolic compounds and hydroxyl radical–scavenging assays. The investigated metal nanoparticle included gold, zinc oxide, copper, silver, zirconium oxide and selenium, and the polymer nanoparticles include chitosan and silica.

Keywords

Metal nanoparticles · Antioxidant activity · Polymers · Synthesis · Characterization

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3.1 Introduction

3.1.1 Nanoparticles Used in Antioxidant Activity

Nanotechnology is one of the most recent areas to be explored for its applications related to engineering, medicine and various other sciences. Nanoparticles are particles in the size range of 1–100 nm and have the most applications in nanotechnology. Nanoparticles in different forms play vital roles in biomedical applications. The different types or forms of nanoparticles include metal nanoparticles (gold, silver, zinc, copper, selenium, etc.), metal oxide nanoparticles (silver oxide, zinc oxide, copper oxide, cadmium oxide and zirconium oxide), polymer nanoparticles (chitosan, silica, polyethylene glycol, cellulose, polyvinyl alcohol and polyvinyl pyrrolidine), carbon nanotubes, magnetic nanoparticles, nanohydrogels, aerogels, graphene nanostructures, nanocomposites, nanoshells, nanohybrids and biomolecules (curcumin, beta cyclodextrins, etc.).

Previously, nanoparticles were synthesized using physical and chemical techniques such as chemical vapour deposition, microwave irradiation, sol–gel techniques, plasma synthesis techniques, mechanical milling, ultrasound techniques, the hydrothermal method, the solvothermal method, the electrodeposition process, electroexplosion and laser techniques. Because of the high cost and environmental factors, researchers have recently been exploring use of green materials for the synthesis of nanoparticles, using microorganisms such as *Bacillus subtilis*, *Klebsiella planticola*, *Klebsiella pneumoniae* and *Aspergillus niger*; plant extracts from *Coleus aromaticus*, *Pongamia pinnata*, etc.; and algal extracts of *Turbinaria conoides*, *Padina tetrastromatica*, etc. [1–6]. Synthesis of nanoparticles using biological methods is very simple and cost effective. The prepared nanoparticles have been characterized using various techniques such as scanning electron microscopy, atomic force microscopy, ultraviolet–visible light (UV-vis) spectroscopy, dynamic light scattering, transmission electron microscopy, Fourier transform infrared spectroscopy, gas chromatography with mass spectroscopy, zeta potential analysis, thermogravimetric analysis, elemental dispersive analysis and x-ray diffraction assays [7–9]. Figure 3.1 shows green synthesis of nanoparticles and their characterization.

These nanoparticles are used in diverse applications such as anticancer activity.

Different types of nanoparticles are used for antioxidant activity in vitro and in vivo. Among these nanoparticles, metal and metal oxide nanoparticles are majorly involved in the activity in different experimental procedures. Figure 3.2 shows the different types of nanoparticles involved in antioxidant activity.

3.1.1.1 Silver Nanoparticles

Silver nanoparticles are the major metal nanoparticles in use and are intensively used in antimicrobial applications for their antibacterial and antifungal activities. In

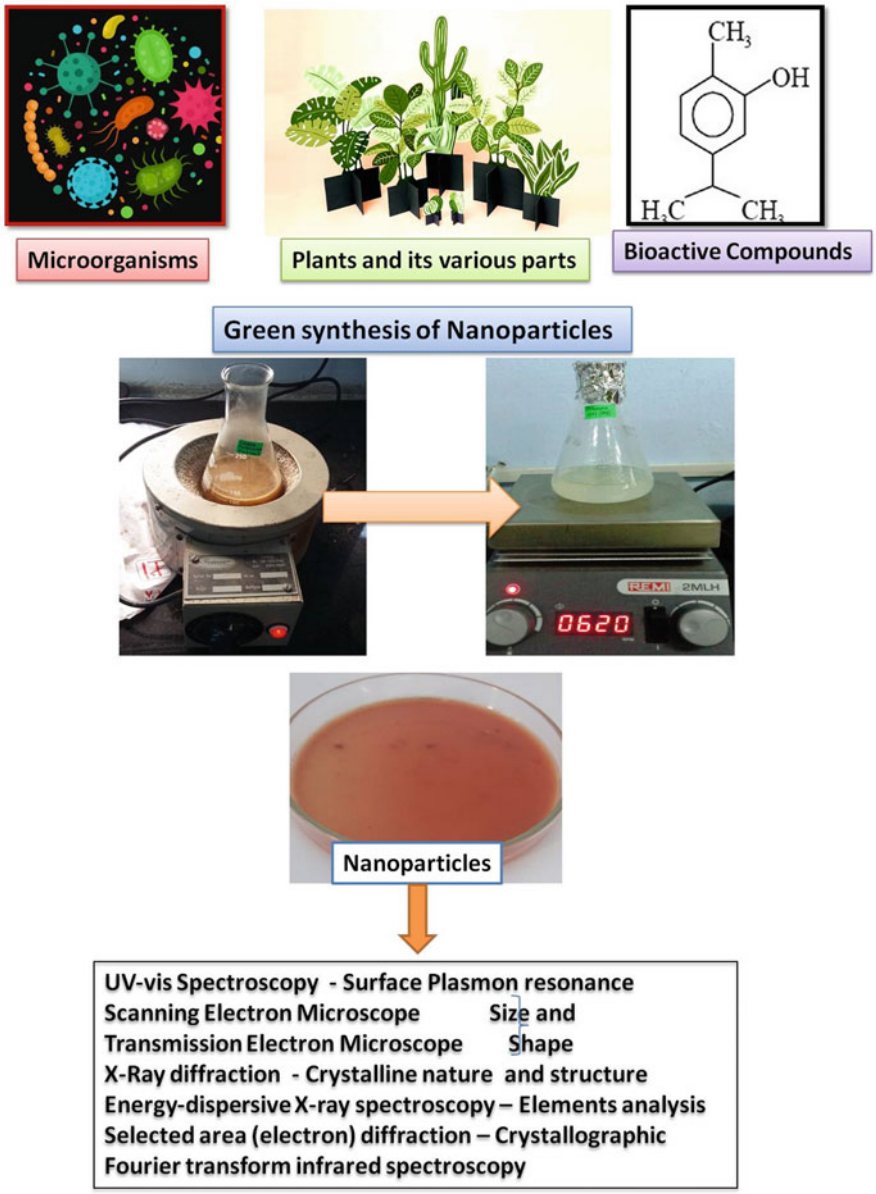

Fig. 3.1 Biosynthesis and characterization of nanoparticles

addition, silver nanoparticle have achieved very good results in anticancer and antioxidant activities [10–13]. Table 3.1 provides information on green synthesis of silver nanoparticles characterized using various techniques and antioxidant activities.

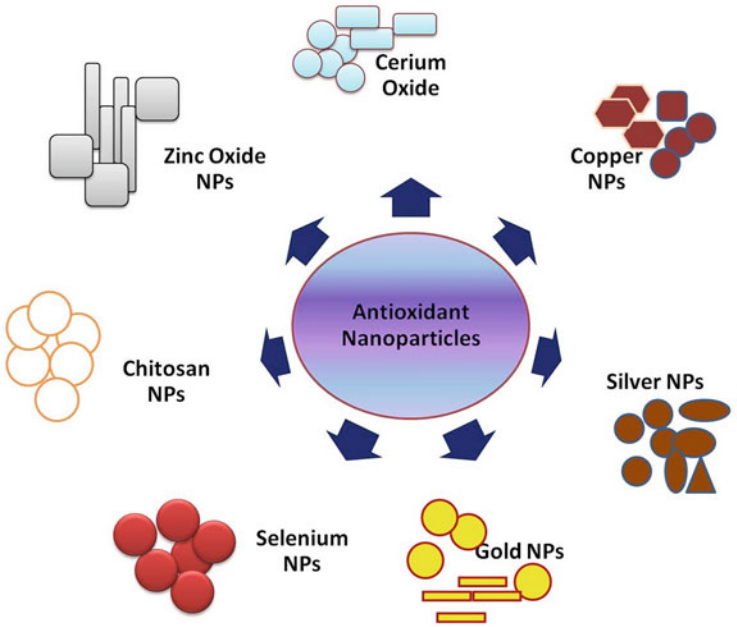

Fig. 3.2 Different nanoparticles (NPs) used in antioxidant activity

3.1.1.2 Gold Nanoparticles

Gold nanoparticles are widely used for delivery of drugs, proteins and genes in biomedical applications because of their surface plasmon resonance. These advanced metal nanoparticles also have applications in photothermal therapy, cancer imaging, identification of pathogens using immune chromatographic techniques, tissue imaging, anti-inflammatory activities and anticancer activities [39–41]. Table 3.2 provides information on gold nanoparticles and their antioxidant activities in various biochemical assays.

3.1.1.3 Zinc Oxide Nanoparticles

Zinc oxide nanoparticles have unique properties with many applications in many fields such as photocatalytic activity; antibacterial and antifungal activity against clinical, animal and plant pathogens; dye degradation and heavy metal degradation activity; and UV-filtering properties [10, 50–52]. Zinc oxide nanoparticles are one of the important types of semiconductor nanoparticles used in multitasking applications, including antioxidant activity, as shown in Table 3.3.

3.1.1.4 Antioxidant Activity of Other Nanoparticles

Apart from silver, gold and zinc nanoparticles, other nanoparticles such as chitosan, titanium dioxide, cerium oxide, selenium, magnetic nanoparticles, silicon dioxide and nickel oxide nanoparticles also show very good antioxidant activity in different

Table 3.1 Synthesis, characterization and antioxidant activity of silver nanoparticles (AgNPs)

Reducing agent	Characterization of NPs	Antioxidant activity: method, concentration, activity level	Reference
Aqueous leaf extract of *Ficus hispida* Linn.f.	TEM: 20 nm Shape: Spherical UV-vis spectroscopy: 423 nm	DPPH assay: 21.07 ± 0.02%	[14]
Aqueous leaf extract of *Cestrum nocturnum*	TEM: 20 nm Shape: Spherical UV-vis spectroscopy: 442 nm SEM: 15–28 nm	DPPH assay: 29.55%, hydrogen peroxide 45.41%, hydroxyl radical 20%, superoxide radical–scavenging activity 8%	[15]
Lippia alba extract	FTIR: 1595 and 1410/cm UV-vis spectroscopy: 408 nm	DPPH assay: 56.13 ± 4.79% FRAP assay: 2436.45 ± 137.16 μM	[16]
Mucuna birdwoodiana, *Phoebe lanceolata*, *Cratoxylum formosum*, *Scurrula parasitica*, *Ceratostigma minus*, *Myrsine africana* and *Lindera strychnifolia* plant extracts	UV-vis spectroscopy: 450 nm	DPPH assay: 29.2%, 35.2%, 44.4%, 42.4%, 35.8%, 28.3% and 30.2%	[17]
Acetic acid and polyvinyl alcohol, chitosan	TEM: 190–200 nm	DPPH assay: EC_{50} (in scavenging DPPH) 0.4 mg/mL FRAP assay: Hydroxyl radical–scavenging activity 77.43% and 85.9% at 1.5 mg/mL and 2 mg/mL, respectively Cytotoxic activity 5–200 μg/mL against Chinese hamster ovary (CHO-K1) cells	[18]
Caesalpinia pulcherrima stem extract	UV-vis spectroscopy: 410 nm TEM: 3–15 nm Crystalline structure	DPPH assay: IC_{50} 664 mg/mL Superoxide anion radical–scavenging activity 72 μg/mL ABTS radical–scavenging activity 216 μg/mL	[19]
Calophyllum tomentosum leaf extract	XRD: Crystalline structure UV-vis spectroscopy: 438 nm	DPPH assay: 90% Nitric oxide radical–scavenging assay: 78.46% Hydrogen peroxide–scavenging assay: 83.94% Reducing power activity 74%	[20]
Streptomyces violaceus MM72	TEM: 50 nm XRD: Crystalline structure	DPPH assay: 89.5% Total antioxidant activity 0.730 at 50 μg/mL FRAP assay: 1.83 AU at 1000 μg/mL concentration H_2O_2-scavenging activity 72.5% Nitric oxide–scavenging activity 60.1%	[21]

(continued)

Table 3.1 (continued)

Reducing agent	Characterization of NPs	Antioxidant activity: method, concentration, activity level	Reference
Phyllanthus acidus extract (leaf and twig)	SEM and DLS: 48.36 and 164.30 nm Shape: Spherical	DPPH assay: EC_{50} of leaf extract AgNPs 58.83 ± 1.65 μg/mL Nitric oxide radical–scavenging assay: EC_{50} of twig extract AgNPs 60.75 ± 1.59 μg/mL Hydroxy radical–scavenging assay: EC_{50} 43.02 ± 1.62 μg/mL	[22]
Citrus limon, *Citrus sinensis* and *Citrus limetta* fruit waste (peel) extracts	TEM: 9–46 nm	DPPH assay: Scavenging activity 87.43%, 67.50% and 95.13% Antimicrobial activity: Agar well diffusion technique Cytotoxic activity against human lung cancer cell line A549	[23]
Garlic, turmeric and green tea extracts	UV-vis spectroscopy: 450 nm XRD: Crystalline structure SEM and TEM: 8 nm Shape: Spherical	DPPH and ABTS hydroxyl radical–scavenging assays: Turmeric-mediated AgNPs showed maximum activity	[24]
White tea extract	TEM: 19.77 ± 3.82 nm for white tea/AgNPs XRD: Crystalline structure	DPPH assay: 88.09 ± 0.08% Cytotoxicity studies on MOLT-4 cells	[25]
Commercial green tea extract (*Camellia sinensis*)	UV-vis spectroscopy: 410 nm DLS: 34.68 ± 4.95 nm	–	[26]
Aconitum toxicum Reichenb. Rhizome alcoholic extract	UV-vis spectroscopy: 70 and 55 nm	DPPH assay: 81.11% for extract 1, 84.32% for extract 2	[27]
Quercetin, rutin and gallic acid, protocatechuic acid, caffeic acid and hesperidin supplied from sigma-Aldrich and Fluka	UV-vis spectroscopy: 407 nm SEM: Spherical nanoparticles, size 76.01 nm	DPPH and ABTS assays: Quercetin showed greater activity than rutin	[28]
Tropaeolum majus L. leaf extract	UV-vis spectroscopy: 463 nm	BHT assay: 98.9% DPPH assay: Ethanol extract 52.5%, aqueous extract 66.1% ABTS assay: Ascorbic acid 81.46%, aqueous extract 56.6%, ethanol extract 43.4% Total antioxidant activity: 550 and 530 μg/mL	[29]
Chitosan–polyethylene glycol hydrogel	UV-vis spectroscopy: 404–408 nm SEM: 99.1 ± 2.3 nm	DPPH assay: Ascorbic acid 22–92%, AgNPs 15–57%, chitosan hydrogel 11–43%, AgNP-loaded chitosan hydrogel 26–85%	[30]

Allium ampeloprasum L. leaf extract	UV-vis spectroscopy: 420 and 440 nm TEM: 2 and 43 nm Shapes: Spherical, quasispherical, hexagonal, ellipsoidal and irregular	DPPH assay: 62.2–82.4% ABTS assay: 64.5–96.8%	[31]
Phenolic compounds purchased from sigma-Aldrich	UV-vis spectroscopy: 420 nm TEM: ≤15 nm	ABTS assay: AgNPs: $R = 0.956$, $p < 0.0001$	[32]
Novel L-arginine–dextran-70 functionalized with RF and HSA	TEM: 41.60 nm UV-vis spectroscopy: ~476 nm	Antioxidant activity of $SNPs^{Arg}$ systems ($SNPs^{Arg}$, $SNPs^{Arg}$/HSA, $SNPs^{Arg}$/RF, $SNPs^{Arg}$/RF/HSA) was monitored by chemiluminescence Antioxidant activity of $SNPs^{Arg}$ was about 11.3%, and that of the $SNPs^{Arg}$/RF/HSA system was increased to 21.24%	[33]
g-C_3N_4 nanosheet–decorated Ag_2S composites	UV-vis spectroscopy (g-C_3N_4 sample): 440 nm UV-vis spectroscopy (Ag_2S): 675 nm	DPPH method: g-C_3N_4/Ag_2S composite exhibited greater DPPH radical–scavenging activity (IC_{50} 1.58 μM) than bare Ag_2S (IC_{50} 2.81 μM)	[34]
Fusarium oxysporum	SEM and AFM: 30–45 nm	–	[35]
Memecylon umbellatum Burm.f. (4-*N*-methyl benzoic acid)	UV-vis spectroscopy: 430 nm High-resolution TEM: 7–23 nm	Superoxide radical–scavenging activity: EC_{50} 66.68 μg/mL (74.76%) DPPH radical–scavenging activity: EC_{50} 53.46 mg/mL (81.57%) Anticancer activity against breast cancer cell line: IC_{50} 42.19 μg/mL	[36]
Trichoderma atroviride	UV-vis spectroscopy: 390–400 nm FTIR: 1115.4 and 3450/cm	DPPH-scavenging activity in a concentration-dependent manner (IC_{50} 45.6 μg/mL)	[37]
Gallic acid and chitosan	TEM: 26.23 ± 9.92 nm	–	[38]

ABTS 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid), *AFM* atomic force microscopy, *BHT* butylated hydroxy toluene, *DLS* differential light scattering, *DPPH* 2,2-diphenyl-1-picryl-hydrazyl-hydrate, EC_{50} half-maximal effective concentration, *FRAP* ferric-reducing ability of plasma, *FTIR* Fourier transform infrared, *g-C_3N_4* graphitic carbon nitride, *HSA* human serum albumin, IC_{50} half-maximal inhibitory concentration, *RF* riboflavin, *SEM* scanning electron microscopy, *$SNPs^{Arg}$* L-arginine–dextran-70–based-silver nanoparticles, *TEM* transmission electron microscopy, *UV-vis* ultraviolet–visible light, *XRD* x-ray diffraction

Table 3.2 Antioxidant activity of gold nanoparticles (AuNPs)

Reducing agent	Characterization of NPs	Antioxidant activity: method, concentration, activity level	Reference
Extra-virgin olive oil	TEM: 15 nm UV-vis spectroscopy: 540 nm	ABTS and DPPH assays, Folin–Ciocalteau method Gallic acid: Reference standard Coefficients: ABTS $R^2 = 0.999$, DPPH $R^2 = 0.996$, Folin–Ciocalteau $R^2 = 0.992$	[42]
Citric acid	TEM: 12 ± 1.5 nm Spherical and uniformly dispersed UV-vis spectroscopy: 525 nm Cyclic voltammetry	DPPH assay: IC_{30} 1.89 E−6 M, IC_{50} 1.15 E−5 M	[43]
Panax ginseng leaf extract	UV-vis spectroscopy: 517 nm (DPPH assay)	DPPH assay: IC_{50} 16.06 μg/mL MTT assay: HDF and murine melanoma B16BL6 cell lines (tyrosinase activity assay)	[44]
DMAHF	UV-vis spectroscopy: 534 nm FTIR TEM: 6–8 nm	DPPH assay	[45]
Chitosan	UV-vis spectroscopy: 551 nm Shapes: Spherical and irregular TEM, XRD, FTIR	Hydroxyl radical–scavenging assay, FRAP assay (0.266 ± 0.007), DPPH assay ($n = 3$, $p \leq 0.05$), ABTS assay	[46]
Starch	UV-vis spectroscopy: 525 nm Size 22 nm TEM: Tert-BHP limit of detection 39 μM	AuNP nanosensor–based peroxyl radical–scavenging assay Classic ORAC assay	[47]
Aqueous leaf extract of *Delonix regia*	UV-vis spectroscopy: 541 and 432 nm TEM: 6–40 nm Shapes: Spherical and irregular	DPPH: SC_{50} 7.35 ABTS assay: SC_{50} 6.21	[48]
Sodium citrate	TEM: 13 nm	Histological assessment Effective: 50 nm AuNPs	[49]

ABTS 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid), *DMAHF* 4′-*N*,*N*-dimethylamino-3-hydroxyflavone, *DPPH* 2,2-diphenyl-1-picryl-hydrazyl-hydrate, *FRAP* ferric-reducing ability of plasma, *FTIR* Fourier transform infrared, *HDF* human dermal fibroblast, IC_{30} 30% of maximal inhibitory concentration, IC_{50} half-maximal inhibitory concentration, *MTT* 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, *ORAC* oxygen radical absorbance capacity, SC_{50} sample concentration reducing DPPH or ABTS concentration to half its initial value, *TEM* transmission electron microscopy, *tert-BHP* tert-butyl hydroperoxide, *UV-vis* ultraviolet–visible light, *XRD* x-ray diffraction

Table 3.3 Antioxidant activity of zinc oxide nanoparticles (ZnONPs)

Reducing agent	Characterization of NPs	Antioxidant activity: method, concentration, activity level	Reference
Citrus pectin powder, chitosan, sodium alginate	UV-vis spectroscopy TEM: 46 nm DLS, XRD, FTIR	DPPH assay IC_{50} values 47.5 and 65 μg/mL Antibacterial activity against gram-positive and gram-negative organisms and yeast Anticancer activity against Ehrlich ascites carcinoma	[53]
Inducible nitric oxide synthase (nos2) gene	TEM: 45 nm	qPCR analysis Western blot analysis	[54]
Psidium guajava leaf extract	UV-vis spectroscopy: 345 nm SEM: Spherical shapes	DPPH assay: 77.80–81.35%	[55]
Thymus vulgaris leaf extract	Size 50–60 nm Shape: Irregular TEM, XRD, EDX, DLS, FTIR	DPPH assay: $\leq$75% antibacterial activity against selected foodborne pathogens	[56]
Mangifera indica leaf extract	UV-vis spectroscopy, TEM, SEM, XRD, EDX Size 45–60 nm Shape: Spherical and hexagonal quartzite	DPPH assay Cytotoxicity assays: A549 lung cancer cell line	[12]
Curcumin	FTIR, field emission SEM, XRD, UV-vis spectroscopy	DPPH assay: 24.25% Stability of curcumin improved ($p < 0.05$)	[57]
Synthesized by aqueous and polyol method	XRD: 10 and 40 nm UV-vis spectroscopy TEM: 10 and 15 nm	DPPH assay: IC_{50} values 39.38 and 43.33 Metal chelation: IC_{50} values 54.17 and 51.6 ABTS assay: IC_{50} values 38.31 and 39.15 Antibacterial activity	[58]
Pithecellobium dulce peel extract	Hexagonal crystalline structure Shape: Spherical Size 11.5 $\pm$ 2 nm	Photocatalytic activity Antifungal activity	[59]
Tecomaca stanifolia leaf extract	UV-vis spectroscopy: 380 nm Shape: Spherical Size 70–75 nm	DPPH assay Anticancer activity IC_{50} 65 μg/mL (A549 cell line)	[60]
Malus pumila and *Juglen regia* plant extracts	UV-vis spectroscopy, TEM, XRD, FTIR, DLS, SEM, EDX Size 12 and 16 nm	DPPH assay Antibacterial activity	[61]
Artemisia haussknechtii leaf extract	UV-vis spectroscopy, TEM, GC-MS, FTIR, AFM, SEM, EDX, powder XRD Size 50–60 nm Shape: Hexagonal wurtzite	Total antioxidant capacity DPPH assay Disc diffusion assay	[62]

(continued)

Table 3.3 (continued)

Reducing agent	Characterization of NPs	Antioxidant activity: method, concentration, activity level	Reference
Oleic acid, gluconic acid, tween 80	Shapes: (1) flower-like nanorods and nanoflakes; (2) nanogranules, size 20–30 nm; (3) assembled hierarchical structure	H_2O_2 free radical–scavenging activity, ABTS assay, DPPH assay	[63]
Ricinus communis plant seed extract	Shape: Crystalline hexagonal arrangement Size 20 nm Powder XRD, FTIR, XRD, TEM	Antioxidant activity DPPH assay, FRAP assay Anticancer activity: IC_{50} of ZnONPs in MDA-MB-231 breast cancer cells: 7.103 μg/mL Antifungal activity	[64]
Coccinia abyssinica tuber extract	Size 10.4 nm Shape: Hexagonal (analysed using TEM)	DPPH assay IC_{50} 127.74 μg/mL Well diffusion assay	[65]
Codonopsis lanceolata root extract	Size and shape: 500 nm with flower-like structure confirmed by XRD and TEM UV-vis spectroscopy: 365 nm	Photocatalytic degradation activity	[66]
Vitamin E and C mixture	DLS, TEM, inductive coupled plasma mass spectrometry Size 35 nm	Lipid peroxidation activity in Nile tilapia tissues	[67]
Aqueous extract of chironji leaves	XRD, TEM and UV-vis techniques: 363 nm Shape: Hexagonal wurtzite	DPPH assay IC_{50} 8025 μg/mL Antibacterial activity Photocatalytic degradation activity	[68]
Copditis rhizome extract	Size 8.50 nm Shapes: Spheres and rods SEM, EDX, FTIR, XRD, TEM, TGA, SAED, UV-vis spectroscopy	DPPH assay: 1 mg/mL (52.34%), >0.5 mg/mL (51.57%), >0.25 mg/mL (51.19%), >0.125 mg/mL (38.12%) Cytotoxicity against RAW 264.7 cells Antibacterial activity	[69]
Water extract of *Garcinia xanthochymus*	UV-vis spectroscopy: 370 nm SEM: Spongy cave-like structures XRD: Pure wurtzite structure	DPPH assay Photocatalytic degradation activity	[70]
Polygala tenuifolia root extract	UV-vis spectroscopy, FTIR, TGA TEM: 33.03–73.48 nm Shape: Spherical	DPPH assay: 45.47%	[71]

ABTS 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid), *AFM* atomic force microscopy, *DLS* differential light scattering, *DPPH* 2,2-diphenyl-1-picryl-hydrazyl-hydrate, *EDX* energy-dispersive x-ray, *FRAP* ferric-reducing ability of plasma, *FTIR* Fourier transform infrared, *GC-MS* gas chromatography with mass spectrometry, IC_{50} half-maximal inhibitory concentration, *qPCR* quantitative polymerase chain reaction, *SAED* selected area electron diffraction, *SEM* scanning electron microscopy, *TEM* transmission electron microscopy, *TGA* thermogravimetric analysis, *UV-vis* ultraviolet–visible light, *XRD* x-ray diffraction

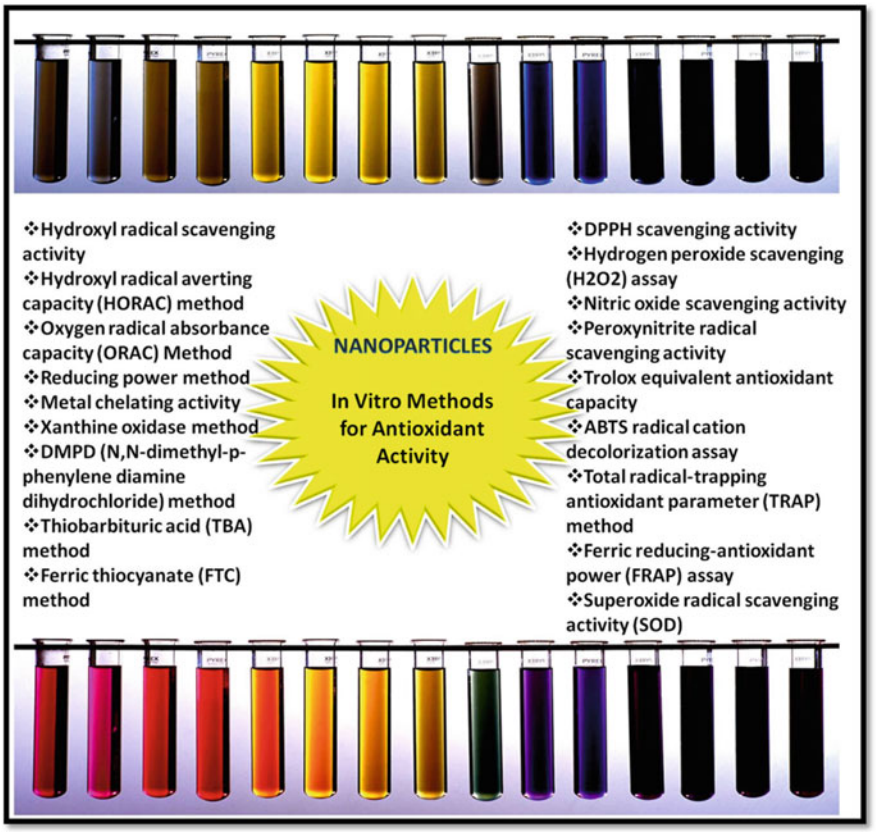

Fig. 3.3 In vitro antioxidant activity of nanoparticles using various assays. *ABTS* 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid), *DPPH* 2,2-diphenyl-1-picryl-hydrazyl-hydrate

assays. Figure 3.3 shows different antioxidant assays used for free radical–scavenging nanoparticles.

3.1.1.5 Antioxidant Activity of Polymer, Magnetic and Oxide Nanoparticles

Chitosan is an important bioactive product, obtained from crab shells and prawn shells. It shows good antimicrobial activity against *Escherichia coli* and *Staphylococcus aureus* and antifungal activity against *Candida albicans*, and it has shown good scavenging activity of 76% in a 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) assay [72]. Super-para iron oxide nanoparticles synthesized using *Stevia* leaf extract had a spherical shape and were 25 nm in size on high-resolution transmission electron microscopy (TEM) analysis. They showed good antioxidant activity in a DPPH assay and a half-maximal inhibitory concentration (IC_{50}) of 65 μg/mL [73]. Manganese oxide nanoparticles prepared using mature seeds of

Atropa belladonna L. showed a crystalline structure (on x-ray diffraction (XRD)) and a spherical shape with a size of 30 nm, confirmed by TEM. The free radical–scavenging activity of MnO_2 nanoparticles, investigated using a DPPH assay with plantlets at 200 mg/L with an IC_{50} of 134.6 μg/mL and Fe^{2+}-chelating activity, also showed the same tendency [74].

Selenium nanoparticles synthesized using pectin showed DPPH radical–scavenging activity of 92%, a Trolox-equivalent antioxidant capacity assay value of 222.18 μmol Trolox per gram of the sample and a ferric-reducing ability of plasma (FRAP) assay value of 127.51 μmol Fe^{2+} per gram of the sample [75]. A hyperbranched polysaccharide from *Lignosus rhinocerotis* also showed good activity in a DPPH assay (24.29%, 23.28%, 44.84%, 52.31% and 43.22%) and in an ABTS radical–scavenging assay (83.18% and 81.54%) [76].

Pisonia alba leaf extract–mediated cerium oxide nanoparticles with the characteristics of a cubic fluorite crystal structure (on XRD), UV-vis spectroscopy values of 258 and 317 nm, and a 12 nm size on TEM showed good antifungal activity and moderate antioxidant activity in a DPPH assay and FRAP assay [77].

3.1.1.6 Antioxidant Activity of Nanoparticles In Vivo

In a recent research article, Qin et al. showed that layered double hydroxide (LDH) nanoparticles possessed a DPPH-scavenging effect, a hydroxyl radical (OH)–scavenging effect and a pro-oxidative Cu^{2+}-chelating effect. This was mainly due to folic acid coupling with the LDH nanoparticles; moreover, folic acid–LDH was successful in increasing glycogen levels in muscle and hepatic glycogen. It was suggested that a folic acid–LDH antioxidant could have indications for use as a novel antioxidant or an antifatigue nutritional supplement [78].

An in vivo study by Zhang et al. revealed that nano-gold loaded with resveratrol (Res-GNPs) showed a better antitumour effect than resveratrol alone. This was due to the fact that the gold nanoparticles could transport more resveratrol to cells and to mitochondria; thus, the gold nanoparticles coupled with resveratrol reduced the cancer effect both in vitro and in vivo [79].

The above studies clearly indicate that nanoparticles, when coupled with antioxidants, provide more protection for healthy cells and provide anticancer effects.

In in vitro studies on sulphoraphane-modified selenium nanoparticles, Krug et al. showed anticancer action in several cancer cell cultures. They also showed that this high antitumour activity and selectivity with regard to diseased and healthy cells is an extremely promising treatment for cancer cells [80]. The different parameters analysed to determine the in vivo antioxidant activity of the nanoparticles are shown in Fig. 3.4.

Khan et al. studied the effects of cobalt-doped tin oxide (Co-doped SnO_2) nanoparticles and revealed that in breast carcinoma cells, green-synthesized Co-doped SnO_2 nanoparticles showed potential antioxidant activity in a DPPH assay and also showed significant anticancer and antitumour activity in both in vitro and in vivo conditions. The multipurpose properties of synthesized

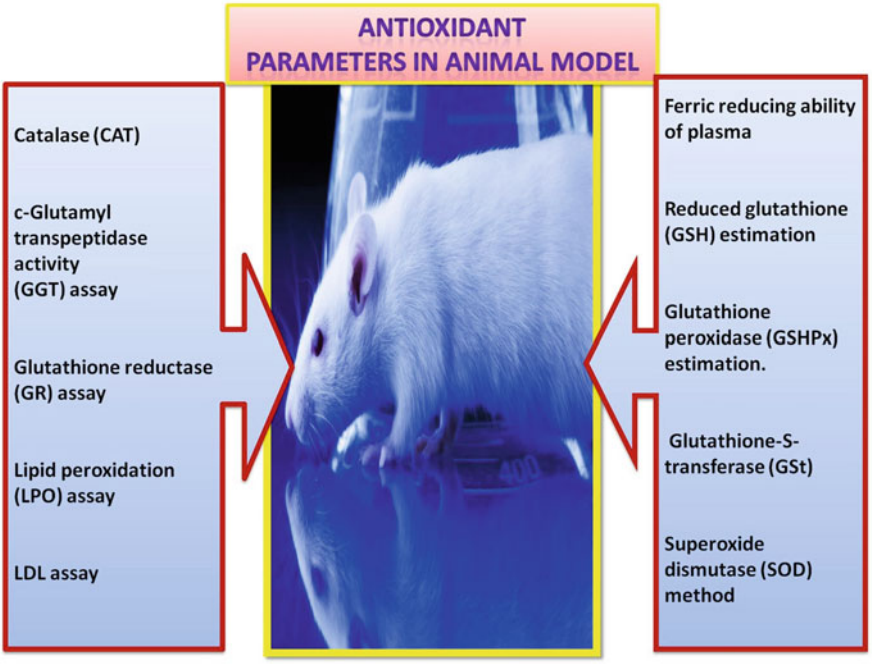

Fig. 3.4 In vivo antioxidant activity of nanoparticles. *LDL* low-density lipoprotein

nanoparticles demonstrated in this study showed that they could be useful for pharmaceutical and nanomedicine applications [81].

A research study by Tang et al. demonstrated the characterization of epigallocatechin-3-gallate (EGCG)–functionalized chitin (CH) derivative nanoparticles (CE-HKNPs) and compared their antitumour activity with that of free Honokiol (HK). The result showed that the CE-HKNPs were effective, inhibiting the cell proliferation of $HepG_2$ cells and decreasing the mitochondrial membrane potential. Moreover, in both in vitro and in vivo conditions they did not elicit any side effects in the cells. It was suggested that CE-HKNPs are an effective delivery system against liver cancer cells [82]

A recent article by Shanmugasundaram et al. described a Sprague Dawley (SD) rat model in which hepatoprotective experiments were conducted against diethyl nitrosamine (DEN)–stimulated liver cancer cells using biocompatible nanoparticles of silver (AgNPs), gold (AuNPs) and their alloy (Ag/AuNPs), synthesized from microbes. The animals treated with nanoparticles showed significant tumour reduction in in vivo studies, and this was also confirmed by other studies. The results showed anticancer activity only in DEN-stimulated liver cells, due to the synthesized AgNPs, AuNPs and Ag/AuNPs. In nanodrug development, microbial biocompatible nanoparticles have been shown to have potential as an effective drug [83].

Sulaiman et al. described an experiment, using an *Oleo europaea* leaf extract, in which copper oxide (CuO) nanoparticles (CuNPs) were synthesized. Because of the stability of the antioxidant effect, the free radical–scavenging activity of the CuNPs against 2,2-diphenyl-1-picryl-hydrazyl was assured. In mice, immune responses were observed in both the thymus and the spleen. After CuNP treatment the thymus, spleen and serum showed reductions in the adenosine deaminase (ADA) enzyme. In a dose-dependent manner, application of CuNPs against AMJ-13 and SKOV-3 cancer cells induced cell death by apoptosis. Normal dermal fibroblast cells showed less significant cytotoxic effects. Thus, CuNPs have the ability to act as an anticancer agent [84].

In contrast, Nemmer et al. found that exposure to cerium oxide nanoparticles (CeO_2NPs) induced lung toxicity. In their study, a noticeable increase in neutrophils in the bronchoalveolar lavage fluid, along with an increase in tumour necrosis factor (TNF) and a drop in the activity of the antioxidant catalase, were stimulated by CeO_2NPs. Increased plasma levels of C-reactive protein and TNF were also noted [85]. In this in vivo study it was found that thrombosis was due to acute pulmonary oxidative damage and systemic inflammation.

Qiao et al. studied andrographolide (ADG), a diterpenoid separated from *Andrographis paniculata* with a range of pharmacological activities including antitumour, anti-inflammatory, anticancer and hepatoprotective effects. They showed that a freeze-dried ADG nanosuspension (ADG-NS) could remain highly stable [86].

Pramanik et al. performed in vitro and in vivo studies on biotin-enriched gold nanoparticles targeted for delivering an anticancer active copper complex, copper (II) diacetyl-bis (N_4-methylthiosemicarbozane), tethered to 20 nm gold nanoparticles (AuNPs) and additionally decorated with biotin for target achievement. They revealed very good anticancer activity against HeLa cells derived from cervical cancer cells; less activity was observed against HaCaT cells. In an in vivo comparison with a nanoparticle conjugate without biotin, using a HeLa cell xenograft tumour model, the biotin-enriched nanoparticle conjugate showed a greater reduction in tumour volume than the control (without biotin), suggesting significant targeting [87].

3.2 Mechanisms of Action

Different metal nanoparticles, polymer nanoparticles, metal-coated polymer nanoparticles and bioactive compound–coated/decorated nanoparticles act as nanoantioxidants. The major mechanisms of action of these nanoparticles mimic the behaviour of catalase (CAT), glutathione peroxidase (GPX), superoxide dismutase (SOD) and chain-breaking activity. Examples of these nanoparticles and their mechanisms of action in different assays are cerium oxide nanoparticles, which show catalase-like behaviour in hydrogen peroxide disappearance on spectrophotometric analysis [88], polyvinyl pyrrolidone–coated gold nanoparticles, which decrease H_2O_2 in spectrometric analysis and show catalase-like behaviour [89],

and gold nanorods, gold with platinum nanorods, core shells and gold with palladium nanorods, which shows catalase-like behaviour in H_2O_2 assays, spectrophotometric analysis and O_2 evaluation using dark electrodes [90].

Nanoparticles such as manganese oxide nanoflowers and grapheme oxide–supported selenium nanoparticles have shown glutathione peroxidase–like behaviour in a glutathione reductase–coupled assay using spectrophotometric analysis [91, 92].

The chain-breaking mechanism is the major action in various antioxidants (also called radical-trapping antioxidants) such as flavonoids, vitamin C, vitamin E and many synthetic alternatives.

A chain-breaking or slowdown mechanism of action was found in some nanoparticles, such as oleic acid–coated cerium oxide nanoparticles, when an AAPH-derived radical-scavenging (oxygen radical absorbance capacity (ORAC)) assay was performed [93]. Polyacrylic acid–protected platinum nanoparticles were analysed using a DPPH assay with spectrophotometric analysis. Inhibition of linoleic acid peroxidation was observed with electron paramagnetic resonance (EPR) detection of AAPH-derived radical–scavenging activity [94]. Zirconium oxide nanoparticles and polyethylene glycol–coated melanin nanoparticles have also shown chain-breaking activity, confirmed by a DPPH assay [95, 96].

Superoxide dismutase–like behaviour is the major mechanism in many antioxidant nanomaterials and xanthine/xanthine oxidase and cytochrome C analysed by spectrophotometric analysis, potassium oxide reaction, EPR study of reactions with potassium oxide with 5-diethoxyphosphoryl 5-methyl-1-pyrroline-*n*-oxide (DEPMPO) and oxide evaluation. The nanomaterials involved in these actions are fullerene, multiwalled carbon nanotubes, trismalanyl C-60, dimercaptosuccinic acid–coated Co_3O_4 nanoparticles, polyvinyl pyrrolidone–coated gold nanoparticles, glycine-coated copper nanoparticles, polyethylene glycol–coated manganese and carbon nanoclusters, palladium nanoparticles, platinum nanopowder and Mn_3O_4 nanoflowers [89, 91, 97–105].

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