

## CHAPTER 11

# Multimodal applications of phytonanoparticles

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### 11.1 Introduction

Nanoparticle synthesis can be performed by various methods such as physical, chemical, and biological approaches. Generally, the physical and chemical methods are considered the best to get uniform-sized nanoparticles with long-term stability. However, these approaches are expensive and release toxic/hazardous materials into the environment. Toxic chemicals used for nanoparticle synthesis in chemical methods make the obtained nanoparticles less suitable for medical, cosmetic, or food applications. Because several nanoparticles have been widely utilized in medical products, disease diagnosis, and cosmetics, improving the biocompatibility of nanoparticles is highly important. For the past decade, substantial consideration has been given to biosynthesis approaches for the production of metal nanoparticles such as silver, gold, copper, and platinum [1, 2]. Bio-synthetic routes of nanoparticle synthesis are considered ecofriendly because the reduced agents and stabilizing agents used are either bacteria, fungi, yeasts, and plants themselves or their active components.

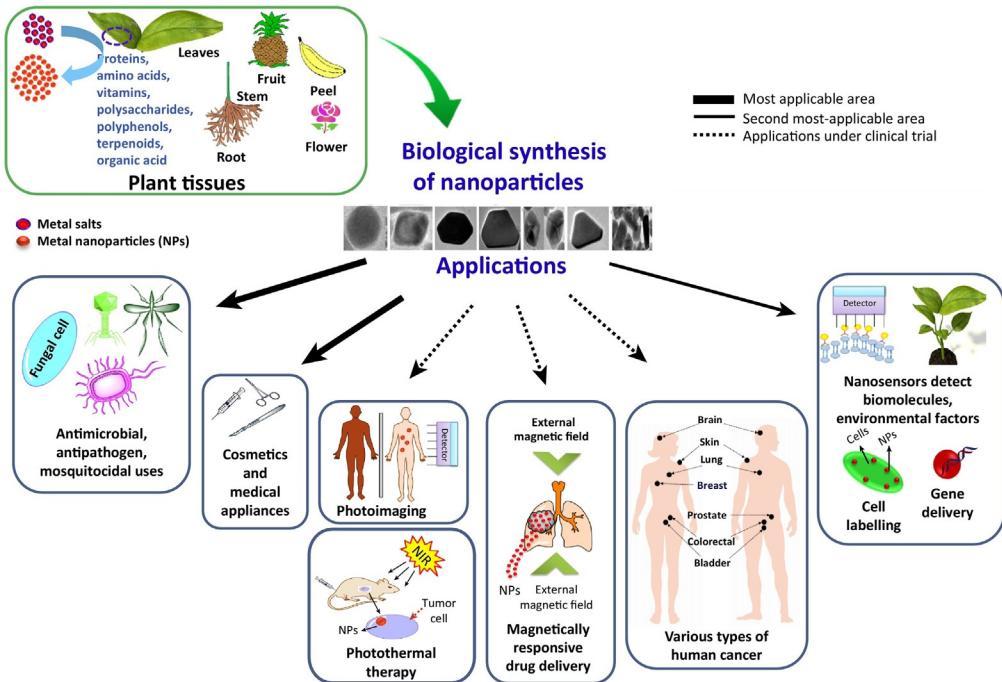
For the past decade, several plant species and plant-derived materials have been identified and used for the green synthesis of various nanoparticles. Several plants contain many biologically active compounds such as alkaloids, phenols, flavonoids, ascorbic acid, citric acid, polyphenolic, terpenes, and reductase, which act as reducing agents of metal salts [3]. Such phytosynthesis approaches are highly promising due to the ability of the plant materials themselves to act as both reducing and capping agents. Phytonanoparticle synthesis can happen with both intracellular and extracellular mechanisms. The selected species of plants growing in metal-rich organic media, metal-rich soil, and metal-rich hydroponic solution can intracellularly synthesize metallic nanoparticles [4]. This approach requires a significant effort to culture, monitor, track, and harvest nanoparticles. Such methods also result in adulteration with plant tissues, other components, plant pathogens, and biomolecules. However, the extracellular routes of nanoparticle synthesis involve the addition of plant extracts (e.g., leaves, roots, shoots, bark, fruits, etc.) to a

boiling metal salt precursor solution and facilitating the reduction of metal ions. Moreover, the use of specific plant-derived components such as biomacromolecules, enzymes, flavonoids, antioxidants, and alkaloids instead of the whole plant extract to achieve a controlled particle formation is a recent advancement of phytosynthesis. Macromolecules such as redox active proteins can also be used to synthesize metallic nanoparticles [5]. The phytosynthesis of silver nanoparticles using extracts of plants such as *Cinnamom zeylanicum* [6], *Geranium* [7], *Coleus aromaticus* [8], *Stevia rebaudiana* [9], *Aloe vera* [10], *Ocimum tenuiflorum* [11], papaya [12], *Cassia angustifolia* [13], lemon [14], *Biophytum sensitivum* [15], *Mimosa pudica* [16], and *Piper nigrum* [1, 17] has already been reported. The presence of biomacromolecules from such medicinal plants can improve the functional properties of the synthesized nanomaterials. Similarly, various plant extracts were used for the synthesis of gold [18, 19], platinum [20], and copper [21] nanoparticles.

Phytonanoparticles are suggested for several applications in the agriculture, environmental, cosmetics, biomedical, and industrial sectors. In the following sections, multimodal applications of phytosynthesized nanoparticles such as silver, gold, copper, etc., in several such fields are detailed.

## 11.2 Applications of phytonanoparticles

Phytonanoparticles have been applied in many fields such as agriculture and medicine as well as several industrial applications. Owing to the higher bioactivity of phytonanoparticles compared with physiochemical nanoparticles, they are preferred in biomedical and cosmetic applications. For example, phytonanoparticles showed higher biocompatibility with endothelial cells, cardiomyoblasts, and Chinese hamster ovary cells (CHO) than chemically synthesized ones [22]. The multimodal applications of phytonanoparticles are summarized in Fig. 11.1. Phytosynthesized silver nanoparticles are mostly utilized in the biomedical sector due to their outstanding antimicrobial activity. Silver, zinc, and other metal nanoparticles are also used in wound dressings, food packaging, and catheters due to their excellent antimicrobial property. Zinc- and titanium-based nanoparticles are mainly used in cosmetics applications owing to their UV-blocking capacity. Another important application of phytonanoparticles is the development of sensors for the recognition of various analytes related to the agriculture, diagnostics, and environmental sectors. Moreover, phytonanoparticles are suggested for use in gene delivery, drug delivery, and cell labeling, offering potential applications in biology and medicine. Some of the highly promising applications of metal and metal oxide nanoparticles are yet to be fully explored such as photothermal therapy, photoimaging, and magnetically induced drug delivery.



**Fig. 11.1** Multimodal applications of phytonanoparticles. Silver nanoparticles are mostly used in applications such as wound dressing, food packaging, catheters, sensors, gene delivery, cell labeling, photothermal therapy, photoimaging, and magnetically responsive gene/drug delivery. Adapted with permission from P. Singh, Y.J. Kim, D. Zhang, D.C. Yang, *Biological synthesis of nanoparticles from plants and microorganisms*, *Trends Biotechnol.* 34 (2016) 588–599.

### 11.2.1 Agricultural applications of phytonanoparticles

Phytonanoparticles provide environmentally friendly agricultural applications such as plant disease management, plant growth promotion, and stress tolerance [23]. Phyto-synthesized silver nanoparticles have shown promising antifungal activity against the spot blotch pathogen of wheat, *Bipolaris sorokiniana* [24]. Additionally, phytosynthesized silver nanoparticles using *Serratia* sp. were also found to inhibit the melanin biosynthesis genes in *B. sorokiniana* [25]. Several other phytopathogens were found to be sensitive to bio-nanoparticles, demonstrating their potential in managing several diseases in agricultural plants [26]. The effect of biosynthesized titanium dioxide ( $\text{TiO}_2$ ) nanoparticles on the growth of *Vigna radiata* and the enrichment of the rhizospheric microbial population

is highly promising [27]. Furthermore, the application of biosynthesized magnesium oxide ( $MgO$ ) nanoparticles improved the quality and yield of cluster bean plants (*Cyamopsis tetragonoloba*). The application of these bionanoparticles resulted in improvements in root-shoot growth and overall chlorophyll pigment in the plants. Biosynthesized zinc oxide ( $ZnO$ ) nanoparticles improved the alkaline phosphatase, acid phosphatase, and phytase activity in the cluster bean rhizosphere [27]. Owing to the anti-microbial and fertilizer action, phytosynthesized nanoparticles are highly promising for avoiding pathogenic outbreaks and promoting plant growth [28]. Such studies point out the potential of various phytonanoparticles in several agricultural applications.

### 11.2.2 Environmental applications of phytonanoparticles

Contaminating the environment with toxic materials due to human activities is a major concern. Various approaches and technologies are used to decontaminate polluted soils and water bodies. Toxic metals such as cadmium, arsenic, lead, barium, chromium, mercury, and nickel form the major metallic contaminants. The major organic contaminants include petroleum, organic solvents, plastics, pesticides, and herbicides. Although there are several physical and chemical environmental remediation methods available, they are not cost-effective, ecofriendly, or safe. Thus, it is important to find novel options that employ ecofriendly methods to eradicate not only metallic residues, but also organic pollutants, petroleum sludge, and military waste.

#### 11.2.2.1 Removal of heavy metals

Heavy metals such as lead (Pb) are a major issue in soil and water. In this direction, *Padina pavonina* and *Sargassum acinarium* were used as a reductant of  $FeCl_3$  to produce  $Fe_3O_4$  nanoparticles [29]. The obtained  $Fe_3O_4$  nanoparticles were loaded in calcium alginate particles and used to remove Pb. The *P. pavonina* phytosynthesized  $Fe_3O_4$  nanoparticle-loaded alginate beads possessed superior capacity for removing 91% of Pb while *S. acinarium*-based nanoparticles removed 78% after 75 min.

#### 11.2.2.2 Water purification

Ensuring the availability of drinking water is a challenging task for almost all countries across the world. The search for novel technologies for better water management is an ever-increasing need. Nanotechnology possesses great potential in water purification through designing advanced large-scale and household water treatment equipment. Preventing the growth of pathogenic microorganisms by modifying or coating the surfaces with antimicrobial agents has gained much attention in water filters. Owing to the enhanced antimicrobial activity, phytosynthesized silver nanoparticles can be used in the membrane filters of water-filtering machines. This approach is approved by the World Health Organization (WHO) [4]. In addition to the excellent antibacterial

efficacy, antimicrobial coatings should show low toxicity and ease of fabrication. Silver nanoparticle-coated surfaces have been largely used as antimicrobial coatings [4, 30].

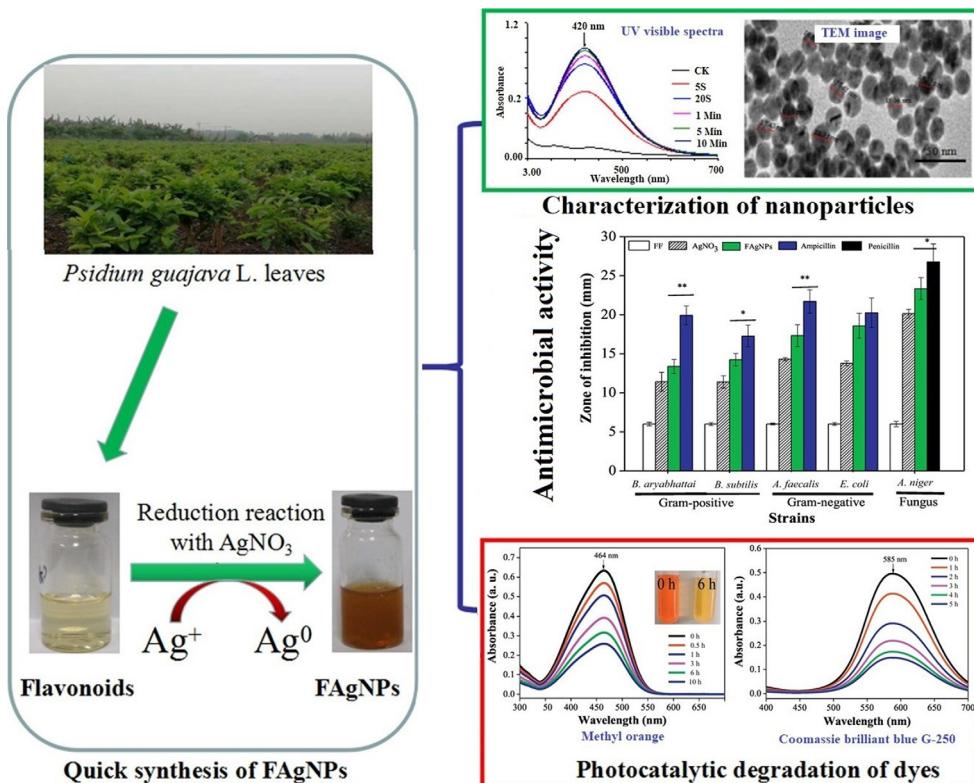
#### 11.2.2.3 Wastewater treatment

Wastewater treatment involves the removal of harmful contaminants from wastewater or sewage, then conversion into an effluent that can be given back to the water cycle with minimum impact on the environment or direct reuse for household purposes. In addition to the biomass, organic-inorganic substances and microorganisms form the major contaminants in wastewater. Nanoparticles such as silver, titanium dioxide, and ZnO hold great promise in wastewater treatment. Phytosynthesized nanoparticles are highly promising due to the potential advantages compared to chemically or physically synthesized nanoparticles. Silver and gold nanoparticles synthesized using the aqueous extract of burdock root possessed excellent bactericidal property against several bacteria and showed excellent catalytic activity for the degradation of pollutants in wastewater [31]. The reductive transformation of nitroaromatic compounds is a major process in wastewater treatment. Owing to the superb catalytic properties, metals such as palladium (Pd) can be used to remove such compounds. *Pantoea* sp.-assisted phytosynthesized palladium nanoparticles can be explored as an effective catalyst for the reduction of nitroaromatics [32]. Palladium nanoparticles showed superior catalytic activity in the reduction of nitroaromatic compounds such as 2-nitroaniline, 4-nitrophenol, 4-nitroaniline, and 2,6-dichloro-4-nitroaniline.

#### 11.2.2.4 Dye degradation

Environmental pollution due to textile dyes is a serious issue for soil and water bodies. Textile wastes are extremely colored, and their dumping in water resources results in unbearable damage to the ecosystem by affecting solar light penetration, which may reduce photosynthesis in aquatic plants and affect all levels of aquatic life. Further, the large solubility of dyes also contaminates both the ground and surface water. Phyto-synthesized silver and gold nanoparticles were able to degrade different types of dyes. Organic pollutants such as of methyl orange, 4-nitrophenol, and rhodamine B were degraded by silver and gold nanoparticles with pseudo-first-order rate constants [31]. Silver nanoparticles generated using the aqueous flower extract of *Ipomoea digitata* showed promising catalytic reduction of methylene blue in the presence of NaBH<sub>4</sub>. It followed pseudo-first-order kinetics with a rate constant of 0.1714 min<sup>-1</sup> [33]. Silver nanoparticles synthesized using *Convolvulus arvensis* extract were exploited as a catalyst for the reduction of azo dyes in the presence of NaBH<sub>4</sub> with promising results [34]. The silver nanoparticles synthesized using dandelion extract showed good catalytic degradation activity for rhodamine B and methyl orange in the presence of NaBH<sub>4</sub> [35]. Dandelion-based silver nanoparticles showed superior dye degradation for rhodamine and methyl orange with

rate constants of 0.1038 and  $0.0393\text{ s}^{-1}$ , respectively. Studies also showed that phytonanoparticles obtained by the reduction of silver nitrate using flavonoids obtained from *Psidium guajava* leaves possessed excellent dye degradation potential. They could effectively degrade organic dyes such as Coomassie Brilliant Blue and methyl orange under solar or UV irradiation (Fig. 11.2) [36]. In another investigation, silver nanoparticles were developed using the fruit extract of *Prosopis farcta* and used for degrading methylene blue in the presence of visible light [37]. The results revealed a considerable color degradation of 70.20% within the first 30 min. *Eriobotrya japonica* leaf extract phytosynthesized silver nanoparticles also showed rapid catalytic degradation of reactive dyes. Bimetallic silver/ZnO nanoparticles were synthesized using the extracts of the oak fruit hull [38]. ZnO NPs and Ag/ZnO NPs were then used to degrade basic violet 3 in aqueous solution. Ag/ZnO hybrid nanoparticles showed faster dye degradation (30 min) compared to ZnO nanoparticles (90 min). Phytosynthesized gold nanoparticles using marine



**Fig. 11.2** Wastewater treatment potential of *Psidium guajava*-mediated synthesized silver nanoparticles. Reproduced with permission from L. Wang, F. Lu, Y. Liu, Y. Wu, Z. Wu, Photocatalytic degradation of organic dyes and antimicrobial activity of silver nanoparticles fast synthesized by flavonoids fraction of *Psidium guajava* L. leaves, *J. Mol. Liq.* 263 (2018) 187–192.

macroalgae *Padina tetrastromatica* and their application for dye degradation indicated that the biosynthesized gold nanoparticles can degrade Congo red and eosin yellow in the presence of sodium borohydride with pseudo-first-order kinetics [39].

Similarly, phytosynthesized copper oxide (CuONPs) nanoparticles using *Ruellia tuberosa* (R. *tuberosa*) aqueous extract also possessed good dye degradation capacity [40]. CuONPs embedded on cotton fabrics showed photocatalytic reduction of crystal violet. In another study, manganese dioxide ( $\text{MnO}_2$ ), copper oxide (CuO), and silver nanoparticles were developed using *Kalopanax pictus* plant extract and the dye degradation potential was evaluated [41]. The Congo red degradation potential of the  $\text{MnO}_2$  nanoparticles was higher than that of the silver and CuO nanoparticles. All the nanoparticles showed a relatively similar degradation capacity against Safranin, indicating the potential of *K. pictus*-synthesized nanoparticles for the degradation of dyes. Tin oxide ( $\text{SnO}_2$ ) nanoparticles synthesized using guava (*P. guajava*) leaf extract showed promising photocatalytic activity, as evident from the degradation of reactive yellow 186 dye under sunlight [42]. The effective degradation of 90% dye was achieved within 180 min at a rate constant of  $0.00476 \text{ min}^{-1}$ . Zinc sulfide phytonanoparticles (ZnS) have been successfully produced using various methanol plant extracts [43]. The photocatalytic degradation of methylene blue dye (MBD) and methyl orange dye (MOD) in the presence of synthesized ZnS nanoparticles was also tested under UV exposure. ZnS nanoparticles synthesized using *Syzygium aromaticum* methanol extracts showed higher dye degradation compared to other ZnS nanoparticles.

Phytosynthesized iron nanoparticles (INPs) using *Lagerstroemia speciosa* also possessed dye degradation properties [44]. The phytonanoparticles were used for the degradation of organic dyes such as brilliant blue, methyl orange, methylene blue, allura red, and green along with hydrogen peroxide under solar light. Decolorization of all the tested dyes presented first-order-rate kinetics with a rate constant in the range of  $13.1 \times 10^{-3}$  to  $17.7 \times 10^{-3} \text{ min}^{-1}$ . Similarly, Iron oxide nanoparticles (IONPs) were synthesized using the aqueous leaf extract of *Daphne mezereum* [45]. These phytonanoparticles were tested for dye-removal activities. The decoloration efficiency was about 81% after 6 h. *Trigonella foenum-graecum* synthesized zero-valent iron nanoparticles ( $\text{Fe}^0$ ) (ZV-Fe NPs) could effectively degrade methyl orange dye under UV light [46]. This reaction followed pseudo-first-order kinetics, and the rate constant  $k_{\text{app}}$  was found to be  $0.025 \text{ min}^{-1}$ . Phytosynthesized hematite nanoparticles using the leaf broth of the *P. guajava* plant could effectively catalyze the degradation of the dyes such as methyl red, methyl orange, eosin yellowish, and methylene blue [47]. Bimetallic iron-silver core-shell nanoparticles, ( $\text{FeO}/\text{AgNPs}$ ) iron-gold core-shell nanoparticles ( $\text{FeO}/\text{AuNPs}$ ), and iron nanoparticles ( $\text{FeONPs}$ ) were synthesized using pomegranate fruit (PEP) peel extract [48]. Core-shell nanoparticles showed the highest aniline blue (AB) dye degradation at  $70^\circ\text{C}$  and pH 10. Moreover, gold nanoparticles, supported on  $\text{Fe}_3\text{O}_4@\text{polyaniline}$  as a magnetic nanocatalyst, showed the reduction of methyl orange (MO) and methylene blue (MB) from

aqueous solutions [49]. Here, gold nanoparticles were synthesized using the extract of *Allium Sp.* The degradation reaction of azo dyes with NaBH<sub>4</sub> in the presence of the phytonanoparticle-based catalyst was several-fold faster than degradation without the nanocatalyst. Calcium hydroxide nanoparticles (Ca(OH)<sub>2</sub>-NPs) were synthesized from calcium oxide using the *Andrographis echooides* leaf extract [50]. Ca(OH)<sub>2</sub>-NPs showed excellent methylene blue dye degradation efficiency under UV, visible, and sunlight (98.96%, 97.52%, and 96.38%, respectively).

Phytosynthesized metal, metal oxide, or metal hydroxide nanoparticles act as promising materials for dye degradation, which will substantially contribute to environmental protection.

#### 11.2.2.5 As a mosquito larvicidal agents

Several diseases such as dengue fever are transmitted through viral vectors such as mosquitos. Killing mosquito larvae in standing water is the best strategy to reduce mosquito-mediated disease outbreaks. Commonly used larvicides include organophosphorate Temephos, which may cause adverse effects such as headaches, loss of memory, and irritability. Silver nanoparticles showed larvicidal properties against the larvae of several species of mosquitoes. Silver nanoparticles synthesized using the leaf extract of *Rhizophora mucronata* showed larvicidal activities against the larvae of *Aedes aegypti* (*A. aegypti*) and *Culex quinquefasciatus* (*C. quinquefasciatus*) [51]. Larvicidal activities such as LC<sub>50</sub> and LC<sub>90</sub> values were measured. The LC<sub>50</sub> values were 0.585 and 0.891 mg/L for *A. aegypti* and *C. quinquefasciatus* larvae, respectively. Moreover, the LC<sub>90</sub> values were 2.615 and 6.291 mg/L for *A. aegypti* and *C. Quinquefasciatus*, respectively.

Similarly, silver nanoparticles synthesized using *Centroceras clavulatum* algal extract [52] showed that the LC<sub>50</sub> values of *C. clavulatum* extract against *A. aegypti* larvae and pupae were 269.361–387.637 ppm, and 446.262 ppm (pupa), respectively. The LC<sub>50</sub> values of *C. clavulatum*-synthesized AgNP were 21.460 to 29.155 ppm (larva), and 33.877 ppm (pupa), respectively. Silver nanoparticles were produced using *Moringa oleifera* seed extract and tested for larvicidal activity against *A. aegypti* [53]. Silver nanoparticles were very effective against *A. aegypti*, with LC<sub>50</sub> values ranging from 10.24 to 21.17 ppm.

Overall, green-synthesized nanomaterials can be used as promising mosquito larvicidal agents to fight viral diseases such as dengue fever.

#### 11.2.3 Cosmetic applications

Cosmetics products have been generally defined as “articles intended to be applied to the human body by being rubbed, poured, sprinkled, or sprayed for cleansing, promoting attractiveness, beautifying, or altering the appearance” [53a]. Cosmeceuticals are cosmetic products having some specific therapeutic effects. In the cosmeceutical industry, nanotechnology has huge potential because the nanoparticles can easily reach the targeted tissue by passing the skin. Nanoparticles are commonly used in cosmetics industry for

improving the properties of different products and formulations. Nanomaterials can also provide improved sensory characteristics and stability to cosmetic products. Zinc oxide and titanium dioxide nanoparticles not only give a better feel and spreading capacity to the cosmetic formulation, but they also give better protection from harmful UV radiation.

Skin penetration studies using a silver nanoparticle gel formulation in rats indicated that they are safe for topical application [54]. Certain nanoformulated creams for sensitive teeth contain calcium phosphate nanoparticles that generate a thin layer of apatite such as natural tooth enamel and reduce pain. Gold and silver nanoparticles are used in body creams and lotions to give the skin a fresher appearance. Silver nanoparticles are used in deodorants, toothpastes, soaps, lip products, wet wipes, and face creams.

Antimicrobial cream formulations can be developed by incorporating phytosynthesized silver nanoparticles [55]. *Withania somnifera* extract-mediated synthesized silver nanoparticles were incorporated into a cream base and tested for their antimicrobial activity against human pathogens such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Proteus vulgaris*, and *Candida albicans*. Results showed that silver nanoparticle-loaded creams hold superior inhibitory potential against these microbes. Similarly, silver nanoparticles synthesized using *Solanum trilobatum* Linn extract with antibacterial properties against multiple bacteria and fungi can be used as an active ingredient in shampoos [56]. The phytonanoparticle-loaded shampoo possessed antidandruff activity against fungal pathogens such as *Pityrosporum folliculitis* and *Pityrosporum ovale*.

Soaps loaded with nanoparticles show fungicidal and bactericidal properties and can be useful in treating sun-damaged skin as well as acne. Silver nanoparticles synthesized using *Coleus vettiveroids* aqueous leaf extract were impregnated in coconut oil-based saponified soap [57]. The soap impregnated with silver nanoparticles exhibited antibacterial activity against both Gram-negative and Gram-positive bacteria. Hand wash containing 15 mg per liter of silver nanoparticles was effective against pathogens [58]. The incorporation of silver nanoparticles in dentifrices effectively destroyed pathogenic yeasts found in the mouth such as *C. albicans* and *Candida glabrata* [59].

There is a good chance of microbial contamination of cosmetics when the user opens and closes the cosmetic containers or bottles during daily use. Thus, the incorporation of preservatives is necessary to prevent microbial contamination in cosmetic products. Parabens and phenoxyethanol are generally used in cosmetic products for antimicrobial properties; however, they may temporarily irritate the skin and increase the skin's UV sensitivity [60]. Due to the antibacterial activity of silver nanoparticles, they can be used as safe alternatives for these preservatives in cosmetics. Thus, phytosynthesized silver nanoparticles can be incorporated into shampoos and toothpastes as preservatives. Although only limited information is available regarding the cosmetic application of phytosynthesized nanoparticles, they have enormous potential as active ingredients in cosmetic products.

## 11.2.4 Biomedical applications of phytonanoparticles

Various types of nanoparticles are extensively used in several biomedical applications, including image contrast agents, antibacterial dressings, cancer treatment, and biosensors. Therefore, ecofriendly and biofriendly nanoparticles synthesized using plants and plant derivatives can find several applications in medical and biomedical products [60a].

### 11.2.4.1 As antimicrobial agents

Phytosynthesized nanoparticles can be used in several biomedical products such as wound dressings, biomaterial implants, catheters, stents, and blood bags due to their antimicrobial properties. Phytonanoparticles possess improved antimicrobial property over their bare counterparts due to the presence of phytochemicals. The phytochemicals present in the plants are responsible for improvements in the inherent antimicrobial activity of silver nanoparticles [1].

Phytosynthesized silver nanoparticles can induce membrane damage in *Candida* sp. and damage in fungal intercellular components [30]. *Garcinia mangostana* leaf extract-based silver phytonanoparticles were found to be very effective against various drug-resistant pathogens [61]. *Artemisia nilagirica* (Asteraceae)-mediated synthesized silver nanoparticles also showed susceptibility against several microorganisms [62]. Silver nanoparticles synthesized using marine seaweed *Sargassum wightii* were effective against *S. aureus*, *K. pneumoniae*, and *S. typhi* [63]. Silver nanoparticles synthesized using other plants such as Tulsi (*Ocimum sanctum*) leaf extract [64], *Origanum vulgare* (Oregano) [65], *Coptidis rhizome* [66], *Carissa carandas* (Karonda) berry water extract [67], and *Salicornia bigelovii* [68], showed efficient antibacterial activity against different pathogenic and nonpathogenic bacteria on par with generic antibiotics. Copper oxide nanoparticles synthesized using brown alga (*Bifurcaria bifurcata*) with dimensions of 5–45 nm exhibited high antibacterial activity against two different strains of bacteria *Enterobacter aerogenes* (Gram-negative) and *S. aureus* (Gram-positive) [69].

Fungal infections are one of the major causes of several infectious diseases. One of the most common pathogens responsible for fungal infections is the *Candida* species [70]. It can result in a nosocomial infection with an associated mortality rate of up to 40% [71]. Silver nanoparticles show antifungal activity against several fungal species, including candida [72]. Recently, studies showed that Tulsi (*O. sanctum*)-mediated AgNPs exhibited antifungal activity against an opportunistic human fungal pathogen [73]. Silver nanoparticles synthesized using extracts of *Shoreatum buggaia*, *Boswellia ovalifoliolata*, and *Svensonia hyderobadensis* showed antifungal activity against *A. niger*, *A. flavus*, *Curvularia* sp., *Fusarium* sp., and *Rhizopus* sp. [74]. Among these, nanoparticles synthesized from *Svensonia hyderobadensis* showed higher activity as compared to AgNPs synthesized using two other plants. However, the exact mechanism of antifungal activity of silver nanoparticles has not been reported. One possible mechanism might be the destruction of the membrane integrity of fungi and the inhibition of the budding process in yeasts.

Silver nanoparticles possess inhibitory effects on several pathogens, including viruses, and offer an excellent opportunity to formulate novel antiviral agents. Phytosynthesized nanoparticles can act as potent broad-spectrum antiviral agents against several pathogenic viruses [75]. Metal nanoparticles can be effective antiviral agents against HIV-1, hepatitis B virus, respiratory syncytial virus, herpes simplex virus type 1, monkeypox virus, influenza virus, and Tacaribe virus [76]. Biometallic nanoparticles are strong antiviral agents and inhibit viral entry into the host system [77]. Phytosynthesized silver nanoparticles using *Phyllanthus niruri*, *Andrographis paniculata*, and *Tinospora cordifolia* were tested for their antiviral activity against chikungunya virus [78]. An in vitro antiviral test demonstrated that nanoparticles synthesized from *A. paniculata* were the most effective, followed by *T. cordifolia* and *P. niruri* ones. The viability of cells infected with chikungunya virus increased three- to four-fold upon treatment with *A. paniculata*-based nanoparticles. Similarly, silver nanoparticles were synthesized using the extract of the alga *C. clavulatum* and tested against the dengue fever virus [52]. Cellular internalization assays demonstrated that untreated infected cells showed a high intensity of fluorescence emission, which denotes a high level of viral internalization. However, AgNP-treated infected cells possessed low levels of fluorescence, indicating a low viral load. In another study, silver nanoparticles generated using *M. oleifera* seed extract were also tested against the dengue serotype DEN-2 [53]. AgNP showed in vitro antiviral activity against DEN-2 infecting vero cells. After 6 h of treatment, the DEN-2 yield was  $5.8 \log 10$  PFU/ml in the control while it was  $1.4 \log 10$  PFU/mL posttreatment with AgNP (20  $\mu$ L/mL), which highlights the strong potential of green-synthesized AgNPs to control dengue fever. Bio-nanoparticles also showed size-dependent interaction with herpes simplex virus types 1 and 2 and with human parainfluenza virus type 3 [79]. Tannic acid (TA-AgNPs)-modified silver nanoparticles showed good antiviral activity against genital herpes infection [80]. Mice treated intravaginally with TA-AgNPs showed a low virus load in the vaginal tissues quickly after treatment. Moreover, vaginal tissues treated with TA-AgNPs exhibited a considerable increase in the number of activated B cells, IFN-gamma + CD8<sup>+</sup> T-cells, and plasma cells. The spleens of treated mice possessed a higher number of effector-memory CD8<sup>+</sup> T cells and IFN-gamma + NK cells in comparison to the placebo control group.

The results of several studies indicated that using phytonanoparticles such as nanosilver as antiviral agents is a viable approach that delivers alternative therapeutic possibilities against devastating viral diseases. Overall, the plant-mediated synthesis of metal or metal oxide nanoparticles can be employed to develop newer, safer, and cheaper therapeutic agents to fight several viral pathogens, with no considerable cytotoxicity on mammalian cells.

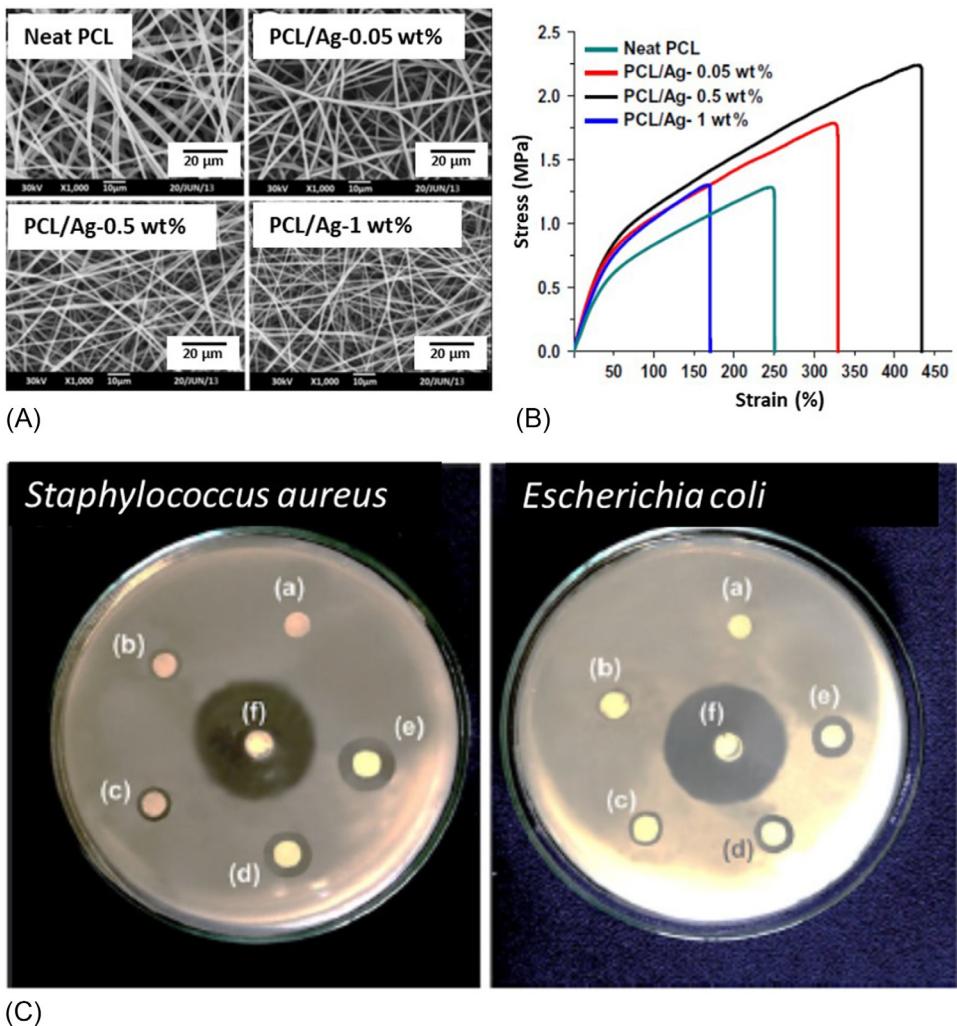
#### **11.2.4.2 As wound healing agents**

An unprotected wound is highly susceptible to microbial invasion, colonization, and pathogenesis. In order to prevent wound infections, a suitable wound dressing material

with a bacterial barrier property, an antibacterial property, and the ability promote wound healing should be used [81]. Despite the lack of thorough validation of the activity, many commercial antimicrobial wound dressings are indicated for the management of various types of wounds, such as burns, chronic ulcers, and diabetic foot ulcers [82]. Several such wound dressings loaded with nanoparticles are able to reduce the healing time and inhibit bacterial growth to a higher extent than standard silver sulfadiazine, without harmful effects on the treated patients [83, 84].

Several biopolymers such as polycaprolactone (PCL) [85–87], polylactic acid (PLA) [88], polyvinyl alcohol (PVA) [16, 89], chitosan [90], gelatin [91], etc., are widely used wound-dressing applications. Electrospinning is a robust technique for the development of porous membranes for wound-dressing applications with microbial barrier properties [92, 93]. *P. nigrum* (black pepper) leaf extract-mediated biosynthesized silver nanoparticles were incorporated in electrospun PCL membranes to provide antibacterial properties [17]. Fig. 11.3A shows the morphological features of the PCL/silver nanocomposite membranes. In the case of PCL/silver nanocomposite membranes, there was a considerable reduction in the fiber diameter as the nanoparticle concentration increased in the composite. From the stress strain curves of the membranes, there was a clear improvement in the tensile strength of the membranes with increasing nanoparticle loading (Fig. 11.3B). The developed membranes containing phytonanoparticles exhibited antibacterial activity against *S. aureus* and *E. coli* in a concentration-dependent way (Fig. 11.3C). Phytosynthesized copper oxide nanoparticles using brown alga (*B. bifurcata*) with 5–45 nm size showed excellent antibacterial property against two different strains of bacteria, *E. aerogenes* (Gram-negative) and *S. aureus* (Gram-positive) [69]. Silver nanoparticles synthesized using *B. sensitivum* were incorporated in nano-micro dual-porous calcium pectinate scaffolds to generate antibacterial wound dressings [15]. Developed wound dressings possessed excellent exudate uptake capacity and antibacterial property, and were also biocompatible with human cells. In addition, these membranes with good antibacterial properties can effectively fight off invading pathogens. Electrospun PVA membranes containing phytosynthesized silver nanoparticles were suggested for wound-healing applications [16]. The extract of *M. pudica* was used for the synthesis of biosilver nanoparticles. Nanoparticle-loaded PVA membranes possessed excellent exudate uptake capacity, blood compatibility, antibacterial activity, mechanical strength, and cytocompatibility. At optimum concentrations, the presence of biosilver nanoparticles enhanced wound healing in an in vitro wound contraction model.

Silver nanoparticles synthesized using *Aspergillus niger* were able to improve wound healing by inhibiting pathogenic bacteria and modulating the wound healing-associated cytokines [94]. Biosilver nanoparticle treatment reduced the time required for the differentiation of fibroblasts into myofibroblasts and had a shorter time for the inflammatory process compared with that observed with conventional wound dressings.



**Fig. 11.3** Phytosynthesized silver nanoparticle-loaded wound dressings. The SEM morphology of PCL dressings loaded with various amounts of silver nanoparticles (A). Stress-strain curves of PCL membranes loaded with different amounts of silver nanoparticles showing the variation in mechanical properties (B). Antibacterial testing of the neat PCL membranes (a), PCL/silver nanocomposite membranes containing 0.05% w/w (b), 0.2% w/w (c), 0.5% w/w (d), and 1% w/w (e) silver nanoparticles. Reproduced with permission from R. Augustine, N. Kalarikkal, S. Thomas, *Electrospun PCL membranes incorporated with biosynthesized silver nanoparticles as antibacterial wound dressings*, *Appl. Nanosci. (Switzerland)* 6 (2016) 337–344.

### 11.2.4.3 In cancer treatment

Several types of nanomaterials are extensively used in cancer therapy [95]. Studies have demonstrated that nanoparticles can activate proapoptotic pathways mediated by the generation of reactive oxygen species (ROS) [96]. Silver nanoparticles generated using the plant extract of *O. vulgare* (Oregano) exhibited concentration-dependent inhibitory activity against the lung cancer cell line, A549 ( $LD_{50} = 100 \mu\text{g/mL}$ ) [65]. A relatively low concentration of gold nanoparticles was able to show apoptosis in malignant cells [97]. Plant-derived nanoparticles can revolutionize cancer treatment without interfering with the viability of normal cells. Green-synthesized silver nanoparticles using *Morinda citrifolia* exhibited a higher cytotoxic effect in HeLa cell lines compared to other chemotherapeutic drugs [98]. Biosynthesized silver nanoparticles by the yeast *Cryptococcus laurentii* exhibited excellent antitumor response in breast cancer cell lines such as MCF7 and T47D [99]. Silver nanoparticles synthesized from the extract of *Ganoderma neo-japonicum* mycelia showed good cytotoxicity against breast cancer cells [100]. Low concentrations of silver nanoparticles (1–10  $\mu\text{g/mL}$ ) successfully inhibited breast cancer cell proliferation and induced membrane leakage. Silver nanoparticles synthesized using *Syzygium cumini* fruit extract showed antioxidant and anticancer activity against Dalton lymphoma cell lines under in vitro conditions [101]. About 100  $\mu\text{g/mL}$  nanoparticle content resulted in the 50% viability of Dalton lymphoma cells. *Salvadora persica* extract was utilized for the synthesis of zinc oxide nanoparticles (ZnO-NPs) under ambient conditions [102]. Phytosynthesized nanoparticles could reduce the viability of the HT-29 cancer cell line in a concentration-dependent manner. Composite hydrogels consisting of chitosan, alginate, and biosynthesized silver nanoparticles showed good anticancer effect on the breast cancer cell line MDA-MB-231 [103]. The  $IC_{50}$  value of chitosan-alginate-AgNPs on MDA-MB-231 was 4.6 mg.

### 11.2.4.4 In biosensing, cell labeling, tracking, and imaging

Metal nanoparticles with plasmonic properties such as silver and gold greatly depend on the shape, size, and dielectric medium that surrounds it [104]. The applicability of such particles in biosensing is of great interest to researchers and industry [105]. The sensing of biomolecules relies on their binding on the surface of metal nanoparticles and subsequent changes in the plasmonic properties of the nanoparticles. The adherence of biomolecules on the surface of nanoparticles increases the refractive index and results in shifting the extinction spectrum. Differently shaped silver nanoparticles are incorporated in biosensors to detect different biomolecules and sense their diverse range of interactions. Phytosynthesized nanoparticles have great potential in biosensing applications.

Optical imaging is a promising imaging technique with huge potential for improving disease diagnosis and treatment. The most commonly used optical imaging techniques for biomedical applications include bioluminescence imaging, fluorescence imaging, optical coherence tomography, Raman imaging, and photoacoustic imaging [106, 107]. Optical

imaging uses nonionizing radiation as the primary imaging illumination source to characterize local anatomy down to the cellular and molecular levels. Thus, optical imaging technologies are becoming important tools to image functional, structural, and molecular information of cells and tissues. One of the major limitations of *in vivo* optical imaging is limited tissue penetration [108, 109]. However, this issue can be at least partially addressed by the use of near-infrared (NIR) optical imaging, due to a reduction in scattering and minimal absorption within the NIR region [110]. Small organic fluorescent dyes used in optical imaging have drawbacks such as a low fluorescence quantum yield, photobleaching, a very fast body clearance, and the lack of precise targeting properties. All such critical drawbacks can be overcome using nanostructured probes. A possible drawback of nanomaterial-based fluorescent probes is related to their composition because they typically contain toxic heavy metals such as cadmium. In this context, low toxic metal nanoparticles such as gold and silver together with silica are now receiving increasing attention as fluorescent probes [111]. As silver nanoparticles are photostable, they can be used as biological probes to continuously monitor dynamic events for an extended period of time. The functionalization of biomolecules on the surface of AgNPs can increase the specificity for the cell membrane. Phytonanoparticles have a large scope in this area as they lend themselves to act as multifunctional constructs.

Magnetite/gold ( $\text{Fe}_3\text{O}_4/\text{Au}$ ) hybrid nanoparticles were synthesized from a single iron precursor (ferric chloride) through a green chemistry route using grape seed proanthocyanidin as the reducing agent [112]. Structural and physicochemical characterization showed that the synthesized nanohybrids were crystalline with a spherical morphology and  $\sim 35$  nm size. Magnetization and magnetic resonance imaging studies revealed that the  $\text{Fe}_3\text{O}_4$  component possessed superparamagnetism with dark T<sub>2</sub> contrast and high relaxivity ( $124.2 \pm 3.02 \text{ mM}^{-1} \text{ s}^{-1}$ ). Phantom computed tomographic imaging demonstrated good X-ray contrast, which can be attributed to the presence of the nanogold component in the hybrid. The cellular uptake of the nanomaterial was visualized using confocal microscopy and Prussian blue staining. The absorption of the nanohybrids was visualized in the intracytoplasmic region of the cell, which is desirable for efficient imaging of cells.

### 11.2.5 Drug or gene delivery applications

Several types of nanoparticles have been identified and utilized as carriers for drug delivery applications [113, 114]. New drug delivery systems based on nanotechnology have been applied in the treatment of human diseases such as cancer, diabetes, and microbial infections as well as in gene therapy [115]. The benefits of these treatments are that the drug is targeted to the diseased cells, and the safety profile is enhanced by the reduced toxic side effects to normal cells. The major advantage of nanodrug delivery systems is that nanoparticles can be conjugated with different types of drugs to deliver them to

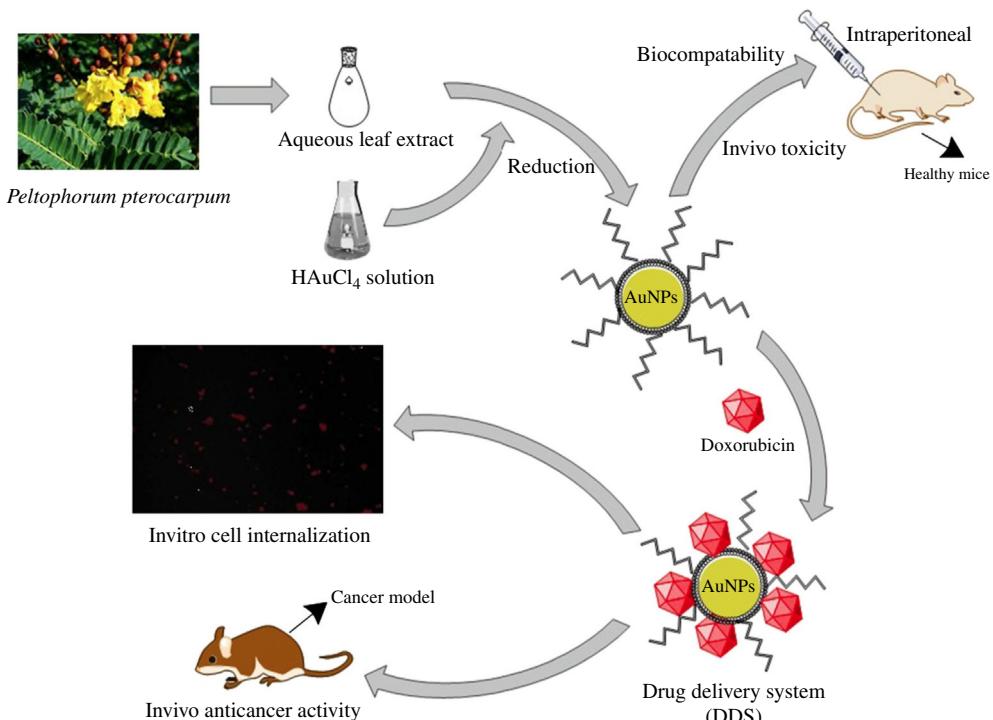
the target site by various methods. Metallic nanoparticles such as those based on gold are suitable for the preparation of drug delivery systems because of their cytocompatibility and immunocompatibility. As is obvious, nanoparticles produced by green approaches are safer for drug delivery applications than chemically synthesized ones. Although chemically synthesized gold nanoparticles have been extensively studied for their potential applications in drug delivery, only a few studies used the phytosynthesized gold nanoparticles for drug delivery applications. Gold nanoparticles conjugated with vancomycin were synthesized by *Trichoderma viride* and found to effectively suppress the growth of vancomycin-resistant *S. aureus* at a low concentration of 8 µg/mL [116]. The delivery of anticancer drugs to cancer cells using biosynthesized gold and silver nanoparticles (b-AuNP and b-AgNP) is also possible. *Butea monosperma* leaf extract was used for nanoparticle synthesis. Nanoparticle-based drug delivery systems conjugated with doxorubicin (DOX) [b-Au-500-DOX and b-Ag-750-DOX] showed significant inhibition of cancer cell proliferation compared to the free drug [117]. *P. pterocarpum*-mediated green-synthesized AuNPs were used as an effective drug delivery system for the delivery of DOX. A schematic representation of the study is shown in Fig. 11.4. Furthermore, in vitro and in vivo anticancer studies of DOX-loaded drug delivery systems were performed on A549 and B16F10 cancer cells and melanoma tumor mouse models, respectively. The internalization and release of free DOX were slow compared to the nanoconjugated form while biosynthesized AuNP-PP-DOX conjugates showed better tumor suppression ability than free DOX.

### 11.2.6 Industrial and technological applications

The development and electrochemical application of biologically synthesized nanomaterials have become important areas of research. *Barbated Skullcup* herb (a dried whole plant of *Scutellaria barbata* D. Don) was used for the synthesis of gold nanoparticles [118]. These phytonanoparticles were coated over a glassy carbon electrode (GCE) to improve the electronic transmission rate between the *p*-nitrophenol and the electrode.

Metal oxide nanoparticles such as TiO<sub>2</sub> are good alternative anode materials for lithium-ion battery applications due to their high structural stability and safety during the charge/discharge cycles. Cobalt doping can improve the intrinsic conductivity of TiO<sub>2</sub> anode materials. Bengal gram bean extract-mediated synthesis of Co-doped TiO<sub>2</sub> nanoparticles and their application as anode materials is reported [119]. The Co-doped TiO<sub>2</sub> shows a higher and stable coulombic efficiency up to 100 GCD cycles, indicating good reversibility.

Silver nanoparticles can be used as colorimetric optical sensors for the detection of metals and gases. For example, *Durenta erecta* (*D. erecta*)-mediated biosynthesized silver nanoparticles can be used for the fabrication of such sensors to detect chromium ions



**Fig. 11.4** Schematic representation of a drug delivery system based on biogenic gold nanoparticles synthesized via *Peltophorum pterocarpum* leaf extract and its in vitro and in vivo anticancer potential. Reproduced with permission from M. Ovais, A. Raza, S. Naz, N.U. Islam, A.T. Khalil, S. Ali, M.A. Khan, Z.K. Shinwari, Current state and prospects of the phytosynthesized colloidal gold nanoparticles and their applications in cancer theranostics, *Appl. Microbiol. Biotechnol.* 101 (2017) 3551–3565.

(Cr<sup>6+</sup>) and ammonia [120]. A fast response time and a lower detection limit up to 0.1 ppm of phytonanoparticles are very useful for the colorimetric detection of Cr<sup>6+</sup> and ammonia. In situ reduction and immobilization of palladium (Pd) nanoparticles on the surface of graphene oxide with *Artemisia abrotanum* extract improved the catalytic performance [121]. Pd (0) nanoparticles were completely spread on the surface of GO.

Nanoparticles play a major role in the development of packaging materials with anti-microbial and antifouling properties. Silver nanoparticles synthesized using the leaf extract of the plant *Protium serratum* were suggested for food packaging and preservation applications due to their potential to combat various foodborne pathogenic bacteria such as *E. coli* ( $IC_{50}=84.28\pm0.36\ \mu\text{g/mL}$ ), *P. aeruginosa* ( $IC_{50}=74.26\pm0.14\ \mu\text{g/mL}$ ), and *Bacillus subtilis* ( $IC_{50}=94.43\pm0.4236\ \mu\text{g/mL}$ ) [122].

Although there is not a lot of information available regarding the industrial application of phytosynthesized nanoparticles, phytonanoparticles can also be used for any application where chemically or physically synthesized nanoparticles are generally used.

### 11.3 Conclusion

The phytosynthesis of nanoparticles is an efficient and ecofriendly method for the synthesis of various nanoparticles of varying compositions. Biochemicals present in the plant extract can act as both reducing and stabilizing agents during the formation of phytonanoparticles. The major benefits of phytonanoparticles are their biocompatibility and bioactivity due to the presence of plant-derived biomolecules. Owing to the superior properties and ecofriendly synthesis route, phytonanoparticles have a lot of potential in various fields such as agriculture, cosmetics, bioremediation, and biomedical applications. An important challenge in nanotechnology is to tailor the electronic, electrical, and optical properties of nanoparticles by controlling the size and shape. The effective utilization of phytosynthesized nanoparticles with various chemical compositions, sizes/shapes, and surface properties can be a novel, ecofriendly, and economically viable approach that can lessen toxic chemicals in the traditional practice.

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