Environmental Chemistry Letters (2022) 20:2531–2571
https://doi.org/10.1007/s10311-022-01425-w

REVIEW

Formation, antimicrobial activity, and biomedical performance of plant-based nanoparticles: a review

Ngoan Thi Thao Nguyen[1,2] · Luan Minh Nguyen[1,2] · Thuy Thi Thanh Nguyen[2,3] · Thuong Thi Nguyen[1,4] · Duyen Thi Cam Nguyen[1,4] · Thuan Van Tran[1,4]

Received: 16 November 2021 / Accepted: 24 February 2022 / Published online: 25 March 2022

Abstract

Because many engineered nanoparticles are toxic, there is a need for methods to fabricate safe nanoparticles such as plant-based nanoparticles. Indeed, plant extracts contain flavonoids, amino acids, proteins, polysaccharides, enzymes, polyphenols, steroids, and reducing sugars that facilitate the reduction, formation, and stabilization of nanoparticles. Moreover, synthesizing nanoparticles from plant extracts is fast, safe, and cost-effective because it does not consume much energy, and non-toxic derivatives are generated. These nanoparticles have diverse and unique properties of interest for applications in many fields. Here, we review the synthesis of metal/metal oxide nanoparticles with plant extracts. These nanoparticles display antibacterial, antifungal, anticancer, and antioxidant properties. Plant-based nanoparticles are also useful for medical diagnosis and drug delivery.

Keywords Nanoparticles · Green synthesis · Plant extract · Phytochemical compounds · Biomedical applications

Abbreviations

UV–Vis	Ultraviolet–visible
FT-IR	Fourier transform infrared
SEM	Scanning electron microscope
TEM	Transmission electron microscopy
AFM	Atomic force microscope
XRD	X-Ray diffraction
EDS	Energy-dispersive spectroscopy
BJH	Barrett, Joyner, and Halenda
DFT	Density functional theory
ROS	Reactive oxygen species
VB	The valence band
CB	The conduction band
CT	Computerized tomography scan
MRI	Magnetic resonance imaging
DPPH	2-Diphenyl-1-picrylhydrazyl
MIC	Minimum inhibitory concentration
MBC	Minimum bactericidal concentration
IC50	Half-maximal inhibitory concentration
AGS	Human gastric adenocarcinoma cell line
HT-29	Human colorectal adenocarcinoma cell line
PANC-1	Human pancreas ductal adenocarcinoma cell line
HepG2	Human liver cancer cell line
MCF-7	Human breast cancer cell line
AIDS	Acquired immunodeficiency syndrome
GSH	Glutathione
A549	Human lung cancer cell line

✉ Duyen Thi Cam Nguyen
ntcduyen@ntt.edu.vn

✉ Thuan Van Tran
tranuv@gmail.com; tranvt@ntt.edu.vn;
ttran@gradcenter.cuny.edu

[1] Institute of Environmental Technology and Sustainable Development, Nguyen Tat Thanh University, 298-300A Nguyen Tat Thanh, District 4, Ho Chi Minh City 755414, Vietnam

[2] Department of Chemical Engineering and Processing, Nong Lam University, Thu Duc District, Ho Chi Minh City 700000, Vietnam

[3] Faculty of Science, Nong Lam University, Thu Duc District, Ho Chi Minh City 700000, Vietnam

[4] NTT Hi-Tech Institute, Nguyen Tat Thanh University, 298-300A Nguyen Tat Thanh, District 4, Ho Chi Minh City 755414, Vietnam

Introduction

Nanotechnology is mainly related to the design, synthesis, structural analysis, and applications of materials with the sizes less than 100 nm (Mohamad et al. 2013). In recent

years, nanomaterials have been extensively discovered with unique properties and brilliant capabilities since they pave the way for developing multidisciplinary researches, and applying for solving many practical problems. Indeed, they have brought many advantages and desirable prospects for human life such as medicine, pharmaceuticals, agriculture, environment, catalysis, food, cosmetics, and electronics (Ghotekar et al. 2020). The main reason may rely on their tiny size, diverse structure, and many biochemical and physicochemical properties, which are suitable for many different fields. Among them, metallic/metal oxide nanoparticles are considered to be the most superior, possibly thanks to their large surface area to volume ratio, high biocompatibility, tunable synthesis, and high stability (Ahmed et al. 2016). This leads to the huge interest of researchers in the development and synthesis of nanoparticles.

To acquire the purposes of green synthesis and sustainable development, various approaches are still essentially considered. Physical and chemical synthesis methods are not necessarily optimal solutions due to many shortcomings of energy consumption, environmental pollution, and high risks for human health (Mohamad et al. 2013). Twelve principles of green chemistry are guidelines for researchers to take new steps toward green synthesis methods (Ivanković 2017). Green synthesis methods mainly aim to bring more environmentally friendly, healthily safe, and performance benefits than physical or chemical methods (Ahmed et al. 2016). Indeed, the green synthesis is highly preferable because this approach uses raw materials that are locally available, low-cost, and easy to collect. In particular, they considerably save the production cost of nanoparticles due to energy saving and simple routes without complicated equipment and machines (Cuong et al. 2022). There are three major biosynthetic pathways for nanoparticles, specifically from microorganisms, biomolecules, and plants. During the biogenic synthesis of nanoparticles, natural compounds found availably in the plant and microbial extracts act as reducing and stabilizing agents. These functional components allow to convert metal sources into nanoparticles (Dabhane et al. 2021). Although the green synthesis methods from microorganisms and biomolecules can bring certain successes, there are still many limitations and challenges in the production of nanoparticles. For example, these methods necessarily require a series of technically and safely serious conditions, whereas the rate of the overall process is very slow to suit for large-scale nanoparticles production (Ghotekar et al. 2021).

Plant extracts may be the best method for the biosynthesis of nanoparticles which can produce nanoparticles in larger amount within a short time with high efficiency and low production cost (Srikar et al. 2016). Plants are prevalently present in ecosystems and can be collected easily. They contain an amount of phytochemicals that can replace highly toxic, expensive, and environmentally harmful chemical reducing agents such as sodium citrate, sodium borohydride ($NaBH_4$), and ascorbate (Ahmed et al. 2016). Indeed, many studies indicated that phytochemicals such as polysaccharides, flavonoids, phenolic acids, and quercetins in plant extracts are capable of excellently reducing metal ions, e.g., Ag^+, Cu^{2+}, and Au^{3+} (Agarwal et al. 2017; Ong et al. 2018; Jadoun et al. 2021). Moreover, they can exhibit many capping, stabilizing, and chelating functions during the formation of nanoparticles. These biocompounds are also easily extracted from different plant parts such as leaves, flowers, stems, roots and other parts of plants, leading to the superiority of plants for the biosynthesis of nanoparticles (Beyene et al. 2017).

In addition to the highly effective green synthesis, plant synthesized nanoparticles make great contribution to the different fields. For water treatment, they can catalyze reactions that degrade toxic pollutants from the aquatic environment (Veisi et al. 2016; Rasheed et al. 2019; Pakzad et al. 2020). With their small size, high biocompatibility, high surface area, excellent stability, good versatility, and many outstanding capabilities, green nanoparticles are suitable for many medical applications such as antibacterial, antifungal, anti-cancer, and treatment of various diseases (Narendhran and Sivaraj 2016; Pansambal et al. 2017; Qasim Nasar et al. 2019; Youssif et al. 2019). For therapeutic effects, nanoparticles have discovered with their potentials for biomedical diagnostics and drugs delivery (Fazal et al. 2014; Sriramulu et al. 2018). Biosynthesized nanoparticles significantly contribute in the advancement of biomedical technology and environmental remediation.

Although the green synthesis of nanoparticles using plant extracts and their antimicrobial performance has been overviewed in the past literatures, their formation and antimicrobial mechanisms were not still insightful. Moreover, a very limited number of previous works profoundly elucidated the biomedical applications involving drug delivery, medical diagnostics, and antiaging of green nanoparticles. These potentials, in our view, are very fascinating and worth considered to widen the scope of the green nanoparticles. In this work, therefore, we aim to overview the green routes for synthesizing nanoparticles and place a great emphasis on the botanical route owing to the clear benignity, safety, cost-effectiveness, and high efficiency of plants (Fig. 1). Botanically synthesized nanoparticles are systematically elucidated from how they are synthesized to their superior applications in antibacterial, antifungal, anti-cancer, and biomedical applications. More importantly, the specific mechanisms in each application are also better clarified and profoundly discussed. Ultimately, the knowledge gaps, limitations, and challenges and prospects are pointed out to orientate further studies.

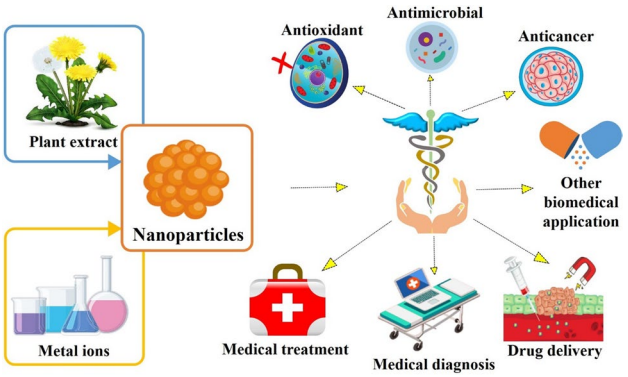

Fig. 1 Biosynthesis of nanoparticles from plant extract for biomedical applications

Synthesis of nanoparticles

General strategy

The unique properties of nanoparticles have fueled the research activities, yielding a wide range of practical utilizations including chemical sensing, heterogeneous catalysis, environmental remediation, nanotechnology, biomedical engineering, and agriculture. There is an increasing demand for tailoring and developing nanoparticles in the simplest pathway. At present, nanoparticles are synthesized by two different routes: "top-down" and "bottom-up" (Fig. 2). The former process is to reduce the size of the original bulk materials to new nano-sized ones through some common methods such as sputtering, chemical etching, and so forth (Jadoun et al. 2021). The latter process is the use of atoms, molecules to assemble or splice small particles together into a nano-sized material through some common methods such as the sol–gel process, green synthesis, and so forth (Rath et al. 2014). Synthesizing nanoparticles can be mainly conducted using chemical, physical and biological approaches. The following sections will vigorously articulate the strengths and weaknesses of each approach.

Physical methods

To synthesize nanoparticles, there are some widely used physical methods such as high-energy ball milling, electrospraying, laser ablation, physical vapor deposition, melt mixing, inert gas condensation, laser pyrolysis, and flash spray pyrolysis (Dhand et al. 2015; Vishnukumar et al. 2017). These methods mostly belong to the top-down approach by using mechanical energy or electrical energy to grind materials into small-size nanoparticles (Dhand et al. 2015). Two of the most noteworthy methods are evaporation and condensation, carried out in a tube furnace to produce metallic nanoparticles at atmospheric pressure (Abbasi et al. 2014). Although the physical methods are eco-friendly because they do not use toxic chemical substances, the grinding of materials is considerably energy-consuming and requires elaborate equipment, leading to high production cost, and difficulty of systematical scalability (Iravani et al. 2014).

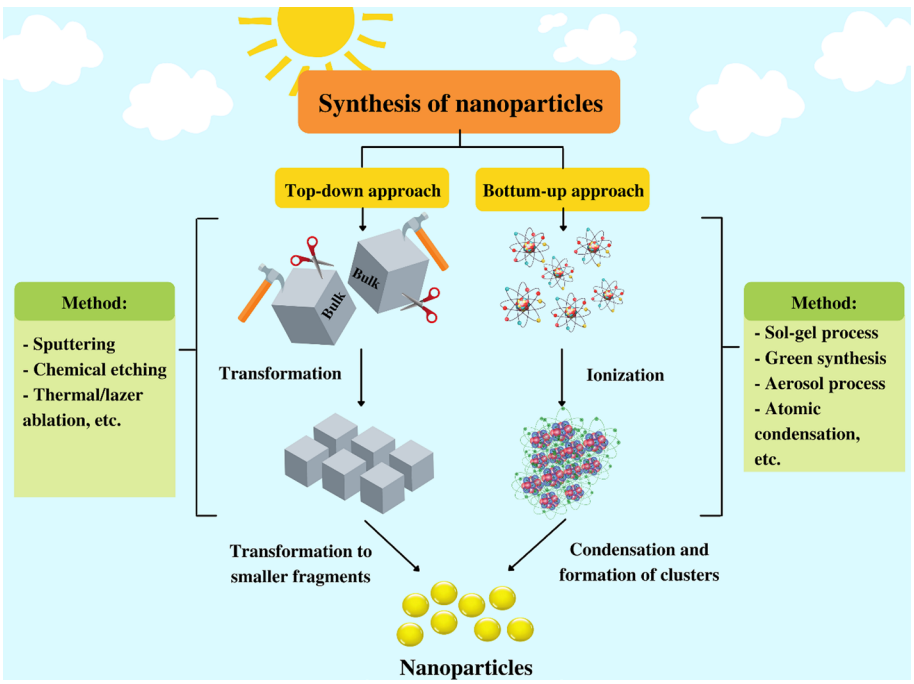

Fig. 2 Synthesis of nanoparticles by top-down and bottom-up methods

Chemical methods

The chemical methods are widely used to synthesize nanoparticles, involving sol–gel, hydrothermal, microemulsion, chemical reduction, and precipitation (Jamkhande et al. 2019). Among them, sol–gel is the most commonly used technique due to tunable implementation and high-yield production. Metal precursors and chemical reducing agents are used for the synthesis (Abinaya et al. 2021). However, chemical techniques not only increase the cost of production but also impose the burden of hazardous waste on the environment and human health (Bandeira et al. 2020). To solve this drawback, the green synthesis of nanoparticles from biological methods has paid great attention during the past decades.

Biological methods

Biological methods adopt bioreducing agents from microbes, e.g., bacteria, fungus, algae and protozoa, biomolecules or macromolecules, e.g., proteins, enzymes, nucleic acids and carbohydrates, and plant extracts to synthesize nanoparticles (Fig. 3). The use of these biological substrates is intended to replace toxic chemical reductants and chemical stabilizers (Abinaya et al. 2021). Biological methods have also many advantages over chemical methods since they are more benign and highly biocompatible. Indeed, microorganisms can secrete enzymes that play a role in reducing and stabilizing metal nanoparticles. However, the microbial synthesis of nanoparticles presents more obstacles than other biological methods because it exhibits a range of difficulties in culturing and maintaining microbial growth (Srikar et al. 2016). In terms of biomolecules for synthesizing nanoparticles, enzymes are the representatives which can bind with metal ions and reduce them to form nanoparticles. They can bind with metal ions and reduce them to form nanoparticles. The main limitation of the biomolecules-mediated synthesis is, however, the poor stability of nanoparticles and prolonged duration (Palomo 2019).

Meanwhile, plant extract-mediated synthesis discloses some large advantages because various phytochemicals presenting in the plant extracts (e.g., polyphenols, alkaloids, flavonoids, and alcoholic) possibly act as biocapping and bioreducing agents in the fabrication process, enhancing the stability of the nanoparticles (Lee et al. 2014; Ikram 2015). For example, Rafique et al. (2017) showed that plant extracts to synthesize nanoparticles bring higher efficiency, easy handling, safer and rapid than other biological methods.

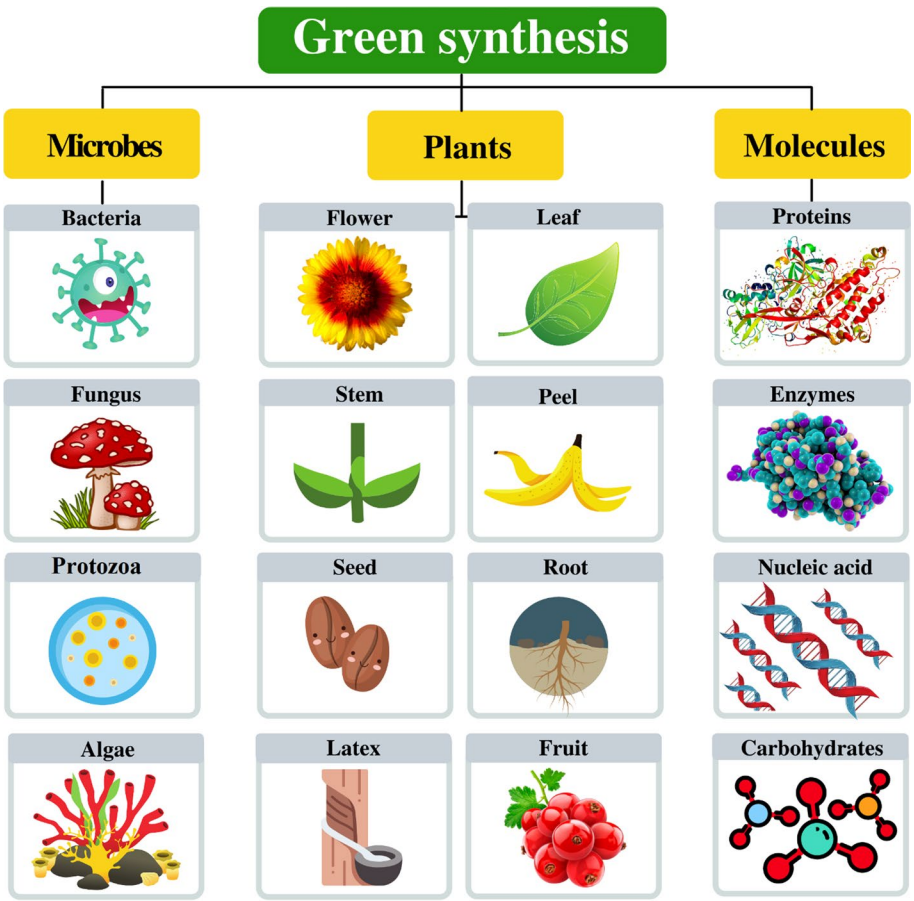

Fig. 3 Green synthesis of nanoparticles using microbes, plant tissues, and biomolecules

Phytochemicals are usually extracted from different parts of plants involving leaves, flowers, roots, seeds, stems, bark, peel, and latex. These compounds have long been known to be excellent antioxidants, thus they are utilized in the reduction process to synthesize various nanoparticles. Singh et al. (2019a, b, c) demonstrated that MgO nanoparticles are formed under the role of phytochemicals as antioxidants. In other words, these phytochemicals are capable of converting the metallic precursors into respective nanoparticles. As another demonstration, Kesharwani et al. (2009) proved that amino acids, alkaloids, polysaccharides, reducing sugar compounds participated in reducing Ag^+ to Ag^0.

In addition to the main role as a reducing agent, the chemical compositions in plant extract also aid to prolong the life of nanoparticles by coverage of nanoparticles, and thus increasing their stability. For example, Dubey et al. (2009) took advantage of flavonoid and terpenoid compounds in *E. hybrida* extract for the longer stability of the silver nanoparticles. Mittal et al. (2013) confirmed the presence of quinol and chlorophyll pigments in the plant extract is accountable for the stabilization of such nanoparticles. More interestingly, the chemical compositions also hinder the agglomeration of nanoparticles during the synthesis, leading to good dispersion and more active sites (Abinaya et al. 2021). Besides, the concentration of extract along with other fabrication conditions such as temperature, pH, or time directly affects the size of nanoparticles. Elemike et al. (2017a, b) investigated the potential of *L. africanum* extracts for synthesizing Ag nanoparticles. The results showed that Ag nanoparticles acquired a smaller size (8–35 nm) upon the optimal pH range from 6.8 to 7 and the temperature of 65 °C. At the concentration ratio of leaf extract/ionic salt solution (1:10), the nanoparticle formation rate was the fastest. From the above arguments, plant extracts can be excellent reducing agents for the synthesis of nanoparticles with high stability, low clustering, and good dispersibility.

Chemical composition of plants

As mentioned, plant extracts bring many benefits and effectiveness to the synthesis of nanoparticles, which could be thanks to the intrinsic presence of phytochemicals such as polyphenols, flavonoids, sugars, terpenes, and so forth originated from the plant species. Phytochemicals can exist in different tissues of the plant such as leaves, flowers, roots, stems, seeds, pods, resins, and bark (Vishnukumar et al. 2018). Table 1 shows the types of phytochemicals presenting in different plant parts. In general, flavonoids, phenolics, quercetin, and terpenoids are main phytochemicals in most plants. They contribute essentially to the reduction, capping and stabilization of nanoparticles during synthesis. For example, Pansambal et al. (2017) confirmed that polyphenols, saponins, flavonoids, coumarins, volatile oils, tannins, and sterols from *A. hispidum* act as capping and chelating agents for the synthesis of CuO nanoparticles. Sundararajan and Ranjitha Kumari (2017) proved the major role of polyphenols and flavonoids in *A. vulgaris* leaf as a bio-capping agent for Au nanoparticles synthesis. In another study, Khan et al. (2020) discovered that the presence of kaempferol, quercetin, caffeic acid, dihydrokaempferol in *P. undulata* extract showed as effective metal reducing agents during the formation of Au and Ag nanoparticles. Chandraker et al. (2019) published that the leaves of *A. conyzoides* contain alkaloids, flavonoids, terpenoids, saponins, tannins, which are all capable of reducing, capping and stabilizing Ag nanoparticles. Among them, tannin and tannic acid are prominent phytochemicals for the efficient reduction process. These studies showed the importance of phytochemicals in plant extracts for the synthesis of nanoparticles.

Role of phytochemicals for nanoparticles biosynthesis

The presence of the phytochemicals from plant extract can benefit the adsorptive, catalytic, biomedical, and biocompatible properties of nanoparticles. For the adsorptive activity, the phytochemicals enrich the surface of nanoparticles by providing new functional groups (Abdullah et al. 2021). Thus, they enhance the surface functionalization and create more physicochemical interactions (e.g., electrostatic interaction, π–π interaction, hydrogen bonding, and so forth) (Wu et al. 2020). For example, Hammad and Asaad (2021) recently compared the methylene blue dye sorption affinity between biologically and chemically synthesized FeO nanoparticles. In this study, iron nanoparticles material produced from *C. vulgaris* extract exhibited a higher surface area (85.7 m^2/g) than the one (71.6 m^2/g) produced by the chemical precipitation method. The authors implicated that the phytochemicals from *C. vulgaris* significantly reduced the particle size (4.47 nm) of FeO nanoparticles in comparison with the chemical synthesis case (9.07 nm). More importantly, the maximum dye adsorption capacity obtained by biologically synthesized FeO nanoparticles (29.14 mg/g) was significantly higher than that of chemically synthesized ones (19.08 mg/g). This confirmed the main role of phytochemicals in enhancing the surface functionalization and improving the adsorption performance.

For the catalytic activity, the presence of phytochemicals aids in lowering the band gap energy of the nanomaterials (Muthuvel et al. 2020a). This results in decreasing the electron-splitting activation energy, promoting the rapid and efficient separation of electrons, and facilitating the formation of reactive oxygen species ($^{\bullet}OH$, $^{\bullet}O_2^-$, H_2O_2) (Khan et al. 2019). In addition, the phytochemicals on the surface of the

Table 1 Phytochemicals present in different parts of the plant, for the synthesis of nanoparticles

Plant (common name)	Plant tissues	Nanoparticles	Phytochemicals	References
C. pumilio	Aerial	Ag	Polyphenols, flavonoid, rutin, quercetin, myricetin, kaempferol and gallic acid	(Mostafa et al. 2019)
A. hispidum (Bristly starbur)	Leaf	CuO	Saponins, coumarins, phenols, flavonoids, volatile oils, tannins and sterols	(Pansambal et al. 2017)
A. vulgaris (Mugwort)	Leaf	Au	Polyphenols, flavonoids and terpenoid	(Sundararajan and Ranjitha Kumari 2017)
P. undulata (False fleabane)	Aerial	Au, Ag, Au–Ag	Kaempferol, quercetin, caffeic acid, dihydrokaempferol	(Khan et al. 2020)
A. conyzoides (Billygoat –weed)	Leaf	Ag	Alkaloids, flavonoids, terpenoids, saponins, cardiac glycosides, resins, steroids, phenols, amino acid	(Chandraker et al. 2019)
A. hispidum (Bristly starbur)	Leaf	Ag	Saponins, coumarins, phenols, flavonoids, volatile oils, tannins and sterols	(Ghotekar et al. 2019)
P. vulgaris (False fleabane)	Flower, leaf, and stems	AgCl	Polyphenols, flavonoid, amino acid, alcohols	(Sharifi-Rad and Pohl 2020)
C. intybus (Chicory)	Leaf	Ag	Terpenoids and phenols	(Behboodi et al. 2019)
S. indicus (East Indian globe thistle)	Leaf	Au	Isoflavone, glycosides, protein	(Balalakshmi et al. 2017)
V. amygdalina (Bitter leaf)	Leaf	$Zn_{1-x}Cu_xO$	Flavonoids, glycosides, saponins, and alkaloids	(Okeke et al. 2020)
O. genistifolia (Klein perdekaroo)	Leaf	Ag/AgCl	Polyphenols, ancaloid, tannin, flavonoid, saponin, glycoside, terpenoids, steroid, protein, carbohydrate	(Okaiyeto et al. 2019)
X. strumerium (Rough cocklebur)	Leaf	Ag	Alkaloid, flavonoid and terpenoid	(Mittal et al. 2017)
A. pseudocotula (Common chamomile)	Aerial	Fe_3O_4	Fatty acids, sesquiterpenoids, diterpenoids, polyphenols compounds, coumarins and terpenoids	(Abdullah et al. 2018)
A. annua (Sweet wormwood)	Stem, bark	ZnO	Terpenoids, flavonoids, caffeoylquinic acids, coumarins, acetylenes and sterols	(Wang et al. 2020)
P. leubnitziae (Stinkbush)	Whole plant	Ag	Flavonoids and alkaloids	(Mofolo et al. 2020)
W. chinensis (Sphagneticola calendulacea)	Leaf	Ag	Polyphenols, flavonoids, triterpenoids, wedelolactones	(Paul Das et al. 2018)
A. factorovskyi	Leaf	Ag	Polyphenols and terpenoids	(Al-Otibi et al. 2020)
A. ciniformis	Leaf	Ag	Alcohols, phenols, alkaloids, tannins, terpenes and terpenoids	(Aslany et al. 2020)
V. amygdalina (Bitter leaf)	Leaf	MnO_2	Flavonoids, alkaloids, steroids, terpenoids, glycosides, tannins, phenols, saponins	(Dessie et al. 2020)
S. costus (Putchuk)	Root	MgO	Sesquiterpenes, alkaloid, triterpenes, lignans and tannin	(Alavi and Karimi 2017a)

nanoparticles also hinder the electron recombination process (Ganesan et al. 2020). For example, *S. nigrum*-derived ZnO nanoparticles yielded high efficiency of 98.89%, compared with 81.94% of chemically produced ZnO nanoparticles for the photocatalytic degradation of methylene blue (Muthuvel et al. 2020b). In another study, Abdullah et al. (2021) indicated the excellent photocatalytic ability of ZnO nanoparticles biofabricated from *M. acuminata* peel for degrading basic blue 100%, while that of chemically synthesized ZnO nanoparticles obtained only 87.71%.

For the biomedical activity, the phytochemicals such as phenolic and flavonoid compound act a capping layer around the nanoparticles, leading to their high durability in contact with bacterial surfaces (Muthuvel et al. 2020a). These

phytochemicals diversify the surface chemistry of nanoparticles, increasing their binding to bacterial cells through electrostatic interactions (Nithya and Kalyanasundharam 2019). Also, they were more capable of supporting the nanoparticles to generate reactive oxygen species than those synthesized by chemical methods (Virmani et al. 2020). In addition, Muthuvel et al. (2020a) pointed that some phytochemicals in plant extracts such as terpenoids, tannins, flavonoids, alkaloids, carbohydrates, saponins have high bactericidal abilities. Accordingly, the inhibition zones of chemical CuO nanoparticles for *B. subtilis* and *E. coli* were 2 and 3 mm, respectively, considerably lower than those (11 and 12 mm) of CuO nanoparticles produced from *S. nigrum* leaves. Nithya and Kalyanasundharam (2019) synthesized ZnO nanoparticles from *C. halicacabum* with inhibition zones for *S. aureus* and *P. aeruginosa* about 20 and 19 mm, while the chemically synthesized ones acquired only 13 and 12 mm, respectively. This may be due to alkaloids acting as a capping agent to bind nanoparticles with the bacterial surface. In another study, Ni nanoparticles from *D. gangeticum* exhibited the inhibition zone of 5.67 mm, compared with 5.14 mm of chemical ZnO nanoparticles against *S. aureus* (Sudhasree et al. 2014). In terms of anticancer activity, Virmani et al. (2020) proved the contribution of phytochemicals in bioactivity of Au nanoparticles. The survey was carried out for HeLa cells with 50% cell viability for green Au nanoparticles and 80% for chemical Au nanoparticles. These findings pave the way for the next steps of nanoparticles from plant extracts in biomedical applications.

For the biocompatibility, Amooaghaie et al. (2015) demonstrated non-toxic phytochemicals coating around the nanoparticles to both reduce the toxicity of nanoparticles and improve their biocompatibility. In this study, Ag nanoparticles produced from *N. sativa* gave the rate of apoptosis in bone stem cells of mice 11 times lower than that of chemical Ag nanoparticles, indicating less cytotoxicity and better biocompatibility of green nanoparticles. Dowlath et al. (2021) performed the investigation for peripheral blood mononuclear cells and compared the biocompatibility of two types of FeO nanoparticles synthesized from *C. halicacabum* and the chemical method. The results showed that the cell viability of green FeO nanoparticles was 84.04%, significantly higher than that of chemical FeO nanoparticles. With promising biocompatibility findings, nanoparticles are suitable for biomedical applications in drug delivery, diagnosis, and treatment of diseases.

For stability, thanks to the coating by phytochemicals, green nanoparticles are more stable than chemically synthesized ones. To elucidate more, the zeta potential of nanoparticles can be measured. If the zeta potential of nanoparticles receives a more negative or positive value, they repel each other more strongly; hence, exhibiting lower clustering and higher stability. Normally, nanoparticles with the zeta potential was more negative than –30 or more positive than 30 stabilize well (Jameel et al. 2020). It was found the zeta potential of Pt nanoparticles from *P. farcta* was higher negative (− 34.6 mV) than that of chemically produced ones (− 15.6 mV). At the same trend, Nithya and Kalyanasundharam (2019) found the zeta potential obtained at –32.06 and –17.89 mV for ZnO nanoparticles from *C. halicacabum*, and chemical method, respectively. The above outcomes made the deduction of higher stability of green nanoparticles than that of chemically produced ones. Mousavi-Khattat et al. (2018) observed the change of durability on zeta potential histograms between green and chemical Ag nanoparticles. They found the remarkable stability of the green Ag nanoparticles after 2 months. Thus, the phytochemicals enhanced the stability and the long shelf life of nanoparticles, enabling them to apply intensively. To sum up, phytochemicals have supplied many benefits for nanoparticles in terms of adsorptive, catalytic, biomedical, stability, and biocompatible properties.

Mechanisms for fabricating nanoparticles using plant extracts

Ag, Au, and Pt nanoparticles

The general mechanism of synthesizing the Ag, Au, and Pt nanoparticles from plant extracts is the bioreduction by biomolecules originating from plants (Fig. 4). Plant extracts often contain functional groups (e.g., carbonyl, hydroxyl, and amine) to react with metal ions and reduce these to nanoparticles with different shapes and sizes. For example, some compounds involving flavonoids, protein, sugars and terpenoids or other bioactive substances possibly participated in the reduction in Ag^+ to Ag^0 (Borase et al. 2014). This was demonstrated by evaluating the significant change in the content of sugars and flavonoids before and after the reduction reaction. Ghotekar et al. (2018) determined the components of *L. leucocephala* leaf extract including tannins, saponins, carbohydrates, coumarins, steroids, flavonoids, phenols, and amino acids. Thanks to the antioxidant groups of polyphenols in *L. leucocephala* extract, Ag nanoparticles could be formed through the reduction in Ag^+. In addition, the authors demonstrated that various substances such as gallic acid, β–sitosterol, mimosine, caffeic acid, and chrysoenol also play a key role in stabilizing the of Ag nanoparticles. In addition, Zheng et al. (2013) revealed that the reduction in Pt(II) into Pt(0) nanoparticles was dependent on many factors such as temperature, reducing sugars, flavonoid contents. Another research also showed that plant extracts exhibited a possible mechanism for the reduction and stabilization of the chloroaurate ions ($AuCl_4^-$) to Au nanoparticles (Huang et al. 2011).

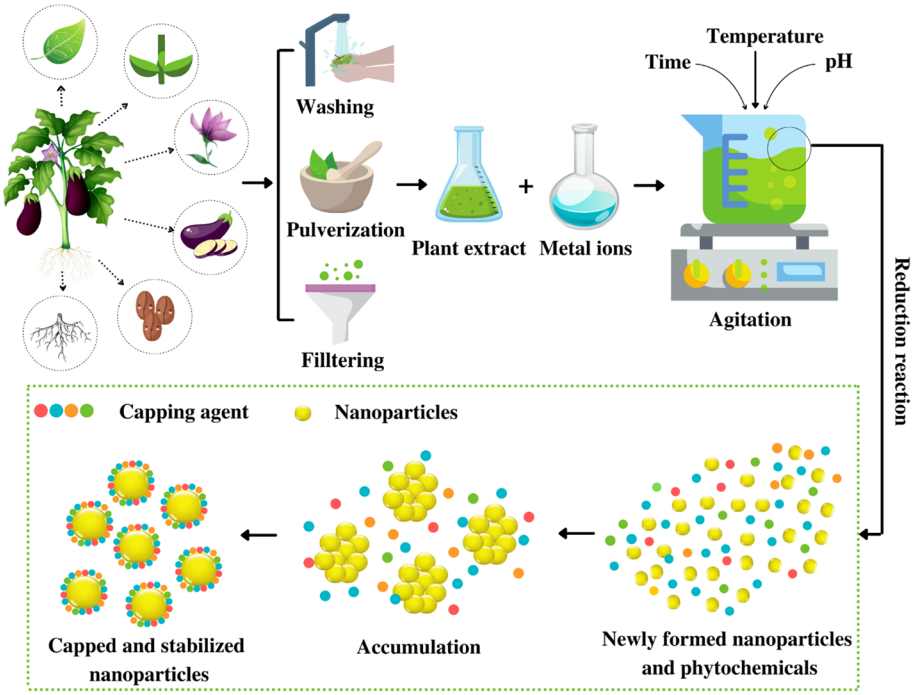

Fig. 4 Mechanism of synthesis of nanoparticles from plant extracts

Cu nanoparticles

Murthy et al. (2020) documented the synthesis of Cu nanoparticles from *H. abyssinica* plant extracts. Phenolic compounds, anthraquinone glycosides, and tannins, which are known to be high antioxidants, bind to Cu^{2+} ions in the precursor salt solution $Cu(NO_3)_2$ and reduce to the Cu^0 form. After the reduction, these biomolecules played a fundamental role in enveloping and stabilizing the Cu nanoparticles. In another study, Naghdi et al. (2018) speculated that the concise mechanism with the incorporation of quercetin, a polyphenol found in *C. reflexa* leaf extract for the formation of Cu nanoparticles. Firstly, Cu^{2+} would oxidize quercetin, forming the intermediate Cu(I)–quinone complex. Cu(I) in this complex continued to oxidize quercetin again to form Cu nanoparticles and quinone compounds. Cu nanoparticles could be highly stabilized with the encapsulation of phytochemicals in the extract. As a consequence, the ratio between Cu^{2+} and plant extract concentration affect the formation of Cu nanoparticles. Indeed, Nagar and Devra (2018) suggested that the precursor salt concentration could significantly affect the shape and particle size of the Cu nanoparticles biosynthesized from *A. indica* leaf extract. Specifically, when the concentration of $CuCl_2$ increased from 6×10^{-3} mol/L to 7.5×10^{-3} mol/L, the particle size also increased from 48.01 to 78.51 nm, respectively. The authors explain that a higher amount of $CuCl_2$ will supply larger amount of nucleus, leading to a higher degree of agglomeration of Cu nanoparticles.

ZnO nanoparticles

The mechanism of forming other green oxide metal nanoparticles such as ZnO nanoparticles is also significantly dependent on phytochemicals in plant extracts. Król et al. (2019) studied ZnO nanoparticle fusion with the aid of biomolecules from *M. sativa* extract. Zinc aqua complex can exchange with their water molecules when binding to protein ligands due to the coordination chemistry of zinc. On the other hand, flavonoids (e.g., quercetin, rutin and galangin) can chelate with Zn^{2+} ions through specific metal ion binding sites (Fig. 5). The Zn–flavonoid complex was formed and calcined at high temperature to form ZnO nanoparticles. In another study, Kumar et al. (2014) demonstrated that phytochemicals such as flavonoids, limonoids, and carotenoids containing free –OH and –COOH can react with $ZnSO_4$ to form the Zn–(flavonoid, limonoids, carotenoid) complex. This complex is then transferred into a furnace at 150 °C to produce ZnO nanoparticles.

Many operating factors also have a great impact on their morphology and particles size. Take temperature as an example, Hassan Basri et al. (2020) studied the effect of synthesis temperature on the morphology of ZnO nanoparticles produced from the pineapple peel extract. At the synthesis temperature of 60 °C, the as-obtained ZnO nanoparticles produced a combination of spherical and rod-shaped structures. Meanwhile, the synthesis condition at 28 °C produced ZnO nanoparticles with a spherical flower-shaped structure. Considering another factor such as extraction concentration, green ZnO particles tended to decrease the size as the

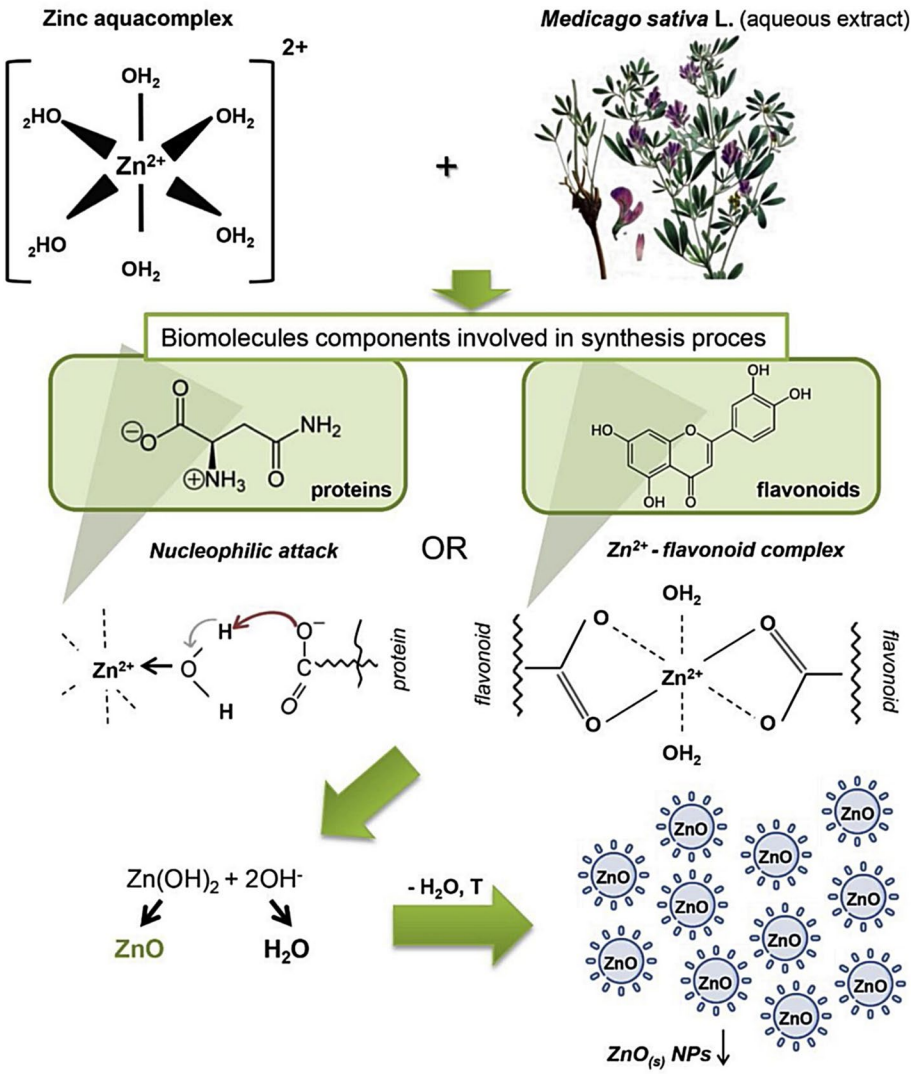

Fig. 5 Formation mechanism of ZnO nanoparticles from *M. sativa* extract through the complexation of zinc and flavonoid or nucleophilic attack. Reproduced with the permission of Elsevier from the reference (Król et al. 2019)

extract concentration increased. Indeed, Soto-Robles et al. (2019) showed that the particle size of ZnO nanoparticles was 5–12 nm in the condition using 8% concentration of *H. sabdariffa* extract, compared with 20–40 nm for 1% concentration condition. As a consequence, the control of operating factors such as temperature and extraction concentration is substantial to produce the green nanoparticles with expectable properties.

MgO nanoparticles

The synthesis mechanism of MgO nanoparticles is also based on the biocapping and chelating mechanism of biomolecules in plant extracts. Specifically, Mg^{2+} ions in the precursor can be chelated with biomolecules to form complexes with metals (Singh et al. 2019a). Isoleucine acid is a phytochemical originating from *L. acidissima* fruit extract and accounts for forming MgO nanoparticles with high stability (Nijalingappa et al. 2019). In this study, the isoleucine–MgO complex was formed after the binding of magnesium nitrate to isoleucine acid. Next, the complex was calcined at high temperature (500–800 °C) so that MgO nanoparticles could be formed with good dispersion and high stability. Suresh et al. (2018) described the possible mechanism of MgO nanoparticles synthesis from insulin plant extracts as follows: (i) diosgenin in the extract reacts with magnesium nitrate salt solution to form complexes with weak hydrogen bonds; (ii) treat this complex at a temperature of about 80 °C to form the precipitation in the form of hydroxide; (iii) the product MgO nanoparticles was created by calcination at 450 °C.

Considering the operating factors, the structure of MgO can be significantly contingent on the pH of the extract solution. In a recent study, Jeevanandam et al. (2020) found that the higher the pH was, the more negative the zeta potential value of MgO nanoparticles had. This means that the stabilization of green MgO nanoparticles increased. By contrast, an unfavorable condition of pH can lead to an increase in the

agglomeration of the MgO nanoparticles, thereby, increasing their particle size. Indeed, the authors reported the characteristic results of MgO nanoparticles at various pH values. At pH 3, hexagonal MgO nanoparticle size was determined to be smaller than 44 nm, but at pH 5 and pH 8, their sizes were higher, at 50.75 and 58.77 nm, respectively. As such, the adjustment of pH is an important step to drive the structure of green MgO nanoparticles.

CuO nanoparticles

For the synthesis of CuO nanoparticles, the process can be supplemented with an additional step by the calcination at a high temperature under oxygen atmosphere (Fig. 6). This condition allows to convert zero-valent Cu into CuO nanoparticles. For instance, Nagore et al. (2021) demonstrated natural biomolecules present in *P. longifolia* leaf extract could be chelated with Cu^{2+} at 85 ℃ so that the chemical components bonded with Cu^{2+} ions. The authors determined these compounds including saponins, flavonoids, tannins, polyphenols, steroids, and alkaloids. After the chelating process, the complex could be calcinated at 400 ℃ in a furnace in the presence of air flow. As a consequence, the CuO crystals are formed. The study also confirmed the important role of phytochemicals in the synthesis of CuO nanoparticles.

Characterization of nanoparticles

Nanoparticles have characteristics in terms of shape, size, surface area, or dispersion. The methods of analyzing the structure of nanoparticles involve a variety of techniques such as UV–Vis spectroscopy, Fourier transform infrared spectroscopy (FT–IR), scanning electron microscopy (SEM), transmission electron microscopy (TEM), energy-dispersive spectroscopy (EDS), and so forth (Fig. 7). State-of-the-art

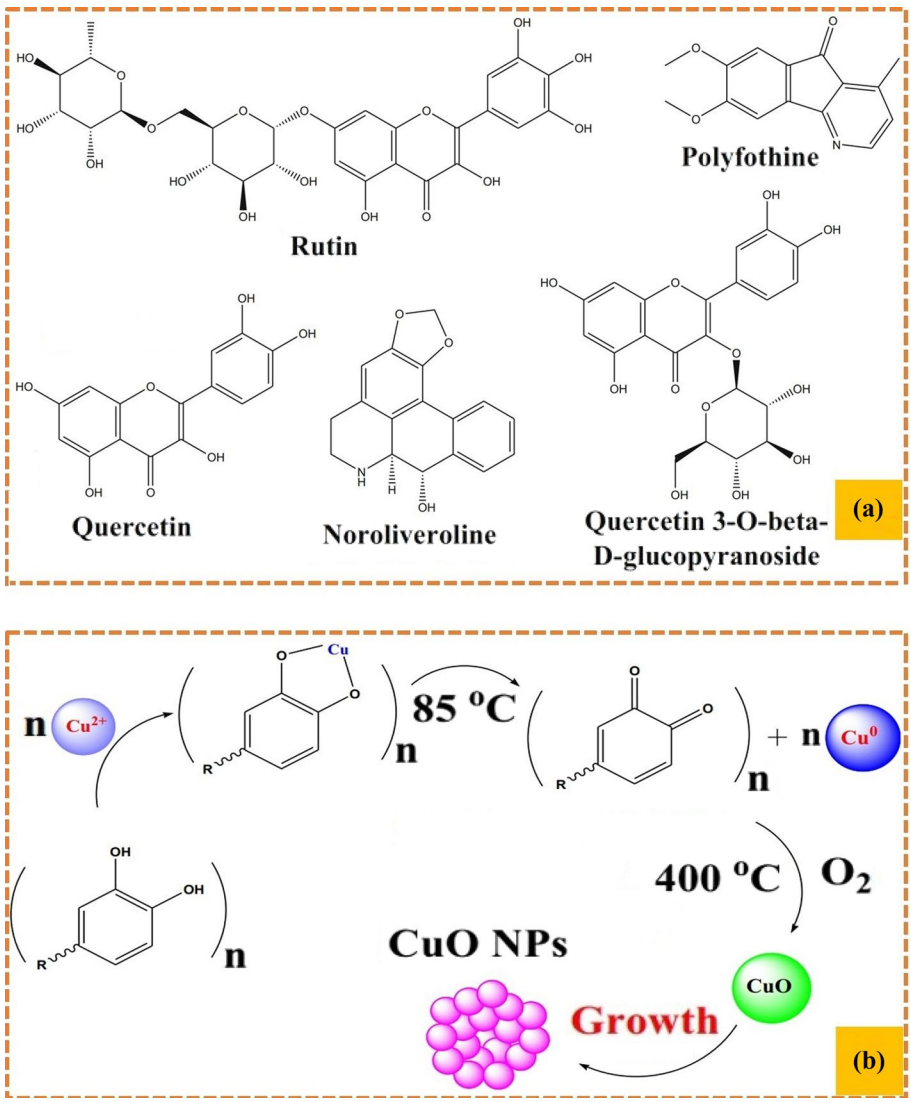

Fig. 6 Main compounds such as rutin, polyfothine, quercetin and noroliveroline in *P. longifolia* leaf extract (**a**); plausible mechanism of green synthesis of CuO nanoparticles using phytochemicals from the *P. longifolia* leaf extract (**b**). Reprinted with the permission of Springer Nature from the reference (Nagore et al. 2021)

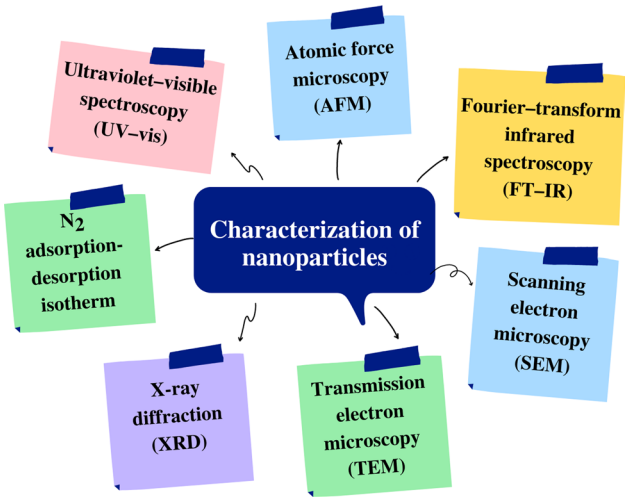

Fig. 7 Characteristic techniques for determining the structure of nanoparticles

structural characterization techniques have greatly supported the study of the synthesis of nanoparticles as well as the observation and determination of the characteristics of the nanoparticles. Table 2 lists the characterization of nanoparticles biosynthesized from plant extracts.

Ultraviolet–visible spectroscopy

Ultraviolet–visible (UV–Vis) spectroscopy is a substantial technique to determine optical properties, the generation and stability of nanoparticles (Förster 2004). This technique is a simple, easy to use, fast, sensitive and selective technique. It involves quantifying the amount of ultraviolet or visible radiation absorbed by a component in a solution (Rajeshkumar and Bharath 2017). When a sample solution containing only the crude extract was added, no typical peak was present. Meanwhile, the botanically synthesized nanoparticle sample gave the typical peaks at the different wavelength region. Table 2 shows some characteristic properties of nanoparticles synthesized from different parts of various plants. Accordingly, the adsorption band of Ag nanoparticles is ranged from 417 to 448 nm (Francis et al. 2018; Yazdi et al. 2019; Ahn et al. 2019; Seifipour et al. 2020). For CuO nanoparticles, the maximum wavelength ranges between 236 and 670 nm (Pansambal et al. 2017; Muthamil Selvan et al. 2018; Nordin and Shamsuddin 2019; Singh et al. 2019c). In addition, MgO and ZnO nanoparticles exhibit the typical summit at the wavelengths of 250–300 nm, and 420–330 nm, respectively (Alavi and Karimi 2017a; Dobrucka 2018; Hameed et al. 2019; Wang et al. 2020; Rajapriya et al. 2020). In addition to demonstrating the presence of nanoparticles synthesized from plant extracts, UV–Vis spectrum can also confirm their stability. By monitoring the UV–Vis spectra of the samples after regular periods, the position of the peaks is mostly constant, indicating high stability of the nanoparticles (Fig. 8a). Many works revealed that the nanoparticles have high stability up to many days or many months (Balashanmugam and Pudupalayam Thangavelu 2015).

N_2 adsorption–desorption isotherm

The nitrogen adsorption–desorption isotherm is used to measure the amount of N_2 that adsorbs onto the nanoparticles surface. This reflects the plot of relative pressure versus volume of nitrogen at the temperature 77 K (Fig. 8b). Based on N_2 adsorption–desorption isotherm, the surface area can be determined by Barrett–Joyner–Halenda (BJH) or density functional theory (DFT) method. The surface area of nanoparticles can be well beneficial for explaining the catalytic, adsorption and different properties. Many studies reported that nanoparticles produced from plant extract exhibited the large surface area (52.6–137.4 m^2/g) (Stan et al. 2017; Singh et al. 2019c; Sethy et al. 2020; Lakshminarayanan et al. 2021). It can be understood that phytochemicals in plant extracts reduce the aggregation of newborn nanoparticles, thereby increasing their surface area, which contributes to the excellent properties and applications of nanoparticles.

Fourier transform infrared spectroscopy

Fourier transform infrared (FT–IR) spectroscopy is used to learn about the surface chemistry of nanoparticles. Specifically, this technique can detect functional groups derived from biomolecules, which contribute to the synthesis of nanoparticles. The resulting spectrum exhibits absorption and transmission by generating a sample molecular fingerprint, which changes the identity of the sample (Rajeshkumar and Bharath 2017). Yazdi et al. (2019) detected many functional groups existing in the surface of Ag nanoparticles produced from *H. trichophylla* flower extract, involving O–H (3397–3410 cm^{-1}), C–H (2921 and 2847 cm^{-1}), C–N (1626 cm^{-1}), N–O (1385 cm^{-1}), and so forth. Sundararajan and Ranjitha Kumari (2017) reported the presence of a wide range of chemical bonds belonging to alcohols, alkanes, aldehydes, and amines on the surface of Au nanoparticles synthesized from *A. vulgaris* extract. These evidences may provide the main hypothesis for the existence of phytochemicals that take part in the formation of nanoparticles.

Scanning electron microscopy

The morphology of nanoparticles is very diverse and important to better understand the structure of nanoparticles. While the atomic force microscopy (AFM) technique produces three-dimensional images with many visualizations (Falsafi et al. 2020), scanning electron microscopy (SEM)

Table 2 Characterization of nanoparticles biosynthesized from plant extracts

Plant name (common name)	Part	NPs	λ_{max} (nm)	Particle size (nm)	Morphology	Chemical bonds	References
A. haussknechtii	Leaf	Ag, Cu, TiO_2	340–350 (Ag),200–300 (Cu), 400 (TiO_2)	10.69 (Ag), 35.36 (Cu), 92.58 (TiO_2)	Irregular (Ag), spherical (Cu, TiO_2)	N–H, C–H, C=C, C–H, C–Cl, C–O, C–Cl	(Alavi and Karimi 2017b)
H. trichophylla	Flower	Ag	448	20–50	Spherical	O–H, C–N, C–C, N–O, C–N, C–Br	(Yazdi et al. 2019)
T. farfara (Coltsfoot)	Flower	Ag, Au	416 (Ag), 538 (Au)	13.57 (Ag), 18.20 (Au)	Spherical	Not reported	(Lee et al. 2019)
E. scaber (Elephant's foot)	Leaf	Ag	420	37.86	Spherical	O–H, C=O, C=C	(Francis et al. 2018)
C. cernuum	Whole plant	Ag	430	13,0	Spherical	Not reported	(Ahn et al. 2019)
S. nodiflora (Node-weed)	Leaf	Ag, Au	413 (Ag), 535 (Au)	19.4 (Ag), 22.01 (Au)	Spherical (Ag), Spherical, triangular (Au)	–OH, C=O, –C–O–C, C–O	(Vijayan et al. 2018)
T. officinale (Dandelion)	Leaf	Co	464	50–100	Spherical	–OH, C–H, –C=O–, C–N, C–O	(Rasheed et al. 2019)
T. collinus (Goats-beard)	Whole plant	Ag	400	7–18	Spherical	–OH, –NH, C–O, –NH_2, C–C	(Seifipour et al. 2020)
S. quettense (Podlech)	Whole plant	Ag	448	48.40– 55.35	Spherical	N–H, O–H, C–O, –C–H, C≡N,–C=C–,C–O, C–N	(Qasim Nasar et al. 2019)
G. tournefortii (Tumbleweed)	Leaf	Au	528	40–45	Spherical	C=C, C=O, –C–O, –C–O–C	(Zhaleh et al. 2019)
C. pumilio	Aerial parts	Ag	446	6–8	Spherical	O–H, –CH, C=O, C–O–C, C=O	(Mostafa et al. 2019)
A. hispidum (Bristly starbur)	Leaf	CuO	390	5–25	Spherical	C–H, C=C, O–H, C–O, Cu–O	(Pansambal et al. 2017)
A. vulgaris (Mugwort)	Leaf	Au	560	12.0	Spherical, triangular, hexagonal	O–H, C–H, N–H, C–N, C–O	(Sundararajan and Ranjitha Kumari 2017)
Pulicaria undulata L. (False Fleabane)	Aerial parts	Au, Ag, Au–Ag	430 (Au), 540 (Ag), 490 (Au–Ag)	10–20	Spherical	O–H, C–H, C–C, C–O	(Khan et al. 2020)
A. conyzoides (Billygoat –weed)	Leaf	Ag	443	14–48	Spherical	N–H, C–H, C=O, C–OH	(Chandraker et al. 2019)
A. hispidum (Bristly starbur)	Leaf	Ag	417	25–45	Quasi-spherical	–OH, C–H, C=O, C–O	(Ghotekar et al. 2019)
P. vulgaris (False fleabane)	Flower, leaf, stem	AgCl	460	28.6	Spherical	C=O, C–Cl, C=C	(Sharifi-Rad and Pohl 2020)
A. turcomanica (Mugwort)	Leaf	Ag	430	20–60	Spherical	O–H, C–H, C=O, C–O–C	(Mousavi et al. 2018)
D. anomala (Stomach bush)	Root	Ag	424	8.724	Round, rod-like, hexagonal, uneven shapes	–OH, –NH, C=C, C–O–C, =C–H, C=O, N–H	(Tripathy et al. 2020)
C. intybus (Chicory)	Leaf	Ag	Not reported	17.17	Spherical	O–H, C–H, C=C, C–H, C–O–C	(Behboodi et al. 2019)

Table 2 (continued)

Plant name (common name)	Part	NPs	λ_{max} (nm)	Particle size (nm)	Morphology	Chemical bonds	References
S. rebaudiana (Sugarleaf)	Leaf	CeO_2–Ni	Not reported	10.56	Spherical	Not reported	(Khatami et al. 2019)
T. officinale (Common dandelion)	Leaf	Ag	546	5–30	Spherical	C=C, C=O, C–OH, –NH_2, –OH	(Saratale et al. 2018)
S. indicus (East Indian globe thistle)	Leaf	Au	531	25	Spherical	–OH, C–H, –C=O, –C–O–C, C–H, N–H, C–Cl	(Balalakshmi et al. 2017)
S. marianum (Blessed thistle)	Whole plant	ZnO, Ag–ZnO	420 (ZnO), 347 (Ag–ZnO)	31.2 (ZnO), 35.3 (Ag–ZnO)	Quasi-spherical (ZnO), spherical (Ag–ZnO)	–OH, Zn–O, C=C, C–N, C–H	(Hameed et al. 2019)
E. odoratum (Chromolaena odorata)	Leaf	Ag/Ag_2O	424	23.6	Spherical	Not reported	(Elemike et al. 2017a), b
V. amygdalina (Bitter leaf)	Leaf	$Zn_{1-x}Cu_xO$	441–635	34–39	Spherical, petal, rod-like	C=C, C=O, C–H, Zn–O	(Okeke et al. 2020)
Zinnia elegans (Common zinnia)	Whole plant	Au	530	<25	Spherical	O–H, C–H	(Kotcherlakota et al. 2019)
O. genistifolia (Klein perdekaroo)	Leaf	Ag/AgCl	270–290	34.2	Spherical	N–H, O–H, C=O, –C–O–C–, –C–O–	(Okaiyeto et al. 2019)
C. tinctorius (Safflower)	Flower	Ag	420	20–70	Spherical, regular polygons	n.a	(Aboutorabi et al. 2018)
D. tombolens (Yellowhead)	Aerial parts	MnO	240	38	Spherical	O–H, C=C, C=O	(Souri et al. 2018)
X. strumerium (Rough cocklebur)	Leaf	Ag	450	20–50	Spherical	O–H, C=C, C–F, C–N, –C–O	(Mittal et al. 2017)
B. eriantha (Blumea)	Whole plant	Ag, Fe	445 (Ag), Fe (365)	10–50	Spherical, irregular	O–H, C–O–C, C=O	(Chavan et al. 2020)
A. pseudocotula (Common chamomile)	Aerial parts	Fe_3O_4	Not reported	11–19	Spherical	CH_3–, CH_2–, –NH, –OH, –C=O, Fe–O, C=C	(Abdullah et al. 2018)
E. purpurea (Purple coneflower)	Whole plant	TiO_2	280	120	Spherical	C–O, C–H, C=C, O–H	(Dobrucka 2017)
A. annua (Sweet wormwood)	Stem bark	ZnO	330	20	Spherical	C–O, N–H, C=C, C=O	(Wang et al. 2020)
T. procumbens (Coat-buttons)	Leaf	Ag	425	54.34	Oval, spherical	C–H, C=C=C, C=O, N–O, S=O	(Rani et al. 2020)
P. leubnitziae (Stinkbush)	Whole plant	Ag	400	100	Spherical	C–H, O–H, C=C, C-N, =CH	(Mofolo et al. 2020)
A. millefolium (Yarrow)	Whole plant	Ag	460	14.27–20.77	Spherical, rectangular, cubical	C–C, O–H, C–H, C=O	(Yousaf et al. 2020)

Table 2 (continued)

Plant name (common name)	Part	NPs	λ_{max} (nm)	Particle size (nm)	Morphology	Chemical bonds	References
W. chinensis (Sphagneticola calendulacea)	Leaf	Ag	408	31.68	Spherical	–OH, C=O	(Paul Das et al. 2018)
T. procumbens (Coat-buttons)	Leaf	CuO	236	16	Rod, spherical	N–H, C–H, C=O	(Muthamil Selvan et al. 2018)
C. benedicti (Blessed thistle)	Whole plant	Au–CuO, CuO–ZnO	350	13 (Au–CuO), 28 (CuO–ZnO)	Spherical	C–H, –NH, C–C, O–H	(Dobrucka et al. 2019)
A. factorovskyi	Leaf	Ag	430	< 100	Spherical	O–H, C=C, C–Cl, N = C = S	(Al-Otibi et al. 2020)
K. grandiflora	Leaf	Ag	429	20–50	Spherical	–OH, –NH, C–H, C–O, C–H, C–C, C–N	(Kanagamani et al. 2019)
A. ciniformis	Leaf	Ag	430	4–77	Spherical	O–H, N–H, C=C, N–H	(Aslany et al. 2020)
V. amygdalina (Bitter leaf)	Leaf	MnO_2	320	20–22	Spherical	–OH, H–O–H, C–H, O–Mn–O, C=O	(Dessie et al. 2020)
S. costus (Putchuk)	Root	MgO	250	30–34	Spherical	–OH, C–H, C=O, Mg–O	(Alavi and Karimi 2017a)
A. arborescens (Ragweed)	Leaf	Ag	414	14	Spherical	C=C, C–O, O–H	(Morejón et al. 2018)
A. tournefortiana	Whole plant	Ag	420	22.89	Spherical	O–H, C–H, P–H,–COO, C=C, C–O–C	(Baghbani-Arani et al. 2017)
C. scolymus (Globe artichoke)	Leaf	ZnO	371	65.9	Spherical	O–H, N–H, –C–H, C–O, C=C, = C–H	(Rajapriya et al. 2020)
A. abrotanum (Southern wormwood)	Whole plant	MgO	300	10	Spherical	O–H, C=O, C–H	(Dobrucka 2018)
O. vulgare (Oregano)	Leaf	Pd	320	2–20	Spherical	O–H, C=O, C–O, C–H	(Shaik et al. 2017)
R. puerariae (Gegen)	Root	Ag	400–430	10–35	Spherical, oval	Not reported	(Balwe et al. 2017)
P. guajava (Guava)	Leaf	CuO	282	2–6	Spherical	Cu–O, C=O	(Singh et al. 2019d)
C. paradisi (Paradise citrus)	Peel	Ag	405	14.84	Spherical	O–H, $-NH_2$, C=O, C=C	(Naseem et al. 2020)
G. arborea (Verbenaceae)	Fruit	Ag	418	8–32	Spherical	Not reported	(Saha et al. 2017)
R. tuberosa (Minnieroot)	Whole plant	CuO	327	20–100	Spherical, cylindrical, cubical	O–H, C=C, C–O, Cu–O	(Vasantharaj et al. 2019)
C. ramiflora (Katong laut)	Fruit	Fe_2O_3	n.a	58.5–78.13	Spherical	–C–NH, C–H, C=O, C–H	(Bishnoi et al. 2018)
A. procera (White siris)	Leaf	Ag	460	6.18	Spherical	Not reported	(Rafique et al. 2019)

Table 2 (continued)

Plant name (common name)	Part	NPs	λ_{max} (nm)	Particle size (nm)	Morphology	Chemical bonds	References
P. granatum (Pomegranate)	Seed	Fe_2O_3	Not reported	25–55	Variable	Not reported	(Bibi et al. 2019)
D. mezereum (Februrary daphne)	Leaf	IO (Iron oxide)	465	6.5–14.9	Spherical	–OH, FeO, C=C	(Beheshtkhoo et al. 2018)
P. farcta (Syrian mesquite)	Fruit	Ag	441	30	Spherical	Not reported	(Medda et al. 2015)
M. koenigii (Curry leaf tree)	Leaf	CuO	670	8.4	Prism, pentagon, hexagon	–OH,–CHO,–COO, Cu–O C=O	(Nordin and Shamsuddin 2019)
L. cubeba (Aromatic litsea)	Fruit	Au	535	8–18	Spherical	O–H, C–H, C=C, C–O	(Doan et al. 2020)
A. indica (Neem tree)	Leaf	Ag	438	10–15	Spherical	–NH, –OH, –C=O, –C–OC–, –C–O–	(Singh et al. 2019b)
M. indica (Mango)	Flower	Au	532	10–60	Spherical	O–H, C=O, C–C	(Nayan et al. 2018)
C. coccineum (Maltese fungus)	Whole plant	Cu	Not reported	14.2	Spherical	C–O–C, O–H, C=C, C–O	(Sebeia et al. 2020)

is a powerful tool to explore their two-dimensional surface morphology. SEM investigation is applied to characterize the shape, size, morphology, and size distribution of the biosynthesized nanoparticles. For example, Yousaf et al. (2020) showed Ag nanoparticles from *A. millefolium* extract owning diverse shapes such as spherical, rectangular, and cubical. Vasantharaj et al. (2019) reported CuO nanoparticles from *R. tuberosa* extract with spherical, cylindrical, and cubical morphologies. Meanwhile, MgO and ZnO nanoparticles from plant extracts can exhibit both spherical shapes (Dobrucka 2018; Rajapriya et al. 2020). However, this technique may be less significant to discovery the structure of nanoparticles, particularly their particle sizes.

Transmission electron microscopy

Transmission electron microscopy (TEM) technique records the electron images of nanoparticle using the electron beam. It gives a very high-resolution to explore the inherent structure of nanoparticles. This technique is not only used to observe the aggregation or clustering of the nanoparticles but also to identify the size distribution of nanoparticles (Fig. 8c). Indeed, Fig. 8d-g shows a marked change in the degree of dispersion of nanoparticles (Ag, Cu, ZnO, MgO). Specifically, almost all Ag nanoparticles are discrete and evenly well-distributed while the slight clustering of Cu, ZnO nanoparticles can occur, and MgO nanoparticles show the strongest aggregation. The inherent morphological difference of mentioned nanoparticles can be attributed to the effect of temperature during their synthesis. Ag and Cu nanoparticles offer a lower degree of clustering possibly because the synthesis occurs at room temperature or slightly higher than room temperature (60–80 °C). Meanwhile, the strong aggregation of ZnO and MgO nanoparticles may relate to the calcination process at high temperature (400–700 °C).

The size of nanoparticles is one of the most important structural features that strongly influences their properties and applications. Many works used TEM technique to calculate the average sizes. For example, Lee et al. (2019) synthesized Au and Ag nanoparticles from *T. farfara* flower bud extract with the particles size in a range from 13.57 to 18.20 nm. Nazar et al. (2018) reported that the average size of Cu nanoparticles from *P. granatum* seeds extract was 43.9 nm. Meanwhile, Hii et al. (2018) synthesized MgO nanoparticles from *C. gigantea* extract with an average size of 53.37 nm. Rajapriya et al. (2019) showed the highest particle size of ZnO nanoparticles from *C. scolymus* extract, at 65.9 nm. This may be due to the clustering of the nanoparticles depending on the synthesis temperature, resulting in different sizes. Indeed, (Siddiqui et al. 2013) synthesized Ag nanoparticles at room temperature, while Lee et al. (2011) produced Cu nanoparticles at about 95 °C. ZnO and MgO nanoparticles could be formed by the calcination of raw

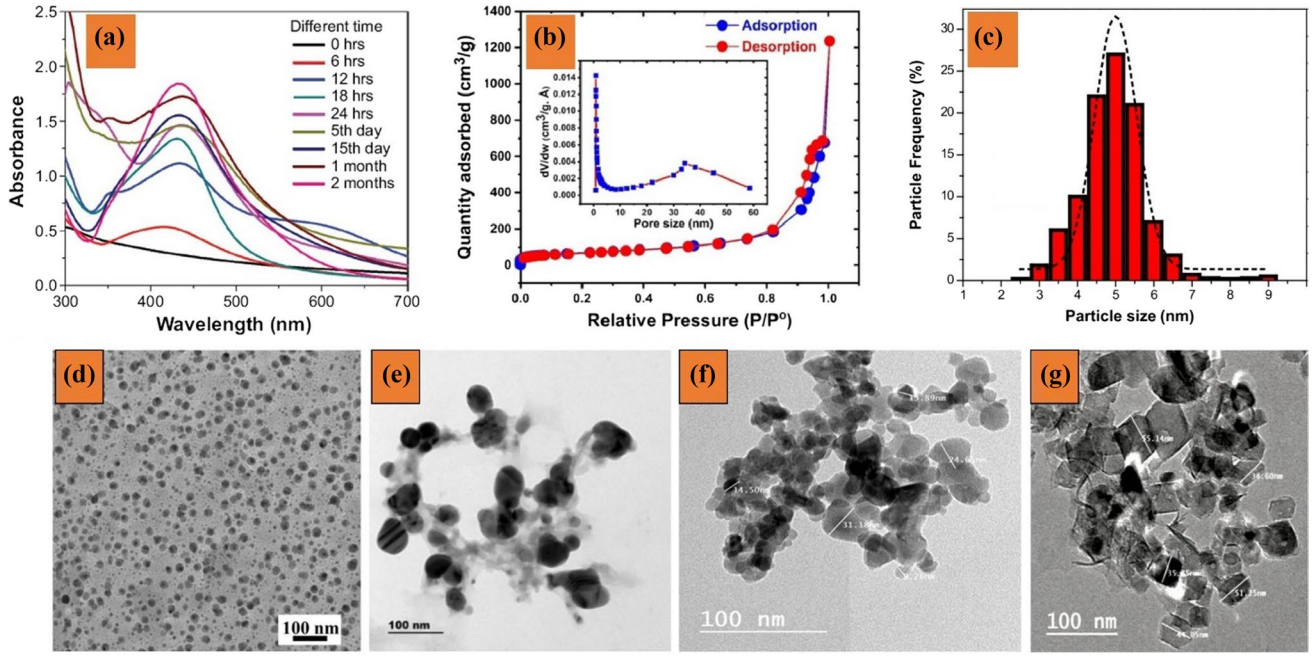

Fig. 8 **a** Ultraviolet–visible absorption spectra for checking stability of Ag nanoparticles from *C. roxburghii* extract at different times, reproduced from the reference (Balashanmugam and Pudupalayam Thangavelu 2015). **b** N_2 adsorption/desorption isotherm of Fe_3O_4 nanoparticles from *A. comosus* extract, reproduced from the reference (Akpomie et al. 2021). **c** Histogram of particle size of Ag nanoparticles from *M. indica* extract, reproduced with the permission of Springer from the reference (Horta-Piñeres et al. 2020). Transmission electron microscope images of (**d**) Ag nanoparticles from *M. recutita* extract, reproduced with the permission of Elsevier from the reference (Uddin et al. 2017); **e** Cu nanoparticles rom *H. abyssinica* extract, reproduced from the reference (Murthy et al. 2020); **f** ZnO nanoparticles from *D. tortuosa* extract, reproduced from the reference (Selim et al. 2020); and **g** MgO nanoparticles from *R. floribunda* extract, reproduced from the reference (Younis et al. 2021)

materials at 200 and 450 °C, respectively (Alavi and Karimi 2017a; Rajapriya et al. 2020).

X-ray diffraction

X-Ray diffraction (XRD) pattern is the characteristic technique to analyze the crystal structure, crystal plane and calculate the crystal size of a nanomaterial (Thamaphat et al. 2008). X-rays can penetrate deeply through materials and provide information about their crystal structure (Huang et al. 2007). If the material has a crystalline structure, diffraction peaks at different angles will be observed by the XRD. The Debye–Scherrer equation measures the particle size from the XRD data by determining the width of the (111) Bragg reflection according to the following equation (Eq. 1).

$$d = \frac{K.\lambda}{\beta \cos \theta} \quad (1)$$

where d is the particle size (nm), K is the Scherrer constant, β is the full width half maximum, θ is half of Bragg angle and λ is the wavelength of X-ray (Kumar Petla et al. 2012). Alavi and Karimi (2018) reported that the XRD sample showed characteristic diffraction peaks of 38.5°, 50.7°, 65.2°, 78.4°, and 81.2°, corresponding to the planes at (111), (200), (220), (311), and (222), determine the face-centered cubic structure of Ag nanoparticles from the extract of *A. haussknechtii*. In addition, the crystal size of Ag nanoparticles is estimated to be around 47 nm by the above formula. In another study, Pansambal et al. (2017) observed that the XRD patterns of CuO nanoparticles from *A. hispidum* showed diffraction peaks at (110), (002), (111), (202), (020), (113), and (311) of face-centered cubic structure. Okeke et al. (2020) confirmed that the Cu-doped ZnO nanoparticles from *V. amygdalina* bring the crystalline structure with the hexagonal wurtzite form. This is confirmed by observing the XRD pattern with the appearance of diffraction peaks at the planes (100), (002), (101), (102), (110), (103), (112), and (201).

Applications of nanoparticles synthesized from plants

Antibacterial activity

Bacteria exist prevalently in the living environment, and some harmful bacteria can enter the body and cause harm to human health. The overuse of antibiotics can induce the rapid development of the drug resistance in bacterial species (Llor and Bjerrum 2014). This raises the concerns about the treatment of infections caused by bacteria. Metallic nanoparticles have demonstrated their great effectiveness in antibacterial activity (Singh et al. 2020). Accordingly, the nanoparticles simultaneously target many biomolecules in bacteria, increasing the stress of bacterial cells to intercept their resistance. Besides, the nanoparticles have outstanding properties such as the small size of particles, large surface area, and good mechanical stability, which are suitable for clinical applications such as antibacterial (Sharma et al. 2020; Yin et al. 2020). Chemically synthesized nanoparticles may raise the toxic degree to the environment and human health. Moreover, the production cost of nanoparticles is likely to be expensive, and hence, it is difficult to attain the critically green chemistry criteria (Chen et al. 2020). Meanwhile, the synthesis of biogenic nanoparticles based on plant extracts is one of the most optimal and environmentally friendly routes. In particular, the presence of a large amount of phytochemicals (e.g., polyphenols, reducing sugars, flavonoids, and alkaloids) in the extract can increase the stability and activity of nanoparticles against microorganisms (Bharathi et al. 2020).

The plausible mechanisms of the antibacterial activity of nanoparticles are still being investigated. Kumar et al. (2020) suggested that the nanoparticles possibly contact with cell walls and membranes of bacteria through the metabolic pathway. Then, the nanoparticles bind with the basic ingredients of bacteria cells such as deoxyribonucleic acid, enzymes, and ribosomes. They are more likely to deactivate the essential functions of enzymes, and proteins. Rajeshkumar and Bharath (2017) offered the hypothesis of the inhibition of transcription and translation by metal ions, causing the destruction of genetic materials inside bacterial cells. Figure 9a illustrates the mechanism of producing

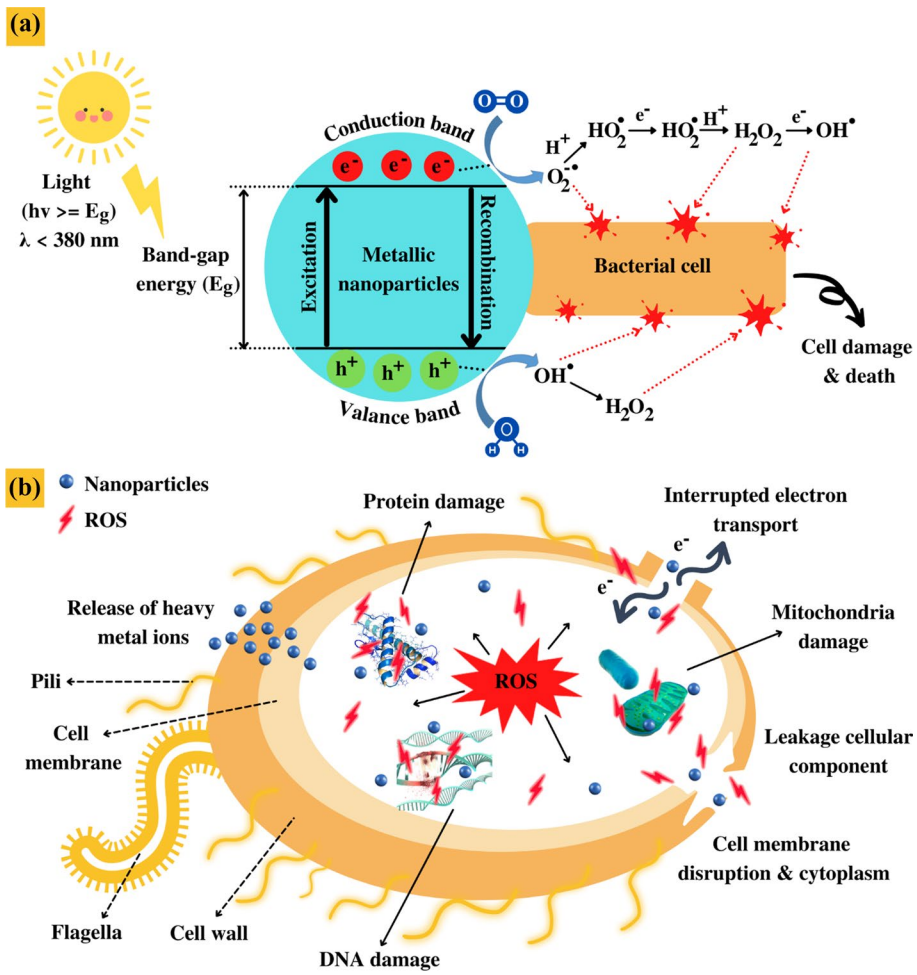

Fig. 9 **a** Mechanism of photocatalytic activity of metal metallic and mechanism producing reactive oxygen species under solar light irradiation, **b** antibacterial mechanistic process of metallic nanoparticles producing from the plants

reactive oxygen species in the presence of nanoparticles under solar light irradiation and their damage to bacterial cells. Specifically, when metallic nanoparticles are exposed to solar light, photons with the excitation energy larger than the band gap of the nanoparticles will shift electrons from the valence band (VB) to the conduction band (CB), creating electron–hole pairs (e^- and h^+). Both entities migrate to the nanoparticle surface and perform the photocatalytic reactions, i.e., h^+ reacts with OH^- or H_2O to produce $OH^•$; e^- reacts with O_2 to form $O_2^{•-}$. The result of these processes is to produce reactive oxygen species that can exhibit a wide range of activities such as cell membrane disruption, leakage of cytoplasm and cellular components, damage of DNA, protein and mitochondria, and finally cells death (Khezerlou et al. 2018). Figure 9b articulates the antibacterial mechanistic process of metallic nanoparticles.

Table 3 displays the antibacterial activity of nanoparticles synthesized from various plant extracts. Accordingly, Ag nanoparticles is the most used nanomaterial in the publications. In fact, Ag ions and Ag-based compounds are immensely noxious to microorganisms and exhibit great antibacterial properties (Khalil et al. 2014). The good bioactivity of Ag nanoparticles can be ascribed to their tiny sizes and high surface area (Franci et al. 2015). Because of such reasons the scientists have also exploited the ability of Ag nanoparticles against infectious diseases in recent decades. For example, commercial products derived from silver nitrate and silver sulfadiazine are used to terminate bacteria such as disinfecting drinking water and caring for burns (Baker et al. 2005). Ag exhibits the best antibacterial properties and has been used in food preservation, novel pesticides, and cosmetics.

Khatoon et al. (2015) informed the synthesis of spherical Ag nanoparticles from *Artemisia annua* leaf extract with particles size about 7–27 nm. In this study, the most prominent application is the antimicrobial activity against *E. coli, S. aureus, P. aeruginosa, S. epidermidis* and *B. subtilis* with wide inhibition zones between 6 and 16.5 mm. This proved a great potential of *A. annua* as a precursor to form Ag nanoparticles for better antimicrobial activities. Baghbani-Arani et al. (2017) notified the synthesis of Ag nanoparticles from *A. tournefortiana* extract. In particular, Ag nanoparticles were created with smaller size of about 22.89 nm than the study by Khatoon et al. (2015). Compared with the same bacterial subjects, minimum inhibitory concentration (MIC) values were in this study obtained from 0.39 to 12.5 µg/mL, which were lower than those (3–21 µg/mL) by Khatoon et al. (2015). This phenomenon can be attributable to the easier penetration of smaller-size nanoparticles into the cell wall of bacteria. Therefore, the production of smaller-size Ag nanoparticles may be more optimal.

Besides, the lowest minimum bactericidal concentration (MBC) values for *S. pyogenes* were 1.56 µg/mL. *P. aeruginosa* and *B. subtilis* have co-values of MBC of about 25 µg/mL. Finally, *E. coli* was the bacteria with the highest MBC values about 50 µg/mL. Thus, it can be concluded that Ag nanoparticles are more resistant to gram-positive bacteria than gram-negative bacteria. Similarly, many works were commensurate with the reported results of better antibacterial activity of nanoparticles to gram-positive bacteria (Raut et al. 2014; Khalil et al. 2014). However, some studies reported the opposite and suggested that Ag is more resistant to gram-negative bacteria (Mukunthan et al. 2011; Dehnavi et al. 2013; Zhang et al. 2014). Indeed, Zhang et al. (2014) noticed that the MIC value of *E. coli* (Gram-negative, 7.8 mg/l) was significantly lower than that of *S. aureus* (Gram-positive, 50 mg/l). Singh et al. (2020) explained that in gram-negative bacteria *E. coli*, there was the formation of negatively charged lipopolysaccharides bonded to positively charged Ag. Gram-positive bacteria are enclosed with a thick layer of peptidoglycans and straight-chain polysaccharides that are cross-linked with embedded proteins, giving the cell stiffness and making it difficult for the nanoparticles to bind to the cell surface. This mechanism is still being questioned, suggesting that more investigations of the impact of Ag nanoparticles on negative- and positive-gram bacteria need to be articulated.

Apart from the synthesis and utilization of Ag nanoparticles, several nanoparticles such as CuO, Au, and ZnO fabricated from various plant extracts were also addressed (Rajakumar et al. 2016; Pansambal et al. 2017; Wang et al. 2020; Rajapriya et al. 2020). For example, Pansambal et al. (2017) have synthesized CuO nanoparticles with particles size range 5–25 nm which has brought high efficiency against *M. tuberculosis*. According to this study, CuO nanoparticles exhibited the termination (99%) of *M. tuberculosis* with the MIC value of 100 µg/mL. Rajakumar et al. (2016) focused on the synthesis of Au nanoparticles from false daisy plants. The results showed the inhibition zone at the nanoparticle concentration of 25 µL/mg toward *E. coli* (~ 24 nm), followed by *S. aureus* (~ 16 nm), and *B. substilis* (~ 12 nm). In another study, Wang et al. (2020) carried out the synthesis of ZnO nanoparticles from *A. annua* stem barks extract. The inhibition zones were in range from 7.4 to 22.3 mm for *E. coli*, *S. typhi*, *S. aureus* and *V. cholerae*. Recently, Ananda Murthy et al. (2021) used *V. amygdalina* leaves as the main raw material to synthesize CuO nanoparticles for antibacterial performance. The results showed that *S. aureus*, *E. coli* and *P. aeruginosa* had an inhibition zone of about 12 mm while that of *E. aerogenes* was 15 mm. As such, the plant extracts can be promising sources to synthesize the types of metallic nanoparticles and pave the way for the diverse anti-bacterial applications.

Table 3 Antibacterial activity of nanoparticles synthesized from various plant extracts

Plant name (common name)	Part	NPs	Main findings	References
A. haussknechtii	Leaf	Ag, Cu, TiO_2	Inhibition zone (mm) at the concentrations of 0.5–60 µg/mL: + Ag NPs: *E. coli* (14–36), *S. aureus* (8–12) + Cu NPs: *E. coli* (10–34), *S. aureus* (4–8), *S. marcescens* (4) + TiO_2 NPs: not found	(Alavi and Karimi 2017b)
A. marschalliana (Mugwort)	Aerial parts	Ag	Inhibition zone (mm) at the concentrations of 100 µg/mL: *S. aureus* (0–15.50), *P. aeruginosa* (0–13,38), *A. baumannii* (0–11,45), *B. cereus* (0–8,66)	(Ardestani et al. 2016)
H. trichophylla	Flower	Ag	Inhibition zone (mm) at the concentrations of 0–250 µg/mL: *E. coli* (9.1), *P. aeruginosa* (8.5), *B. subtilis* (8.2), *S. aureus* (10.2)	(Yazdi et al. 2019)
T. erecta (Marigold)	Flower	Ag	Inhibition zone (mm) at concentration of 5–1280 µg/mL: *E. coli* (9–25.5), *P. aeruginosa* (13.5–31.5), *S. aureus* (9–38)	(Padalia et al. 2015)
C. tinctorius (Safflower)	Flower	Ag	Bacterial removal percentage (%): + Ag–fabric treated at 40 °C: 98 + Ag–fabric treated at 80 ℃: 85	(Aboutorabi et al. 2018)
T. farfara (Coltsfoot)	Flower bud	Ag	Minimum inhibitory concentration (µg/mL) against: *E. coli* (10), *E. faecalis* (> 40), *P. aeruginosa* (10), *S. aureus* (40)	(Lee et al. 2019)
T. collinus (Goatsbeard)	Whole plant	Ag	Inhibition zone (mm) at the concentrations of 6000–7000 µg/mL: *S. aureus* (2–10), *E. coli* (4–8)	(Seifipour et al. 2020)
A. tournefortiana	Whole plant	Ag	Minimum inhibitory concentration (µg/mL) against: *S. pyogenes* (0.39), *B. subtilis* (3.12), *P. aeruginosa* (12.5)	(Baghbani-Arani et al. 2017)
A. millefolium (Yarrow)	Whole plant	Ag	Inhibition zone (mm) at the concentrations of 100 µg/mL: *S. aureus* (14.33), *P. aeruginosa* (13.67), *E. coli* (10.33), *S. enterica* (11.95), *B. subtilis*: (6.75)	(Yousaf et al. 2020)
S. quettense (Podlech)	Whole plant	Ag	Minimum inhibitory concentration (µg/mL) against: *E. coli, K.pneumonia* and *B. subtilis* (11.1–33.3)	(Qasim Nasar et al. 2019)
E. scaber (Elephant's foot)	Leaf	Ag	Inhibition zone (*) (mm) against: *B. subtilis* (14–16), *L. lactis* (21–24), *P. fluorescens* (18–23), *P. aeruginosa* (21–22), *A. flavus* (9–12), *A. penicillioides* (6–139)	(Francis et al. 2018)
W.chinensis (Sphagneticola calendulacea)	Leaf	Ag	Inhibition zone (mm) at the concentration of 12.25–200 µg/mL: *E. coli* (17.2– 35.1), *L. monocytogenes* (11.9– 27.3)	(Paul Das et al. 2018)

Table 3 (continued)

Plant name (common name)	Part	NPs	Main findings	References
X. strumerium (Rough cocklebur)	Leaf	Ag	Minimum inhibitory concentration (μg/mL) at concentrations of 1–100 ppm against: *E. coli* (35), *S. aureus* (40), *P. aeruginosa* (45)	(Mittal et al. 2017)
A. factorovskyi	Leaf	Ag	Inhibition zone (mm) against *S. aureus* (19), *F. solani*: (1.5)	(Al-Otibi et al. 2020)
A. annua (Sweet wormwood)	Leaf	Ag	Inhibition zone (mm) at concentration of 5–20 μg/mL: *E. coli* (6–13), *S. aureus* (9–16.5), *P. aeruginosa* (8–16), *S. epidermidis* (10–19), *B. subtilis* (7.5–15)	(Khatoon et al. 2015)
K. grandiflora	Leaf	Ag	Inhibition zone (mm) at concentration of 10–100 μg/mL: *P. aeruginosa* (17), *E. coli* (22)	(Kanagamani et al. 2019)
T. officinale (Common dandelion)	Leaf	Ag	Inhibition zone (mm) at concentration of 20 μg/mL: *X. axonopodis* (22), *P. syringae* (19.5)	(Saratale et al. 2018)
S. nodiflora (Nodeweed)	Leaf	Ag, Au	Inhibition zone (mm) against bacteria: + Ag NPs: *B. subtilis* (9.1), *Streptococcus* spp. (8.8), *Pseudomonas* spp. (11), *E. coli* (14) + Au NPs: *B. subtilis* (7.5), *Streptococcus* spp. (6.9), *Pseudomonas* spp. (8.1), *E. coli* (9)	(Vijayan et al. 2018)
T. procumbens (Coatbuttons)	Leaf	Ag	Inhibition zone (mm) against bacteria: *E. coli* (15.33), *S. aureus* (15.33), *P. aeruginosa* (14.33)	(Rani et al. 2020)
A. hispidum (Bristly starbur)	Leaf	Ag	Inhibition zone (mm) at concentration of 18–19 μg/mL: *S. pyogenus* (23 mm), *E. coli* (12 mm)	(Ghotekar et al. 2019)
A. hispidum (Bristly starbur)	Leaf	CuO	Percent inhibition (%) of *M. tuberculosis*: 99	(Pansambal et al. 2017)
P. vulgaris (False fleabane)	Flower, leaf, stem	AgCl	Inhibition zone (mm) at concentration of 20–40 μg/mL: 25–38	(Sharifi-Rad and Pohl 2020)
A. scoparia (Virgate wormwood)	Aerial part	Au, Ag, Cu, Au–Ag, Au–Cu, Ag–Cu	The minimum inhibitory concentration /minimum bactericidal concentration values (μM): + AuNPs: *E. coli* (> 500/> 500), *S. epidermis* (> 500/500) + AgNPs: *E. coli* (15.6/31.2), *S. epidermis* (31.2/125) + CuNPs: *E. coli* (250/500), *S. epidermis* (> 500/> 500) + Au–AgNPs: *E. coli* (7.8/31.2), *S. epidermis* (7.8/62.5) + Au–CuNPs: *E. coli* (> 500/> 500), *S. epidermis* (> 500/> 500) + Ag–CuNPs: *E. coli* (31.2/125), *S. epidermis* (31.2/62.5)	(Shankar et al. 2016)

Table 3 (continued)

Plant name (common name)	Part	NPs	Main findings	References
S. marianum (Blessed thistle)	Whole plant	ZnO, Ag–ZnO	Minimum inhibitory concentration (µg/mL) against bacteria: + ZnO NPs: *B. subtilis* (50), *S. epidermis* (250), *P. aeruginosa* (250), *K. pneumonia* (150), *E. coli* (100) + Ag–ZnO NPs: *B. subtilis* (50), *S. epidermis* (150), *P. aeruginosa* (150), *K. pneumonia* (250), *E. coli* (150)	(Hameed et al. 2019)
S. altissima (Lategoldenrod)	Leaf	Ag	The optical density values at 600 nm (OD_{600}) at 5–20 µg/mL against *E. coli* and *B. subtilis* were 0.1 and 9, respectively	(Kumar et al. 2016)
O. genistifolia (Klein perdekaroo)	Leaf	Ag/AgCl	Minimum inhibitory concentration (µg/mL) against: *L. ivanovic* (1), *E. cloacae* (0.5), *S. uberis* (0.5), *S. aureus* (0.5), *M. smergatis* (0.25), *Vibrio* spp. (0.25)	(Okaiyeto et al. 2019)
V. amygdalina (Bitter leaf)	Leaf	$Zn_{1-x}Cu_xO$	Minimum inhibitory concentration (µg/mL) against *S. aureus* and *E. coli* (10–2.5), *P. aeruginosa* (5)	(Okeke et al. 2020)
B. eriantha (Blumea)	Whole plant	Ag, Fe	Inhibition zone (mm) at the concentrations of 0.5–60 µg/mL: + Ag NPs: *B. cereus* (35.2), *B. subtilis* (30.12), *S. aureus* (20.17), *E. Coli* (25.24) + Fe NPs: *B. cereus* (24.12), *B. subtilis* (26.45), *S. aureus* (17.06), *E. Coli* (11.55)	(Chavan et al. 2020)
A. annua (Sweet wormwood)	Stem bark	ZnO	Inhibition zone (mm) at concentration of 20–80 µg/mL: *E. coli* (8.6–11.3), *S. typhi* (7.6–12.3), *S. aureus* (7.4–22.3), *V. cholerae* (7.9–22.1)	(Wang et al. 2020)
C. benedicti (Blessed thistle)	Whole plant	Au– CuO, CuO– ZnO	Minimum inhibition concentration (%) against bacteria: + CuO–ZnO NPs: *S. aureus* (0.3125), *P. aeruginosa* (2.5), *E. coli* (0.625), *C. albicans* (1.25) + Au–CuO NPs: *S. aureus* (2.5), *P. aeruginosa* (2.5), *E. coli* (1.25), *C. albicans* (2.5)	(Dobrucka et al. 2019)
E. prostrata (False daisy)	Leaf	Au	Inhibition zone (mm) at the concentrations of 25 µg/mL: *E. coli* (24), *S. aureus* (16), *B. substilis* (12)	(Rajakumar et al. 2016)
S. costus (Putchuk)	Root	MgO	Inhibition zone (mm) at the concentrations of 5–1280 µg/mL: *E. coli* (15 mm), *P. aeruginosa* (16 mm), *S. aureus* (14 mm), *B. subtilis* (10 mm)	(Alavi and Karimi 2017a)
C. scolymus (Globe artichoke)	Leaf	ZnO	Minimum inhibition concentration (µg/mL) against: *S. aureus* (> 0.7), *E.coli* (25), *P. aeruginosa* (> 100)	(Rajapriya et al. 2020)

Anticancer activity

Cancer diseases are increasingly detected in many recent years, affecting the physical and mental health of patients. They can cause many anxiety, distress, and depression behaviors. According to the International Cancer Research Organization, there are about 18.1 million new cases of cancer and 9.6 million cases of death each year around the world (Bray et al. 2018). It is forecasted that by 2025, this number will increase to 19.3 million, of which patients are mainly from developing countries. Therefore, the treatments and therapies against cancer diseases have paid special attention from scientists. Some cancer treatments involve hormone therapy and immunotherapy, but these often result in some abnormalities in the patient body. Specifically, they possibly damage normal cells and vital organs, exacerbating the patient health, and causing the reduction in life quality (Han et al. 2019). Metallic nanoparticles have a huge potential in the detection, diagnosis and treatment of cancer diseases (Ikram et al. 2021). Their high selectivity between diseased and normal cells minimizes the risks of side effects and limits the damage to normal cells (Saravanan et al. 2020). The reason may be owing to different electrostatic interactions between nanoparticles and these cells (Javed et al. 2021).

The anticancer mechanism of metallic nanoparticles is quite complex and still under investigation. Lee et al. (2019) suggested that the plausible anticancer mechanism of metallic nanoparticles could be due to the reactive oxygen species-dependent apoptosis and caspase-mediated apoptosis in cancer cell lines (Fig. 10). When metallic nanoparticles come into contact with cancer cell membranes, cell surface provokes the invagination of nanoparticles by endocytosis to generate the intracellular membrane-bounded vesicles (Doherty and McMahon 2009). This allows endocytosed nanoparticles to enter the intracellular space without elimination. They are then released to produce reactive oxygen species which can perform the tasks of malfunctioning a variety of mitochondria and enzymes, protein oxidation, deoxyribonucleic acid (DNA) damage, nuclear destruction, and decreasing major non-protein free-radical scavengers (Bethu et al. 2018). In particular, reactive oxygen agents are likely to induce cell cycle arrest in the growth and preparation for mitosis phase as well as meiosis phase (Patil and Kim 2017). They are ascribed to increasing the ratio between B-cell lymphoma protein 2-associated X and B-cell lymphoma protein, which determines cell susceptibility to apoptosis. This process is finalized through the stimulation of caspase -3, -8, -9 (proteins related to apoptosis). Many works also indicated that reactive oxygen species increase the level of tumor protein P53 as known to inhibit cancer cells (Kordezangeneh et al. 2015; Patil and Kim 2017; Kim et al. 2019). Based on the mentioned mechanisms, nanoparticles

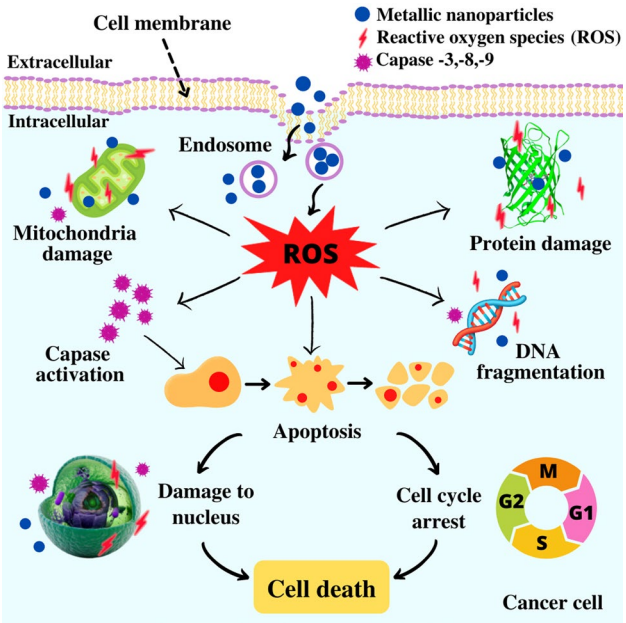

Fig. 10 Anticancer mechanistic process of metallic nanoparticles producing from the plants. The formation of reactive oxygen species may play a main role in protein damage, DNA fragmentation, and so forth, finally causing apoptosis inhibition, cell death. Abbreviations: ROS, reactive oxygen species; DNA, deoxyribonucleic acid; cell cycle (as shown in bottom right corner): G1 (growth), S (DNA synthesis), G2 (growth and preparation for mitosis), M (mitosis or cell division)

through reactive oxygen agents can contribute greatly to killing cancer cells.

Table 4 summaries the anticancer activity of nanoparticles synthesized from various plant extracts. For example, Lee et al. (2019) reported that *T. farfara* flower bud extracts could be used to synthesize Ag nanoparticles and Au nanoparticles. Through the structural characterization by the atomic force microscopy images, the average particle sizes of Ag nanoparticles and Au nanoparticles were determined, at 56.24, and 41.96 nm, respectively. Both Au nanoparticles and Ag nanoparticles presented good anticancer abilities to cells including human gastric adenocarcinoma (AGS), human colorectal adenocarcinoma (HT-29), and human pancreas ductal adenocarcinoma (PANC-1). However, the minimum inhibitory concentration values of Au nanoparticles were between 2 and 4 times lower than Ag nanoparticles for all cells, indicating that Au nanoparticles were more likely to be resistant against cancer line cells than Ag nanoparticles. It could be explained due to the smaller particle size of Au nanoparticles, leading to better penetration into the cell membrane. Agreeing with this finding, Patil and Kim (2017) confirmed that the higher surface area of the gold nanoparticles allows the presence of more surface atoms, hence more exposure of nanoparticles in cancer cells.

Qasim Nasar et al. (2019) noticed that Ag nanoparticles synthesized from *S. quettense* extracts could be against liver

Table 4 Anticancer activity of nanoparticles synthesized from various plant extracts

Plant name (common name)	Part	NPs	Optimal conditions and results	References
T. farfara (Coltsfoot)	Flower	Ag, Au	Minimum inhibition concentration (μM) against human gastric adenocarcinoma cell line (Ag NPs: 338.0, Au NPs: 77.9), human colon cancer cell line (Ag NPs: 275.3, Au NPs: 87.0), human pancreatic cancer cell line (Ag NPs: 166.1, Au NPs: 71.2)	(Lee et al. 2019)
C. cernuum	Whole plant	Ag	The percentage of cellular uptake (%) at the concentration of 0.025–0.1 μg/mL against on murine melanoma cell line (17.3), epithelial carcinoma cell line (22.6)	(Ahn et al. 2019)
P. leubnitziae (Stinkbush)	Whole plant	Ag	Half-maximal inhibitory concentration value (μg/mL) against: the glioma cell line (0.64–0.71)	(Mofolo et al. 2020)
S. quettense (Podlech)	Whole plant	Ag	Half-maximal inhibitory concentration value (μg/mL) against: human liver cancer cell line (62.5)	(Qasim Nasar et al. 2019)
A. turcomanica (Mugwort)	Leaf	Ag	Half-maximal inhibitory concentration value (μg/mL) against: murine fibroblast cell line (14.56), human gastric adenocarcinoma cell line (4.88)	(Mousavi et al. 2018)
E. scaber (Elephant's foot)	Leaf	Ag	Half-maximal inhibitory concentration value (μg/mL) against: human skin carcinoma cells (15.68), fibroblast cells (65.49)	(Francis et al. 2018)
C. intybus (Chicory)	Leaf	Ag	Half-maximal inhibitory concentration value (μg/mL) against: breast cancer cell line (507.58)	(Behboodi et al. 2019)
T. officinale (Common dandelion)	Leaf	Ag	Cell viability (%) at the concentrations of range 10–200 μg/mL against: human liver cancer cell line: 2–99	(Saratale et al. 2018)
W. chinensis (Sphagneticola calendulacea)	Leaf	Ag	Half-maximal inhibitory concentration value (μg/mL) against: human liver cancer cell line (25)	(Paul Das et al. 2018)
K. grandiflora	Leaf	Ag	Percentage cytotoxicity cells (%) at the concentration of 200 μg/mL against: Dalton's lymphoma ascites cell line (100)	(Kanagamani et al. 2019)
A. ciniformis	Leaf	Ag	Cell viability estimated (%) at the concentrations of range 0.78–100 μg/mL against: human gastric adenocarcinoma cell line (2–99)	(Aslany et al. 2020)
A. biebersteinii (Yellow milfoil)	Flower	Ag	Half-maximal inhibitory concentration value (μg/mL) against: breast cancer cell line (20–99)	(Baharara et al. 2015)
A. marschalliana (Mugwort)	Aerial parts	Ag	Half-maximal inhibitory concentration value (μg/mL) against: human gastric adenocarcinoma cell line (21.05)	(Ardestani et al. 2016)
E.prostrata (False daisy)	Leaf	ZnO	The percentage necrosis of cell (%) at the concentrations of 1–500 μg/mL against human liver carcinoma cell line (14.5–86.5)	(Chung et al. 2015)
E. prostrata (False daisy)	Leaf	Pd	Percentage cytotoxicity cells (%) at the concentration of 1–500 μg/mL against: human liver cancer cell line (7.5–76.5)	(Rajakumar et al. 2015)
C. benedicti (Blessed thistle)	Whole plant	Au–CuO, CuO–ZnO	Dead cells percentage (%) against the rat glioma cell line: 0.2–90 (Au–CuO NPs), 0.1–80 (CuO–ZnO NPs)	(Dobrucka et al. 2019)
S. costus (Putchuk)	Root	MgO	Half-maximal inhibitory concentration value (%) against: human breast cancer line cell (52.1–67.3)	(Alavi and Karimi 2017a)

cancer cells A375. Half-maximal inhibitory concentration value (IC50) of Ag nanoparticles (62.5 µg/mL) was significantly lower than that of *S. quettense* extract (251 µg/mL). Consequently, Ag nanoparticles were more likely to destroy human liver cancer (HepG2) cells than the crude extract. This finding demonstrated that Ag nanoparticles presented higher cytotoxicity than plant extracts. Similarly, Francis et al. (2018) showed Ag nanoparticles produced from *E. scaber* extract attained a superior anticancer property than *E. scaber* extract. Indeed, IC50 value to liver cancer cells A375 obtained for Ag nanoparticles produced from *E. scaber* significantly was threefold lower than that of *E. scaber*. This result proves that metallic nanoparticles (Au and Ag) acquired a significant potential to human cancer therapies.

Amina et al. (2020) focused on the synthesis of MgO nanoparticles from putchuk root extract for the resistance of breast cancer cell lines (MCF-7). According to the results, 67.3% of cancer cells were destroyed, showing that the synthesized MgO nanoparticles may contribute significantly to the cancer treatment field. In another study, Ahn et al. (2019) have successfully synthesized Ag nanoparticles from *C. cernuum* extracts. Obtained nanoparticles had an average size of about 13.0 nm, and spherical morphology, which plays a key role in the enhancement against mus musculus skin melanoma cells (17.3%) and human lung cancer cells (22.6%) at concentrations between 25 and 100 ng/mL. To sum up, the synthesized MgO nanoparticles may be beneficial as promising anticancer agents.

Antifungal activity

Currently, acquired immunodeficiency syndrome (AIDS) and organ transplants provide the ideal environment for the infection of opportunistic fungi, which are becoming one of the main originators of mortality and morbidity (Webster et al. 2008). In addition, the fungi also affect the agricultural economy, cause seasonal diseases, and reduce the quality of crops. Therefore, antifungal researches using biogenic nanoparticles are being interested enormously. Synthesis of nanoparticles from plant extracts is one of the most potential and environmentally friendly methods for expanding the antifungal applications in the medicinal and agricultural fields.

Similar to mentioned antibacterial and anticancer mechanisms, metallic nanoparticles also adopt the same mechanism of producing reactive oxygen species and free radicals by releasing metal ions from their nanostructure to exterminate fungal species (Lipovsky et al. 2011). As illustrated in Fig. 11, nanoparticles approach the surface of microorganisms and cause many damaging interactions with the cell wall, leaking out intracellular components (Reddy et al. 2015). Specifically, they disrupt cell walls by altering redox homeostasis and oxidative stress. This deconstruction leads to the homeostatic imbalance and loss of membrane integrity, from which nanoparticles enter the cells (Kumari et al. 2019). Through the mechanism of reactions with the phosphorus or sulfur moieties of DNA, nanoparticles can also prevent DNA replication, ceasing the growth of microorganisms, leading to cell death (Shanmugam et al. 2016). In addition, they induce a variety of activities, e.g., protein denaturation and damage, enzyme inhibition and disruption, denature ribosome, and inhibition of ribosome synthesized proteins. In particular, metallic nanoparticles are also capable of inhibiting glutathione-producing enzymes (GHS)—an enzyme that plays an antioxidant role, which reduces the resistance of fungi (Sun et al. 2018).

Table 5 shows the good antifungal performance of nanoparticles synthesized from various plant extracts. Indeed, Vijayan et al. (2018) carried out the fabrication of Ag and Au nanoparticles from *S. nodiflora* leaf extract for the performance of antifungal activities. Accordingly, the inhibition zone of Ag nanoparticles against *Aspergillus* spp. and *Penicillium* spp. obtained about 12.9 mm, and 10.9 mm, respectively. Under the same conditions, Au nanoparticles have the smaller zone inhibition for both *Aspergillus* spp. and *Penicillium* spp. (~9 mm). These outcomes clarified that Ag nanoparticles acquired a better relatively antifungal potential than that of Au nanoparticles. The reasonable interpretation possibly relies on the particle size of Ag nanoparticles (19.4 nm) smaller than that of Au nanoparticles (22.01 nm), making them easier to enter cell membranes and destroy fungal cells. In another study, Qasim Nasar et al. (2019) have synthesized Ag nanoparticles from *S. quettense* extract with the significantly larger particle size between 48.40 and 55.35 nm compared with that by Vijayan et al. (2018). However, the antifungal results against *Aspergillus* spp. seemed to be more promising since the inhibition zone was wider, at 13.2 mm. As a result, Ag nanoparticles biosynthesized from *S. quettense* extract achieved better antifungal results than those biosynthesized from *S. nodiflora*. This finding is attributable to the significant presence of phenolic and flavonoid compounds found in the plant extracts of *S. quettens, i.e.,* with their amount of 40–56 µg per mg dried extract. Hence, the antifungal behaviors of metallic nanoparticles are not only reliant on the particle size but also on bioactive compounds present in the plant extracts during the synthesis.

Apart from the use of precious metallic nanoparticles such as Au, Ag, and ZnO nanoparticles could be used for the antifungal performance against *C. albicans*, *C. tropicalis,* and *F. oxysporum*. Indeed, Rajapriya et al. (2019) have successfully synthesized ZnO nanoparticles from *C. scolymus* (globe artichoke) leaf extract. In this study, the minimum inhibitory concentration of ZnO nanoparticles against *C. albicans* and *C. tropicalis* was ~100 and 0.35 µg/mL, respectively. This result demonstrated that ZnO attained a considerably higher antifungal behavior against *C. tropicalis* (approximately 300 times) than that against *C. albicans*.

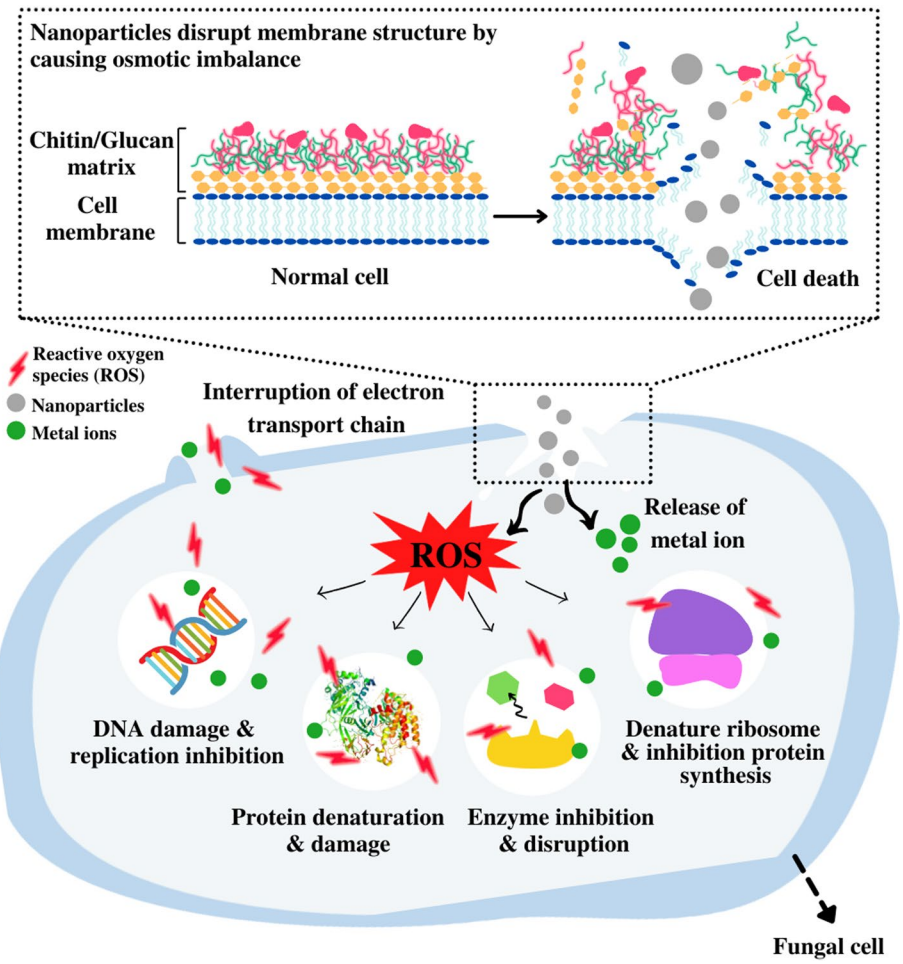

Fig. 11 Antifungal mechanism of metallic nanoparticles producing from the plants. The reactive oxygen species are responsible for protein damage, DNA replication inhibition, enzyme inhibition, and so forth, causing fungal cell death. Abbreviations: ROS, reactive oxygen species; DNA, deoxyribonucleic acid

Jebril et al. (2020) conducted an investigation on the antifungal activity of Ag nanoparticles from *M. azedarach* leaf extracts. Accordingly, the percentage of inhibition against *V. dahliae* of Ag nanoparticles were 18, 33, and 51% at the range concentrations of 20, 40, and 60 ppm, respectively. It could be concluded that higher the concentration of Ag nanoparticles, better the antifungal activity. In another study, Narendhran and Sivaraj. (2016) carried out the production of ZnO nanoparticles from *L. aculeata* extract for the antifungal effect. The results indicated that the inhibition zones against *A. flavus* and *F. oxysporum* were found at 21, and 19 mm, respectively. For other nanoparticles, Pagar et al. (2020) reported a promising antifungal activity of green CuO nanoparticles produced by using leaves extract of *Moringa oleifera*. In general, metallic nanoparticles (majorly, Au, Ag, and ZnO) biofabricated from plant extracts acquire great potentials in inhibiting a wide range of fungal species.

Antioxidant activity

For a long time, researchers have concluded that free radicals are one of the causes of human disease and aging processes (Chen et al. 2012). Cells that perform functional activities such as immunity and respiration in the body can produce free radicals. When free radicals are, however, overproduced, they will pair with other biomolecules such as proteins, nucleic acids, lipids and carbohydrates in the body. This phenomenon can cause a wide range of negative effects on humans such as atherosclerosis, aging, cardiovascular disease, inflammation. More seriously, free radicals are responsible for cancer diseases (Javed et al. 2021). In addition, the chemical compounds in foods exposed under air are likely to react with oxygen, which loses nutritional value, and increases rancidity as well as discoloration (Das et al. 2013). Free radicals in foods can be harmful to human health. Although butylated hydroxytoluene, n-propyl gallate, and butylated hydroxyanisole are effective antioxidants, they are highly carcinogenic agents, hence not widely used (Das et al. 2013). Some nanoparticles (ZnO, Ag) incorporated into food packaging membranes have played the potentials for antimicrobial activities and applications against free radicals (Al-Naamani et al. 2016; Yu et al. 2019).

Biogenic nanoparticles have recently been known for their high antioxidant capacity, biocompatibility, and

Table 5 Antifungal activity of nanoparticles synthesized from various plant extracts

Plant name (common name)	Part	NPs	Optimal conditions and results	References
S. nodiflora (Nodeweed)	Leaf	Ag, Au	Inhibition zone (mm) against fungal: + Ag NPs: *Aspergillus* spp. (12.9) *Penicillium* spp. (10.9) + Au NPs: *Aspergillus* spp. (9) *Penicillium* spp. (9)	(Vijayan et al. 2018)
S. quettense (Podlech)	Whole plant	Ag	Inhibition zone (mm) against *A. niger* (13.2), *A. fumigatus* (12), *A. flavus* (10), *Mucor* spp. (11)	(Qasim Nasar et al. 2019)
C. scolymus (Globe artichoke)	Leaf	ZnO	Minimum inhibition concentration (µg/mL) at the concentration of 100 µg/mL against: *C. albicans* (> 100), *C. tropicalis* (0.35)	(Rajapriya et al. 2020)
A. retroflexus (Redroot pigweed)	Leaf	Ag	Minimum inhibition concentration (µg/mL) at the concentration of 50–400 µg/mL against: *M. phaseolina* (159.80), *A alternata* (337.09), *F. oxysporum* (328.05)	(Bahrami-Teimoori et al. 2017)
M. azedarach (Chinaberry)	Leaf	Ag	The percent inhibition (%) at the concentration of 20–60 µg/mL against: *V. dahliae* (18–51)	(Jebril et al. 2020)
N. arbor-tristis (Night-flowering jasmine)	Flower	ZnO	Minimum inhibition concentration (µg/mL) at the concentration of 256 µg/mL against: *A. alternata* (64), *A. niger* (16), *B. cinerea* (128), *F. oxysporum* (64), *P. expansum* (128)	(Jamdagni et al. 2018)
L. aculeata (West Indian lantana)	Whole plant	ZnO	Inhibition zone (mm) against: *A. flavus* (21), *F. oxysporum* (19)	(Narendhran and Sivaraj 2016)
A. vera	Leaf	Ag	Minimum inhibition concentration (µg/mL) against both *Aspergillus* spp. and *Rhizopus* spp. (21.8)	(Medda et al. 2015)
C. sparsiflorus (Bonpland's croton)	Leaf	Ag	Inhibition zone (mm) against *Mucor* spp. (0.1), *Tricoderma* spp. (0.1), *A. nigar* (0.1)	(Kathiravan et al. 2015)
T. majus (Common nasturtium)	Leaf	Ag	Minimum inhibition concentration (µg/mL) against: *P. notatum* (31.2), *A. niger* (125), *C. albicans* (250), *T. viridiae* (62.5), *Mucor* spp.(29)	(Valsalam et al. 2019)
C. paniculatus (Intellect plant)	Leaf	Cu	The percent inhibition (%) against: *F. oxysporum* (59.25–76,29)	(Mali et al. 2020)
Z. nummularia (Jujube)	Leaf	ZnO	Minimum inhibition concentration (µg/mL) at the concentration of 25–125 mg/mL against both *C. albicans* and *C. glabrata* (1,25), *C. neoformans* (10)	(Padalia and Chanda 2017)
S. arvensis (Wild mustard)	Seed	Ag	The percent inhibition (%) at the concentration of 2.5–40 µg/mL against *N. parvum* (15–83)	(Khatami et al. 2015)

stability (Mohanraj and Chen 2007; Naahidi et al. 2013). These properties may be derived from plant extracts, which contain various bioactive compounds known as phytochemicals including isoflavones, alkaloids, and polyphenols. They not only supply a good platform to produce nanoparticles but also improve their properties in terms of surface area, particle size, and surface functionality. As a result, they are used to serve as promising antioxidants against free radicals which are beneficial in the medical fields and food preservation (Fig. 12). The green synthesis of nanoparticles from plant extract is recognized as one of the most economical and environment-friendly methods. Table 6 summarizes the results of antioxidant activities of biosynthesized nanoparticles from recent works.

The methods of determining the antioxidant activities of nanoparticles have been studied. 2-diphenyl-1-picrylhydrazyl (DPPH) is a free radical scavenging trap for other radicals, allowing to monitor antioxidant properties. This is owing to its ability in inhibiting free radicals (Zhaleh et al. 2019). The DPPH-based method presents as one of the most widely used

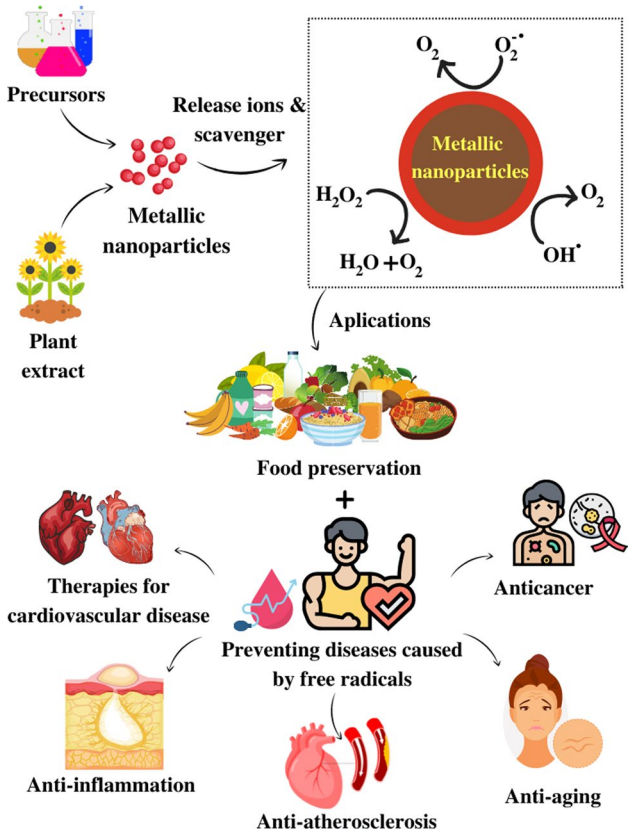

Fig. 12 Nanoparticles in the medical field and food preservation

ones because it provides a simple protocol, screening results rapidly and high reliability (Javed et al. 2021). Nelson et al. (2016) suggested a possible mechanism how metallic nanoparticles worked out antioxidant activity of metallic nanoparticles. The nanoparticles firstly eliminate $^{\bullet}O_2^-$ to O_2, H_2O_2 reduced to H_2O and O_2, and followed by the formation of O_2 from $OH^{\bullet}$ or H_2O_2. Specific for CeO_2 nanoparticles, the chain initiates a series of reactions to remove free radicals, i.e., (1) and (2) are the reduction reaction of $^{\bullet}O_2^-$, (3) is reduction in H_2O_2, (4) and (5) is the reduction in $OH^{\bullet}$.

$$O_2^- + Ce^{3+} + 2H^+ \rightarrow H_2O_2 + Ce^{4+} \quad (2)$$

$$^{\bullet}O_2^- + Ce^{4+} \rightarrow O_2 + Ce^{3+} \quad (3)$$

$$H_2O_2 + 2Ce^{4+} + 2OH^- \rightarrow 2H_2O + O_2 + 2Ce^{3+} \quad (4)$$

$$Ce_2O_3 + 2[^{\bullet}OH] \rightarrow 2CeO_2 + H_2O \quad (5)$$

$$2CeO_2\left(\text{in presence of aqueous } H^+\right) \rightarrow Ce_2O_3 + {}^1/_2O_2 \quad (6)$$

Table 6 exhibits the antioxidant performance of nanoparticles synthesized from various plant extracts. As an example, Kharat and Mendhulkar (2016) have reported that Ag nanoparticles synthesized from *Elephantopus scaber* leaf extracts. In this literature, the IC50 values of Ag nanoparticles from *E. scaber* extract were between 41.86 and 126.6 µg/mL. By using the same leaf extract, Francis et al. (2018) successfully produced Ag nanoparticles with a small average particle size of ~ 37.86 nm. In addition, IC50 value of Ag nanoparticles from *E. scaber* extract was found at 6.629 µg/mL which was considerably lower than that of Ag nanoparticles reported by Kharat and Mendhulkar (2016). This indicated the antioxidant activity of Ag nanoparticles has been improved. The underlying reason might be the microwave-assisted synthesis procedure, enhancing the better stability of Ag nanoparticles (Francis et al. 2018). Ag nanoparticles from *E. scaber* extract also showed a comparative antioxidant activity better than crude extract. As a result, the use of microwaves may contribute to the enhancement of the antioxidant activity of Ag nanoparticles.

Other plant extracts were reportedly used to synthesize and test antioxidant activity of Ag nanoparticles. Indeed, Ahn et al. (2019) investigated the potential of *C. cernuum* extract for such purposes. Accordingly, IC50 value against DPPH radical scavenging of Ag Nanoparticles was obtained at 121 µg/mL. Park et al. (2020) explained that several biocompounds such as sesquicineole, α-bisabolol, and myrtenal compounds in *C. cernuum* extract supported the superior antioxidant activity. Yousaf et al. (2020) pointed out Ag nanoparticles synthesized from *A. millefolium* extract had an excellent antioxidant performance. Accordingly, the IC50 value of Ag nanoparticles against DPPH (7.03 µg/mL) was higher than that of ascorbic acid (vitamin C, 4.29 µg/mL), a popular natural antioxidant. In other words, as-mentioned results demonstrated that Ag nanoparticles produced from *A. millefolium* extract exhibited even more antioxidant effectiveness than vitamin C. This finding suggests a prospective future for the researches on bio-based Ag nanometallic antioxidants.

Apart from the synthesis of Ag nanoparticles, many studies also carried out the synthesis of other metallic nanoparticles (*e.g.* Au, ZnO, CuO) from different plant species and measure their antioxidant activities (Rajeshkumar et al. 2018, 2019; Zhaleh et al. 2019). Indeed, Zhaleh et al. (2019) synthesized Au nanoparticles from *G. tournefortii* leaf extract, and the IC50 value against DPPH was about 194 µg/mL. Likewise, Rajeshkumar et al. (2018) implicated that ZnO nanoparticles from leaf mango extract acquired outstanding antioxidant activity. As evidenced by the percentage of inhibition toward DPPH, the value for ZnO Nanoparticles was in range from 22 to 93%. Rajeshkumar et al. (2019) performed another study on the antioxidant ability of CuO nanoparticles from *C. arnotiana* extract. Accordingly,

Table 6 Antioxidant activity of nanoparticles synthesized from various plant extracts

Plant name (common name)	Part	NPs	Optimal conditions and results	References
E. scaber (Elephant's foot)	Leaf	Ag	Half-maximal inhibitory concentration value (µg/mL) against DPPH: 6.629	(Francis et al. 2018)
E. scaber (Elephant's foot)	Leaf	Ag	Half-maximal inhibitory concentration value (µg/mL) against DPPH: 41.86–126.6	(Kharat and Mendhulkar 2016)
S. nodiflora (Nodeweed)	Leaf	Ag, Au	Half-maximal inhibitory concentration value (µg/mL) against DPPH: 54.3–215	(Vijayan et al. 2018)
A. millefolium (Yarrow)	Whole plant	Ag	Half-maximal inhibitory concentration value (µg/mL) against DPPH: 7.03	(Yousaf et al. 2020)
C. cernuum	Whole plant	Ag	Half-maximal inhibitory concentration value (µg/mL) against DPPH: 0.121	(Ahn et al. 2019)
G. tournefortii (Tumbleweed)	Leaf	Au	Half-maximal inhibitory concentration value (µg/mL) against DPPH: 194–330	(Zhaleh et al. 2019)
C. arnotiana	Leaf	CuO	The percentage of radical scavenging (%) against DPPH: 18–21	(Rajeshkumar et al. 2019)
M. indica (Mango)	Leaf	ZnO	The percent inhibition (%) against DPPH: 22–93	(Rajeshkumar et al. 2018)
A. millefolium (Common yarrow)	Whole plant	Ag	Half-maximal inhibitory concentration value (µg/mL) against DPPH: 7.03	(Yousaf et al. 2020)
C. nocturnum (Queen of the night)	Leaf	Ag	The percentage of radical scavenging (%) against DPPH: 29.55	(Keshari et al. 2020)
P. guajava (Guava)	Leaf	Ag	Half-maximal inhibitory concentration value (µg/mL) against DPPH: 52.53	(Wang et al. 2018)
P. anisum (Anise)	Seed	Au, Ag	Half-maximal inhibitory concentration value (µg/mL) against DPPH: 45.53 (Ag NPs), 191.58 (Au NPs)	(Zayed et al. 2020)
A. katsumadai (Hainan galangal)	Seed	Ag	The percent inhibition estimated (%) against DPPH: 22–89.9	(He et al. 2017)
N. oleander (Nerium)	Leaf	Au	The percent inhibition estimated (%) against DPPH: 42–78	(Tahir et al. 2015)
B. ciliata (Fringed bergenia)	Rhizomes	Ag	The percentage of radical scavenging estimated (%) against DPPH: 60	(Phull et al. 2016)

the percentage of radical scavenging activity of CuO nanoparticles was about 21%. It can be concluded that diverse metallic nanoparticles (Ag, Au, CuO, ZnO) from various plant extracts have great potentials for antioxidant activities. Also, the common antioxidants can be replaced by such biogenic nanoparticles in health therapies, and medical technologies.

Drug delivery

Treatments for diseases in biomedical fields are being investigated to address a wide range of restraints of normal drug delivery systems including nonspecific biological delivery and targeting, poor oral bioavailability, and insufficient water solubility (Rahman et al. 2020). Nanotechnology has long been attractive to researchers due to its affordable applications in delivering drugs to target organs, tissues or cells in cancer treatment or biocarriers by crossing the blood–brain barrier (Lockman et al. 2002; Haley and Frenkel 2008). Nanoparticles represent the surface functionalization and exhibited large surface area to facilitate the drug loading (Faraji and Wipf 2009). In addition, nanoparticles show high biocompatibility and lessen drug resistance because they can accumulate in the body without being detected by the resistance protein P-glycoprotein (Cho et al. 2008). Specifically, the biosynthesis of nanoparticles using plant extract can be the optimal resolution due to the presence of phytochemicals that contribute to their stability and benignity (Yew et al. 2020).

The blood–brain barrier known as the "tough guardian" is the barrier that covers the inner nerve cells (Fig. 13). They play an important role in protecting the brain and regulating homeostasis, minimizing the penetration of foreign substances (Chen and Gao 2017). Therefore, it is difficult to transform drugs inside and support early treatment of nerve cell damage. Nanoparticles can bypass the blood–brain barrier without altering their integrity thanks to the small size and the process of endocytosis. As a result, neuroleptic drugs can be transported into neuron cells to support treatment by pathways such as through endocytosis or transport through the tight junction (Nair et al. 2012).

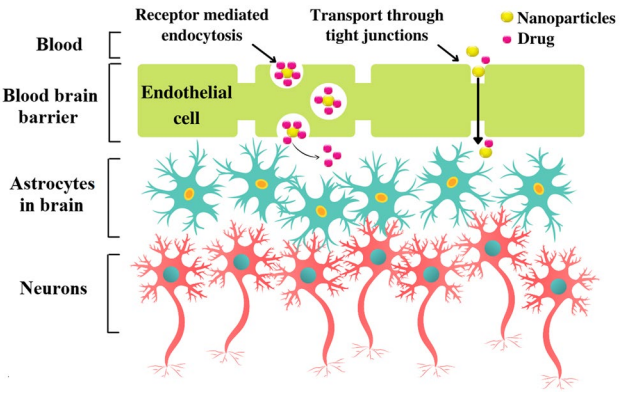

Fig. 13 Transport mechanism of nanoparticles across the blood–brain barrier for drug delivery application

In recent researches on cancer treatment, nanoparticles from plant extracts exhibit the potential to act as the distribution system of anticancer drugs to tumors of patients (Table 7). Because conventional chemotherapeutic agents may not deliver specifically to target organs, potentially causing damage to other healthy cells, a reduction in their dose may result in ineffective treatment (Cho et al. 2008). Therefore, nanoparticles have solved the above problems, especially magnetic nanoparticles (Fig. 14). First, the drug will be loaded on nanoparticles and injected into the blood capillaries, then locate the sites of cancer cells and tumors using external magnetism. This access can pinpoint the exact site of drug delivery without affecting other non-target organs (Yew et al. 2020). Then, the nanoparticles will approach cancer cells through the endocytosis pathway and release the drug, and thus, kill the cancer cells (Haley and Frenkel 2008). For example, Taghavi et al. (2016) synthesized Fe_3O_4 nanoparticles to deliver the drug deferasirox, resulting in a cell death percentage of about 69.3% human leukemia cell lines. In another study, Pham et al. (2016) produced Fe_3O_4 nanoparticles coated with curcumin to inhibit lung cancer cells, acquiring an IC50 value of 73.03 µg/mL. Sriramulu et al. (2018) carried out the synthesis $ZnFe_2O_4$ nanoparticles from *A. marmelos* leaf extract to carfilzomib drug delivery. Accordingly, 95% of carfilzomib was released by nanoparticles in 360 min.

In addition to magnetic nanoparticles, other nanoparticles (e.g. Ag, Au nanoparticles) are also capable of delivering drugs for cancer treatment effectively. Specifically, Ganeshkumar et al. (2013) reported that Au nanoparticles from *P. granatum* peel extract could load fluorouracil drug (78%) for breast cancer treatment. This study also indicated that 22.92% of the drug was released after 48 h. More interestingly, IC50 value of fluorouracil–Au nanoparticles against breast cancer cells was 4 times lower than that of the free fluorouracil. Similarly, Pooja et al. (2015) showed that Au nanoparticles from gum of *Sterculia* genus extract could deliver gemcitabine hydrochloride to human lung cancer cells. According to the results, IC50 value of drug–Au nanoparticles was about twofold lower than the free drug.

Table 7 Applications of green nanoparticles synthesized from plant extract for drug delivery

Plant (common name)	Part	NPs	Drug	Result	Ref
P. granatum (Pomegranate)	Peel	Au	Fluorouracil	+ Percentage of drug (%) bound to nanoparticles: 78 + Percentage of drug (%) release after 2 days: 22.92 + Half-maximal inhibitory concentration value (µg/mL) against breast cancer cells: 0.15–0.50	(Ganeshkumar et al. 2013)
P. annua (Annual meadowgrass)	Leaf	Ag	*E. dracunculiodes*	+ Percentage of drug (%) bound to nanoparticles: 85 + Percentage of drug (%) release after 30 days: 96 + The percentage inhibiting estimated (%) against squamous cell carcinoma: 40	(Gul et al. 2021)
Sterculia genus	Gum	Au	Gemcitabine hydrochloride	+ The percentage drug loading (%): 19.2 + Half-maximal inhibitory concentration value (µg/mL) against human lung cancer cells: 0.67	(Pooja et al. 2015)
A. marmelos	Leaf	$ZnFe_2O_4$	Carfilzomib	Percentage of drug (%) release after 6 h: 95	(Sriramulu et al. 2018)
J. regia (Walnut)	Bark	Au	Zonisamide	+ Percentage of drug (%) release after 11 days: 76,167 + Percentage of treatment (%) for acute spinal cord injury: 80	(Fang et al. 2019)

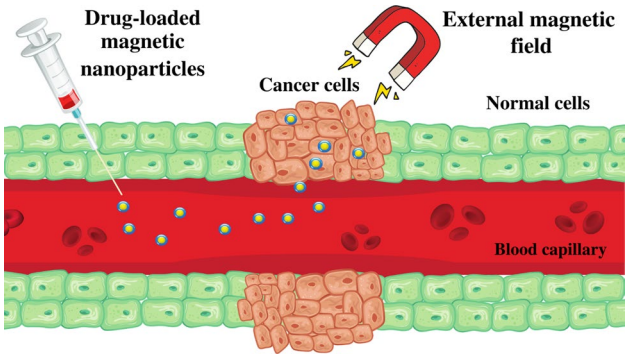

Fig. 14 Targeted drug delivery mechanism using magnetic nanoparticles

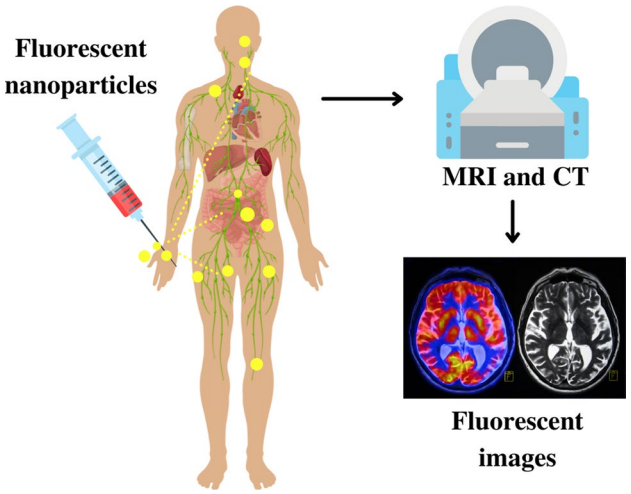

Fig. 15 Fluorescent diagnostic techniques using nanoparticles for magnetic resonance imaging (MRI) and computed tomography (CT) scans

Such outcomes showed the high affinity of nanoparticles to drug molecules in drug delivery systems for cancer treatment. Similarly, Fang et al. (2019) investigated the use of Au nanoparticles from walnut bark extract as a promising zonisamide biocarrier with 80% efficiency of acute spinal cord injury. Gul et al. (2021) performed the loading of herbal drug *E. dracunculiodes* on Ag nanoparticles produced from *P. annua* extract. As a result, 96% of the drug was released after 30 days whereas the percentage of inhibiting squamous cell carcinoma was ~ 40%. In conclusion, both magnetic and metallic non-magnetic nanoparticles bring high drug delivery potentials, greatly benefiting medical technology.

Medical diagnostics

Recent advances in medical nanotechnology are expanding in the early diagnosis of dangerous diseases such as cancer and stroke. Typically, some methods such as computed tomography (CT), and magnetic resonance imaging (MRI) are prevalently used. These diagnostic methods are, however, limited because they can only detect tumors and diseased tissues with a size of more than a few millimeters or equivalent to 10 million cells (Singh et al. 2018). The nanoparticles exhibit unique optical and surface plasmon resonance properties, whereas their scattering ability is five times greater than that of conventional dyes used in diagnostic techniques (Radwan and Azzazy 2009). Moreover, their small size and high biocompatibility bring them an easy approach to the tissues or organs to perform probe functions. Therefore, nanoparticles are used in diagnostic methods such as photoimaging, signal, fluorescence, and surface-enhanced Raman scattering (Boisselier and Astruc 2009).

Cancer is a dangerous disease, the second leading cause of human death in the world (Singh et al. 2018). The normal diagnostic methods can only detect the tumors at the grown periods, causing difficulty in cancer treatment. Therefore, early diagnosis is necessary to prevent these diseases. Mukherjee et al. (2013) noticed the synthesis of Au nanoparticles from *O. scandens* leaf extract for the diagnosis of lung and breast cancers. The results were observed by the olympus fluorescence microscope that nanoparticles can spontaneously emit red fluorescence toward both cancer cells. The authors also suggested the red emission phenomenon was ascribed to the encapsulating phytochemicals and the light scattering of nanoparticles. As an example, Fig. 15 describes the fluorescent diagnostic technique using nanoparticles for photo-imaging and computed tomography scans. In another study, Chanda et al. (2011) reported the cancer diagnostic ability of Au nanoparticles from cinnamon extract. Accordingly, the photoacoustic signal for prostate cancer cell lines was stronger in the presence of Au nanoparticles than the other.

In addition to supporting cancer diagnosis, nanoparticles can also diagnose various diseases, i.e., ischemic stroke is a disease with a high mortality rate. Whereas an ischemic attack occurs, the quantity of neurons lost is equivalent to the number of neurons lost in 36 years of normal aging. This would accelerate the rate of death in short time (Lakhan et al. 2009). Biomarkers such as S100 calcium binding protein B and glial fibrillary acidic protein have long been known to be used for the diagnosis of strokes, but unable to detect them early and clearly. Sarmah et al. (2017) showed the more pronounced signals of these biomarkers associated with Au nanoparticles and iron oxide nanoparticles in the detection of strokes by computed tomography scans, and MRI techniques. Fazal et al. (2014) investigated Au nanoparticles from cocoa bean extract for X–ray contrast in computed tomography scan. At the same concentration, Au nanoparticles gave a signal intensity about 1.5 times larger than Omnipaque, which is well known as a contrast agent used for X-ray imaging. Beside the cell diagnosis, Kumar Sur et al.

(2018) proved Ag nanoparticles from reetha and shikakai leaf extracts could detect *M. tuberculosis* bacteria for early diagnosis of tuberculosis. Through surface-enhanced Raman spectroscopy technique, the authors observed the signal of laser fluorescence from this bacterial species when they were exposed to Ag nanoparticles. With the encouraging vision, nanoparticles-based technologies promote the development of diagnostic methods for early detection of dangerous diseases such as cancer, strokes, tumors, and tuberculosis.

Antiaging

Skin aging can affect aesthetics and raise the risks for skin cancers. Skin aging is caused by many factors, i.e., internal factors by age or genetic and external factors by constant exposure under ultraviolet irradiation or pollutants in daily life (Puizina-Ivic 2008). The free radicals are underlying to activate collagenase, elastase, and tyrosinase enzymes to digest collagen in the triple helix region, breaking down the elastin, and synthesizing toxic melanin (Eun Lee et al. 2019). Mostafa et al. (2019) showed that Ag nanoparticles from *C. pumilio* plant extract may be against enzymes that cause skin aging. The interaction between the hydroxyl groups of phenol in plant extract with the enzymes functional groups or the hydrophobic interaction between the benzene ring of phenol and enzyme may change the structure, reducing the enzyme activity. The inhibition percentages of anti-elastase, anti-collagenase and anti-tyrosinase enzymes in the keratinocyte cell line were 91, 76, and 79%, respectively. Likewise, nanoparticles can also be used as a shield against ultraviolet rays. Khatami et al. (2019) discovered Ni-doped CeO_2 nanoparticles synthesized from *S. rebaudiana* extract were a promising filter against ultraviolet agents. Sunscreen's ability to absorb ultraviolet rays is measured based on sun protection factor. If this factor is above 30, the filter can prevent 98% of ultraviolet rays from skin surface (Jose and Netto 2019). The results of sun protection factor from three samples are acceptable: CeO_2 (38.98) < Ni 1%-doped CeO_2 (40.15) < Ni 3%-doped CeO_2 (42.54). The authors explained that the smaller the nanoparticle size is, the narrower the band-gap, the better the ultraviolet-absorbing material. It can be seen that nanoparticles from plant extracts support potential anti-aging products for human health and the environment.

Other biomedical treatments

Bionanotechnology has long been studied and applied in various biomedical fields from diagnosis to treatment. Conventional specialty drugs can have many side effects, prompting researchers to find more optimal treatments. The characteristic of nanoparticles such as small size, large surface area, high stability and biocompatibility brings them great potential as effective agents in diseases treatment (Dutta et al. 2015).

Malaria is still a worrisome disease for mankind, every year there are about 283 million cases and 755,000 deaths over the world according to the annual report of the World Health Organization (Kumar et al. 2015). As infected with malaria, the disease-causing parasite (e.g., *P. falciparum*) binds with red blood cells to form parasitized red blood cells. Although chemotherapy is widely used to cure malaria, it possibly causes a high resistance to drugs and affects nonspecific parasites. Meanwhile, green synthesized nanoparticles exhibit the ability to combine with drugs and targeted treatment (Mohammadi et al. 2021). For example, Tripathy et al. (2020) demonstrated that *Dicoma anomala* roots biosynthesized Ag nanoparticles can reduce the number of red blood cells from 2.5% of the total red blood cells to 0.5% after 48 h.

Diabetes mellitus is characteristic of glucose homeostasis caused by defects in insulin secretion and action, leading to the impairment of glucose metabolism (Prajapati et al. 2008). It is reported that the number of people with diabetes has been worldwide increasing at an alarming rate. It was forecasted to be new 366 million cases by 2030 (Wild et al. 2004). However, hypoglycemic agents to treat diabetes are thought to have side effects such as lactic acidosis, liver problems, and diarrhea (Rajalakshmi et al. 2009). Daisy and Saipriya (2012) reported that nanoparticles from *C. fistula* bark extract could participate in hypoglycemic activity. According to the results, the total proportion of hemoglobin in the blood of diabetic rats treated with Au nanoparticles decreased from 13.59% to 10.40%.

Alzheimer is a form of disease dementia resulting in problems regarding memory, cognition, and behavior (Hajipour et al. 2017). To treat Alzheimer's, drugs are recommended to use against acetylcholinesterase, an enzyme that breaks down acetylcholine, causing a reduction in nerve cell communication (Soreq and Seidman 2001). Youssif et al. (2019) synthesized Ag nanoparticles from *Lampranthus coccineus* and *Malephora lutea* extracts against acetylcholinesterase. The results revealed that *L. coccineus*–Ag nanoparticles had higher anti-acetylcholinesterase activity (1.95 ng/mL) than that of *M. lutea*–Ag nanoparticles (1.23 ng/mL). More interestingly, both Ag Nanoparticles were more effective than rivastigmine, an anti-acetylcholinesterase drug used in the treatment of Alzheimer. To sum up, green nanoparticles have shown promising applications in the treatment of diseases such as skin aging, malaria, diabetes, Alzheimer, both cancers and various types of infections. They may probably contribute to other diseases treatment in biomedical technologies.

Challenges

Nanotechnology is evolving and has bright future prospects. In particular, the use of plant extracts for nanofabrication is increasingly being developed and gradually replacing chemical or physical production technologies with the economic, ecological, and safety benefits. In the near future, nanoparticles biofabricated from plant extracts can be incorporated into large-scale production from locally available plant species. These strengths can open new commercialized opportunities for biogenic nanoparticles; and hence, lowering the production cost. This possibly leads to boosting the density of bionanomaterials in the material sciences. In addition to their outstanding biomedical and environmental applications, nanoparticles can also have great prospects in many other technologies. For example, the bio-based nanoparticles can act as green catalysts for the synthesis of novel bioactive compounds (Balwe et al. 2017). They have many potentials for antioxidant and free radical scavenging activities (Yousaf et al. 2020). These antioxidants can firmly link to food preservation, antiaging, and other biomedical applications. In particular, some of the outstanding applications of nanoparticles are to produce biopesticides, biofertilizers, and even bionanosensors applying for smart agricultural fields (Shang et al. 2019).

However, paralleling with the advanced technologies of nanoparticles, there can have many challenges and potential drawbacks. *Firstly*, these nanomaterials can have potentially affected human health. While many studies have performed in vitro and reported on antibacterial, anti-cancer as well as the treatment of many diseases, the effects of administering nanoparticles directly into the body still need a satisfactory answer (Zhang et al. 2014; Bethu et al. 2018; Youssif et al. 2019). *Secondly*, their special physicochemical properties need to be monitored for better understanding of underlying influential mechanisms because the nano-scaled materials exhibit more significantly variable behaviors than the macroscopic ones (Ojha 2020). *Thirdly,* for environmental and agricultural applications, the aspects of negative effects on living organisms are also of great concern. Animals, and aquatic organisms may be exposed directly or indirectly from residues of post-use nanomaterials discharged in soil and water environments (Marambio-Jones and Hoek 2010). *Fourthly*, the actual efficiency of biomedical and environmental applications of bio-based nanoparticles needs to be addressed as many studies are carried out in the simulated or theoretical mode. *Fifthly*, the adoption of plants to synthesize nanoparticles on a large scale will lead to worrying concerns about caring for well-grown plants to accommodate conditions containing the necessary biological compounds. These undesirable effects require further insights and advancements with many specified researches. *Sixthly*, the biggest obstacle limiting the applications of nanoparticles is the lack of a standardized set of regulations necessary for their utilization. Their uncontrolled use without unified regulations will cause many inevitable effects. *Ultimately*, the field of nanotoxicology is still in its infancy to ensure the safety of nanoparticles (Baruah et al. 2016). These challenges need to be addressed before large-scale commercialization and development of nanoparticles from plant extracts can be made.

Conclusion

Here, we systematically illuminated the formation, antimicrobial activity, and biomedical performance of green nanoparticles synthesized from plant extracts. Besides, this review assessed the significance of phytochemicals in the formation and properties of green resultant nanoparticles. These compounds act as reducing, capping, stabilizing and chelating agents during biosynthesis. The antimicrobial and antifungal activities of green nanoparticles were vigorously discussed with emphasis on the promising therapeutics against infectious diseases. The role of nanoparticles in drug delivery, disease diagnosis and treatment were also shed light on. Pathways using plant-based nanoparticles are opening new potential frontiers to treat diseases such as diabetes, malaria or Alzheimer.

Acknowledgements The authors would love to appreciate the effort of researchers all over the world in the fight against the COVID-19 pandemic. We also acknowledge Mina Rees Library, The Graduate Center of the City University of New York (CUNY) for granting access to databases, Freepik company projects at www.freepik.com, and Canva® graphic design platforms at www.canva.com for many graphic resources reproduced in this work.

Authors contributions NTTN contributed to conceptualization, data curation, investigation, methodology, writing—original draft. LMN contributed to data curation, investigation, validation, writing—original draft. TTTN contributed to writing—review & editing, data curation, validation. TTN contributed to writing—review & editing, data curation, validation. DTCN contributed to conceptualization, writing—review & editing, validation, data curation, supervision. TVT contributed to conceptualization, writing—review & editing, validation, data curation, supervision, project administration. All authors read and approved the final manuscript.

Funding There was no external funding for this study.

Availability of data and material The authors declare that all data and materials support their published claims and comply with field standards.

Code availability The authors declare that software application or custom code supports their published claims and comply with field standards.

Declarations

Conflict of interest The authors declare that there are no conflicts of interest.

Compliance with Ethical Standards The authors declare that.
The manuscript has not been published anywhere nor submitted to another journal.
The manuscript is not currently being considered for publication in any another journal.
All authors have been personally and actively involved in substantive work leading to the manuscript and will hold themselves jointly and individually responsible for its content.
Research does not involve any Human Participants and/or Animals.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

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