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Plant-based metallic nanoparticles as potential theranostics agents: bioinspired tool for imaging and treatment

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Adila Nazli[1], Muhammad Waleed Baig[1], Muhammad Zia[2], Muhammad Ali[2], Zabta Khan Shinwari[2], Ihsan Ul Haq[1] ✉

[1]*Department of Pharmacy, Quaid-i-Azam University, Islamabad 45320, Pakistan*
[2]*Department of Biotechnology, Quaid-i-Azam University, Islamabad 45320, Pakistan*
✉ *E-mail: ihsn99@yahoo.com*

Abstract: Theranostic approach provides us a platform where diagnosis and treatment can be carried out simultaneously. Biosynthesis of theranostic-capable nanoparticles (NPs) can be carried out by phytoconstituents present inside the plants that can act as capping as well as stabilising agents by offering several advantages over chemical and physical methods. This article highlights the theranostic role of NPs with emphasis on potential of plants to produce these NPs through ecofriendly approach that is called 'Green synthesis'. Biosynthesis, advantages, and disadvantages of plant-based theronostics have been discussed for better understanding. Moreover, this article has highlighted the approaches required to optimise the plant-mediated synthesis of NPs and to avoid the toxicity of these agents. Anticipating all of the challenges, the authors expect biogenic NPs can appear as potential diagnostic and therapeutic agents in near future.

1 Introduction

Nanotechnology is defined as the science and engineering that involve design, synthesis, characterisation, and application of materials and devices whose smallest organisation, in at least one dimension is on nanometre scale or 1 billion of a metre [1]. Nanoparticles (NPs) possess approximate size of 100 nm or less. Nanotechnology involves application of science to control the matter at molecular level. It is an emerging field which is gaining importance in various fields such as mechanics, optics, biomedical science, drug gene delivery, non-linear optical devices etc. Small size and large surface to volume ratio of NPs make them excellent candidates for biomedical applications [2, 3]. NPs have brought revolution in biomedical field, healthcare, drug as well as gene deliver, and optical devices [4]. Theranostics is a concept that involves incorporation of diagnostic as well as therapeutic function on a single platform [5]. Theranostic nanoparticles (TNPs) contain polymers in which diagnostic as well as therapeutic agents have been incorporated simultaneously having capabilities such as controlled drug release, targeted drug release, multimodality diagnosis, as well as therapy [6]. They can be applied in various diagnostic techniques such as computerised tomography (CT), magnetic resonance imaging (MRI), ultrasound, radiation therapy etc. [7]. TNPs have brought revolution in biomedical field and various products have become commercially available while some are undergoing different phases of clinical trials [8]. Various physical and chemical approaches are available for synthesis of these NPs, but recently, biological systems arranging from prokaryotes to eukaryotes are gaining more attention. By using biological systems, NPs of desired shape and characteristics can be obtained if we ensure selection of appropriate organism, optimal condition for cell growth and enzyme activity, and optimal reaction conditions. Plants are natural nanofactory that contains capping as well reducing agents such as enzymes, proteins, and polysaccharides for synthesis and stabilisation of NPs. Up till now, a wide variety of TNPs has been prepared from plant extracts through green synthesis (Fig. 1) that offer more appropriate platform with significant advantages over other biological entities [3]. Green bionanomaterials involve metals such as silver, copper, gold, titanium, and iron that can be prepared from various biological entities with potential to be applied for various biomedical applications [18]. Metal NPs are promising biological detection tools because of their enhanced optical detection capabilities where incident light is associated with plasmon excitation of the metal resulting in million fold greater light scattering than any other molecule [19]. Green synthesis approach has resulted in initiation of new era of biotechnology [4].

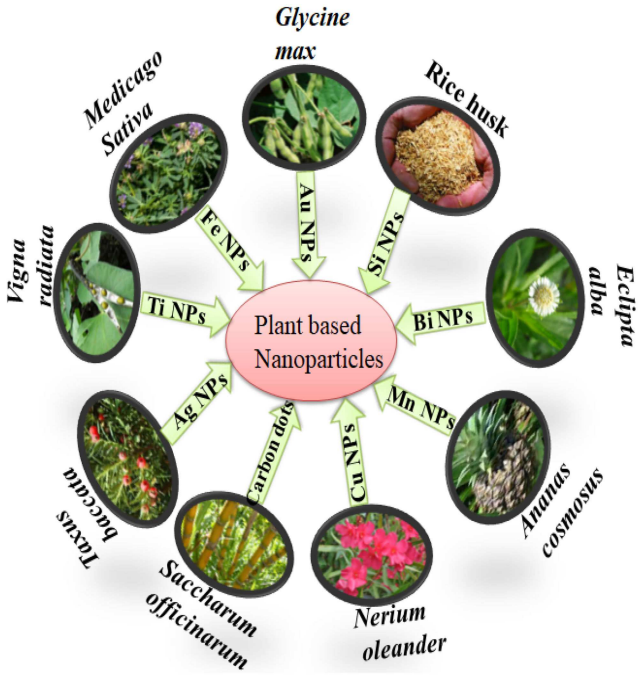

Fig. 1 *Representation of types of nanoparticles synthesise via different plants [9–17]*

2 Bio-synthesised NPs as theranostics

Among a number of plants-based green synthesised metallic NPs, few are studied for their theranostic potential as shown in Fig. 2.

2.1 Gold NPs as theranostics

Gold nanoparticles (Au NPs) have been studied as potential candidate as theranostic agents. Photoacoustic (PA) imaging is a technique that generates three-dimensional image of an anatomical structure due to absorption in near infrared region (NIR). Gold nanocages are ideal agents for PA imaging [24]. Au NPs can be used in optical imaging probes due to their properties such as supermagnetism, fluorescence, and surface plasmon resonance (SPR). When compared with bismuth sulphide and iodinated NPs, their size and shape can be easily controlled and modification can be done by introducing different functional groups [25]. Most of the applications of Au NPs are based on a phenomenon known as localised surface plasmon resonance (LSPR). SPR is a state of oscillation of electrons when they are irradiated by incident light, creating intense peaks at resonant wavelengths. Au nanostructures have LSRP in the NIR ranging from 700 to 900 nm. Nanostructures made up of other metals also exhibit strong LSPR but due to bioinert nature, Au NPs are potential candidate for these applications [26]. Light absorption and scattering of property of Au NPs enable them to diagnose and treat cancer. Moreover, their surface can be modified by attaching sulphur, phosphorus, and nitrogen ligands. In contrast to Au NPs, quantum dots (QDs) do not possess surface functionalisation property and can cause more toxicity [27]. Au NPs accumulate at target site and cause irreversible cell destruction and imaging by irradiating light due to SPR [28]. Hyperthermia is non-invasive approach for treatment of cancer in which tissues are exposed at high temperature for selective damage of cancerous cells. Owing to high metabolic rate, cancerous cells are more sensitive to high temperature which cause production of heat shock proteins and disrupts cellular metabolism resulting in apoptosis of cancerous cells [29]. Au NPs can be designed to absorb light at SPR wavelength (808 nm) which is then converted into heat, thus producing hyperthermic effect [30]. The viability of human pulmonary carcinoma cell line A459 was inhibited while bronchial epithelial cell line 16 HBE and primary adult stem cell MSC exhibited little cytotoxicity after incubation with Au NPs. It was believed that interaction between Au-nanorods and lysosome membrane facilitates the release of Au NPs resulting in apoptosis of cell lines. More selective targeting of cancerous cells can be achieved by attachment of cytokines and hormone receptors. TNF-α is a cytokine that synergise antitumour response when attached with Au NPs promote accumulation of conjugates at the site of tumour because TNF receptors facilitate accumulation of TNF-α in cancerous cells [31].

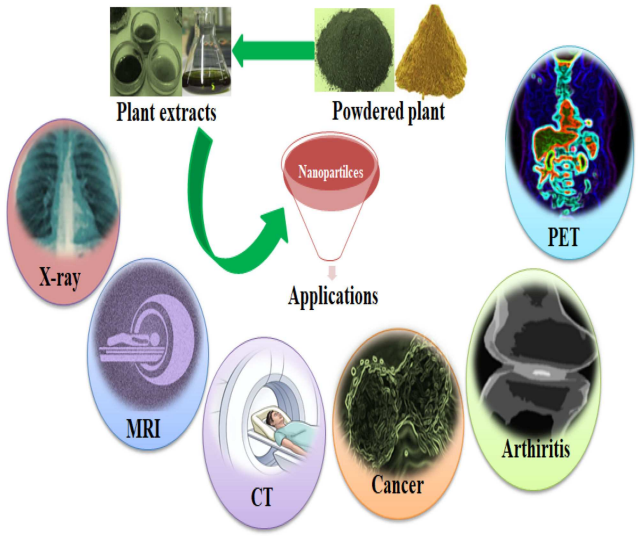

Fig. 2 *Applications of plant-based nanomaterials in disease diagnosis and treatment [20–23]. MRI, magnetic resonance imaging; CT, computed tomography; PET, positron emission tomography*

Plant-based green synthesised Au NPs have been revealed to inhibit the growth of cancerous cells [32]. Up till now Au NPs have been produced from many plants those are capable to play role in various biomedical fields as shown in Table 1. It has been reported that Au NPs with theranostic potential can be produced from various plants such as *Nyctanthes arbortristis* [38], *Centella asiatica* leaf extract [22], *Cinnamomum zeylanicum* [35], *Rosa hybrida* [39], *Chrysopogon zizanioides* leaf extract [40], and *Glycine max* [9]. Gum Arabica has been used to produce and stabilise Au NPs that possessed potential to play role in diagnostic techniques [33]. In addition, it was revealed that tea contain capping agents for preparation of Au NPs [34]. In addition to that *Butea monosperma* [44], *Amaranthus spinosus* [21], *Spheranthus amaranthoides* [41], *Moringa olifera* [43], *Syzgium aromaticum* [36], *Crocus sativus* [37], and *Punica granatum* [42] can also produce Au NPs with theranostic potential.

Table 1 Characteristics and applications of plant-based Au NPs acting as theranostic agents

Plant name	Size, nm	Shape	Diagnosis	Treatment	References
Acacia senegal	151	—	CT	cancer therapy	[33]
Glycine max	15 ± 4	spherical	molecular imaging	cancer therapy	[9]
Camellia sinensis	40	spherical	bio imaging	—	[34]
Cinnamomum zeylanicum	25	spherical	NIR absorber (cancer diagnosis)	—	[35]
Syzgium aromaticum	5–10	spherical, elliptical	biomedical imaging	photo thermal therapy	[36]
Centella asiatica	9.3, 10.9	spherical	biomolecular imaging	cancer therapy	[22]
Crocus sativus	15 ± 5	spherical, triangular	—	cancer therapy	[37]
Nyctanthes arbortrist	19.8 ± 5	triangular, pentagonal, rod shaped, spherical	contrasting agents in bioimaging	cancer therapy	[38]
Rosa hybrida	10	cubic	bio imaging	cancer therapy	[39]
Chrysopogon zizanioides	20–50	cubic	—	biosensor	[40]
Amaranthus spinosus	10.74	spherical, triangular	molecular imaging, i.e. PET, MRI, SPECT	—	[21]
Spheranthus amaranthoides	39–47	spherical	cancer diagnosis	cancer therapy	[41]
Punica granatum	70.90 ± 8.42	—	—	carrier for drug delivery targeting breast cancer	[42]
Moringa olifera	3–5	hexagonal, triangular	—	cancer therapy	[43]
Butea monosperma	10–3050–7530–100	sphericaltriangularhexagonal	—	efficient drug delivery for future cancer therapy	[44]

CT, computed tomography; NIR, near infrared region; PET, positron emission tomography; MRI, magnetic.

2.2 Iron oxide nanoparticles as theranostics

Iron oxide nanoparticles (IONPs) possess imaging and therapeutic capabilities due to super magnetic behaviour and surface modification ability; therefore, they are potential candidates for non-invasive diagnosis as well as treatment of cancer [45]. Large surface area of IONPs allows attachment to different ligands and receptors ensuring site-specific and controlled drug release. While attachment of molecular markers to IONPs enables them to visualise and detect changes in metabolic pathways; thus have potential for its manipulation in bioimaging. In addition, these factors can ensure site-specific controlled drug release with reduced drug wastage, thus minimising frequency of drug administration with fewer side effects [46]. In short, IONPs are biodegradable, biocompatible coating allows incorporation of multiple moieties, high drug loading capability, ease of surface modification by ligands ensuring targeted drug delivery [47]. When IONPs are used for imaging of cancerous tissues; different mechanisms have been reported behind differentiation of cancerous cells from normal cells. First, passive targeting of super iron oxide nanoparticles (SIONPs) is done through permeability and retention effect (EPR) effect in which cancerous cells because of damaged vasculature are more permeable due to enhanced EPR so they uptake more NPs when compared with normal cells. Second method of passive targeting is liver and spleen imaging via reticular endothelial system targeting, NPs can be internalised by macrophage-enriched organs such as liver, spleen, and bone marrow.

When tumorous tissues are present in these organs, they contain less macrophages that results in decreased internalised NPs when compared with normal tissue and hence, week MRI signal in these organs are prone. IONPs provide advantages over other contrast agents such as high magnetic signal strength, low toxicity, long-lasting contrast enhancement, and improved delineation of tumour margins [48]. Biomedical applications of IONPs have been depicted in Fig. 3.

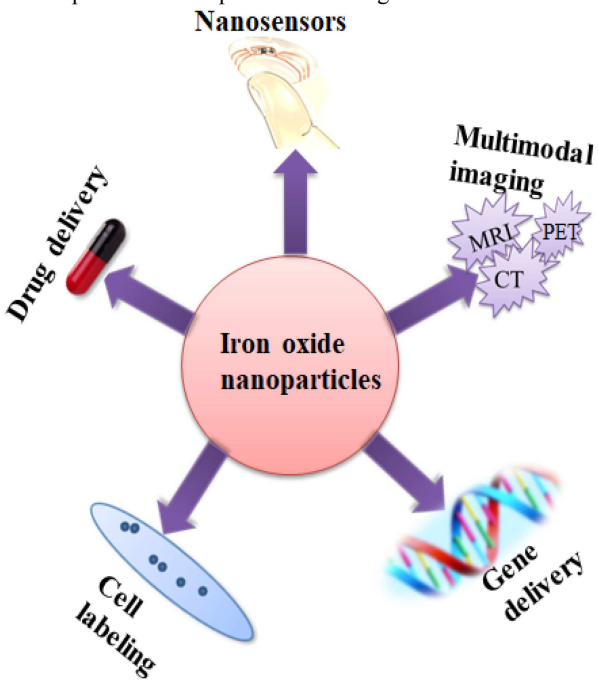

Fig. 3 *Representation of biomedical applications of IONPs [49–51]*

The best approach for synthesis of IONPs involves their production from plants that can produce stable NPs with a variety of shapes through environment-friendly process [3]. It has been reported that IONPs with theranostic potential can be synthesised by various plants (Table 2) such as grape seed [20], brown seaweed [52, 53], plantain peel extract [54], aloe vera extract [55], and alfalfa [17]. In addition, synthesis of IONPs from various other plants such as *Camellia sinensis* [56], eucalyptus [57], Sorghum bran extract [58], *Hordeum vulgare* and *Rumex acetosa* [59], and *Sageretia thea* [60] has also been reported but their potential as theranostic agents. However, all these IONPs need to be further studied for their practical applications.

2.3 Titanium dioxide NPs as tool for theranostics

Photothermal therapy (PTT) involves the use of a photosensitiser with strong optical absorption property which converts light energy into heat, thus generating hyperthermia which eventually causes selective damage to cancerous cells with minimum side effects. Photodynamic therapy (PDT) involves the use of photosensitiser that undergoes excitation after absorbing photons from visible light and transfer the absorbed energy to oxygen and reactive oxygen species (ROS). Titanium dioxide nanoparticles (TiO_2 NPs) can produce ROS when used as photosensitiser during PDT. TiO_2 NPs have recently emerged as potential photosensitiser acting as a multicomponent nanocomposite for PTT and PDT. In addition to that TiO_2 NPs after conjugation with folic acid can be used for site-specific delivery of anticancer drugs [61, 62]. TiO_2 NPs are used as candidate for cell imaging and as a contrast agent in MRI [63, 64] and optical coherence tomography [65]. TiO_2 NPs has been used for diagnostic and therapeutic purpose for rheumatoid arthritis [23]. PTT when applied alone can cause damage of healthy tissues; therefore, TiO_2 multicomponent nanocomposites for PTT and PDT triggered by NIR light allow synergistic tumour treatment and also overcome the obstacles of UV light excitation [61]. Green synthesis of TiO_2 NPs has been carried out by using various plants such as *Annona squamosa* peel [66], *N. arbortristis* leaf extract [67], *Jatropha curcas* aqueous [68], *Euphorbia prostrata* leaf extract [69], Hibiscus flower [70], and *Vigna radiata* [16] which have potential to be used in various biomedical applications as shown in Table 3.

2.4 Silver nanoparticles as theranostic agents

Silver nanoparticles (Ag NPs) brought revolution in biomedical field by acting as diagnostic as well as therapeutic modality. Antitumour potential of Ag NPs has been reported against Dalton's lymphoma ascites. The study reveals that activation of caspase 3 enzyme is responsible for apoptosis in the target cells [71]. Cytotoxic activity of Ag NPs showed mitotic arrest and chromosome instability against normal human lung fibroblasts (IMR-90) and human glioblastoma (U251) [72]. Ag NPs have also been reported for their cytotoxic activity against acute myeloid leukaemia [73], A549 (human lung cancer cell line), B16 (mouse

Table 2 Characteristics and applications of bioinspired IONPs as theranostic agents

Plant name	Size, nm	Shape	Therapy	Diagnosis	References
Medicago sativa	3.1	cubic	targeted drug delivery, substrate in cancer treatment	—	[17]
Vitis vinifera	35	spherical	—	X-ray contrast agents, MRI, CT bioimaging	[20]
Sargassum muticum	18 ± 4	cubic	cancer therapy with anticancer activity against Jurkat cells, MCF-7 cells, HeLa cells, HepG2 cell lines	—	[52, 53]
plantain peel	50	spherical	applicable in biomedical fields and efficient site-specific drug delivery	—	[54]
Aloe barbadensis	6–30	cubic	tumour hyperthermia	MRI	[55]

MRI, magnetic resonance imaging; CT, computed tomography.

Table 3 Characteristics and applications of bioinspired TiO_2 NPs acting as theranostic agent

Plant name	Size, nm	Shape	Applications	References
Nyctanthe arbortristis	100–150	spherical	TiO_2 NPs can be applicable for all biomedical applications including cancer therapy as well as cell imaging	[63, 67]
Annona squamosa	23 ± 2	spherical	TiO_2 NPs have potential for biomedical applications such as photodynamic therapy for cancer treatment, cell bioimaging, and targeted drug delivery	[63, 66]
Jatropha curcas L.	25–50	spherical	TiO_2 NPs produced by this plant can be used for all biomedical application including cancer treatment and cell imaging	[63, 68]
Vigna radiata	—	oval	TiO_2 NPs showed cytotoxic activity against osteosarcoma cell lines thus could be tested for its potential as anticancer agent	[16, 63]
Hibiscus flower	—	—	TiO_2 NPs possessed potential for various biomedical applications including their role as theranostic	[63, 70]

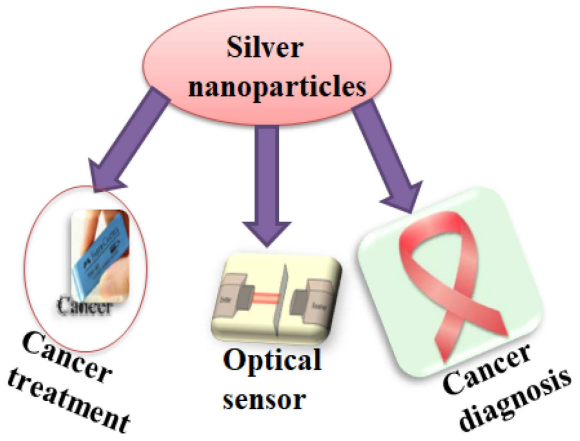

Fig. 4 *Biomedical applications of Ag NPs [15, 74, 78]*

melanoma cell line), and MCF7 (human breast cancer cells) [74]. Advances in the applications of Ag NPs led their utilisation in various applications such as biosensing, diagnostic imaging, and cancer diagnosis as well as cancer therapy thus acting as theranostic agents [75].

Aptamer-based silver nanoprobes can be used for intracellular protein imaging as well as for single protein spectral analysis. They can act as a contrast imaging agent for dark field light scattering microscopy as well as allow intracellular microenvironment analysis [76]. Biosensor array has been developed using Ag NPs to indicate serum levels of p53 protein in patients with head and neck squamous cell carcinoma. This biosensor provides promising tool for tumour diagnosis [77]. Biomedical applications of Ag NPs have been represented in Fig. 4. Green synthesis of Ag NPs with theranostic potential has been carried out from various plants (Table 4) such as *Olax scandens* leaf extract [74], *Ablemoschus esculentus* pulp extract [81], *Allophylus cobbe*, *Artemisia princeps*, and *Typha angustifolia* [86], oak fruit [82], *Sargassum vulgare* [83], *Plumeria alba* [84], *Cyamopsis tetragonaloba* [78], *Taxus baccata* extract [15], *Dimocarpus Longan Lour* [85], *Alternanthera sessilis* [79], and *Ganoderma neo-japonicum imazeki* extract [80].

2.5 QDs and carbon nanotubes

QDs are actually NPs made up of semiconductor and luminescent materials. QDs exhibit narrow, symmetric, and size-tunable emission spectra which is responsible for multicolour applications. In addition, they also give strong fluorescence string for prolong time period which makes them superior for bioimaging. QDs generate fluorescence through Froster resonance energy transfer because of their unique properties, i.e. broad absorption, size-dependent narrow emission, and resistance to photobleaching [88]. Several plants like Aloe [89], Orange peel [90], *Trapa bispinosa* [91], *Jinhua bergamot* [92], and *Sccharum officinarum* [14] etc. have been utilised for green syntheses of carbon nanotube (Table 5). However, further studies are needed to explore theranostic potential of these agents.

3 NPs produced by plants whose theranostic potential required to be explored

3.1 Copper nanoparticles

Copper nanoparticles (Cu NPs) are also considered potential candidate as theranostic agents (Fig. 5) because of their properties such as strong absorption in NIR region and high heat to light transformation capacity; they can cause selective damage to tumour cells. Moreover, they exhibit fluorescence signal and are capable to be applied for optical imaging and image-guided phototherapy [94], for ultrasound and MRI with high spatial resolution scan [95]. Green synthesis of Cu NPs has been reported from many plants. Crystalline nature Cu NPs up to the size range of 15–30 and 10–60 nm were prepared from *Aloe barbadensis* [96] and *Citrus medica Linn.* [97], respectively. Similarly, *Glorosia superba L.* extract was used as a fuel for synthesis of Cu NPs [98] and rod-shaped nanoparticles were obtained from *Carica papaya* [99]. Highly stable Cu NPs were prepared from *Tabernaemontana divaricate* leaves [100] and *Euphorbia esula L.* [101]. It has been revealed that *Ginkgo biloba* [102] and *Nerium oleander* [13] contain reducing and stabilising agents for copper resulting in Cu NPs formation. Spherical-shaped Cu NPs up to the size range of 26–30 nm were obtained from *Acalphya indica* [103] while ultra-small Cu NPs up to 2.90 nm were prepared from Lemon grass tea [104]. Well-dispersed and crystalline nature Cu NPs were fabricated by using *Calotropis gigantea* extract [105]. Herbal extracts such as tamarind and lemon juice were used to produce cubic NPs up to 20–50 nm size [106]. Amorphous Cu NPs with anticancer potential were produced by using *Ficus religiosa* leaves [107]. Moreover, *Tinosporia cardifolia* extract produced Cu NPs with sponge-like structure and 6–8 nm size [108]. Microwave-assisted synthesis of Cu NPs was carried out by using *Terminalia arjuna* bark extract [109], but theranostic potential of all these NPs still needs to be explored.

3.2 Manganese oxide nanoparticles

Manganese oxide (MnO_2) nanoparticles NPs also have magnetic property so are considered potential candidate as theranostic agent. MnO_2 nanorods have been recently reported as radiofrequency responsive materials. Their ability to heat up upon irradiation of specific radiofrequency waves elevates temperature of surrounding tissues therefore can be used as a hyperthermic agent to induce cancerous cell death [110, 111]. Typically, gadolinium contrast agents are used for T1MR imaging, but they cause nephrogenic systemic fibrosis.

MnO_2 NPs with paramagnetic behaviour provides an MRI contrast agent for lung cancer bioimaging as well also ensures targeted drug delivery to cancerous cells [112]. Spherical-shaped MnO_2 NPs with 40–50 nm size were fabricated from *Ananas comosus* [12]. Needle-shaped MnO_2 NPs <100 nm size were synthesised from *Sapindus mukorossi* [113]. Similarly, *Cucurbita pepo*-mediated MnO_2 NPs synthesis was also carried out [114]. A reduction in metal ions was achieved through lemon while curcumin was used as stabilise resulting in spherical- and eclipsed-

Table 4 Characteristics and applications of plant-based Ag NPs acting as theranostic agent

Plant name	Size, nm	Shape	Therapy	Diagnosis	References
Cyamopsis tetragonaloba	10	cubic	—	optical sensors can be used for detection ammonia content in biological fluids	[78]
Alternanthera sessilis	<100	cubic	therapy for prostate cancer, breast cancer	—	[79]
Ganoderma neo-japonicum imazeki	5	spherical	cancer therapy, arthiritis, and neovascularisation	—	[80]
Olax scandens	0–60	spherical	anticancer agent1	can be used as diagnostic tool for cancer	[74]
Taxus baccata	75.1	spherical	these NPs can be used for tracking and imaging techniques for cancer diagnosis	cancer therapy	[15]
Ablemoschus esculentus	6.7	—	cytotoxic activity against Jurkat cell lines, having potential to be applied as anticancer agents	—	[81]
Oak Fruit Hull (Jaft)	40	spherical	anticancer agents against MCF-7 cell lines	—	[82]
Sargassum vulgare	10	—	showed anticancer activity against cancerous human myeloblastic leukaemic cells HL60 and cervical cancer cells lines	—	[83]
Plumeria alba	36.19	spherical	showed anticancer activity against COLO 205 cells	—	[84]
Dimocarpus Longan Lour.	9–32	cubic	therapy for prostate cancer	developing role as a diagnostic agent	[85]
Allophylus cobbe, Artemisia princeps, Typha angustifolia	2–100	—	anticancer activity	diagnose tumour	[86, 87]

Table 5 Characteristics and applications of bioinspired carbon dot

Plant name	Size, nm	Shape	Applications and Research gaps	References
orange peel	2–7	spherical shape	theranostic potential was not evaluated	[90]
Trapa bispinosa	5–10	spherical shape	these can be used in biomedical applications like delivery of active pharmaceutical ingredient and genes inside the cells	[91]
Sccharum officinarum	3	—	can be used in fluorescent imaging probes for bioimaging applications	[14]
aloe	5	spherical shape	theranostic potential was not evaluated	[89]
Jinhua bergamot	—	—	these probes showed photoluminisence so there potential for bioimaging should be explored	[92]

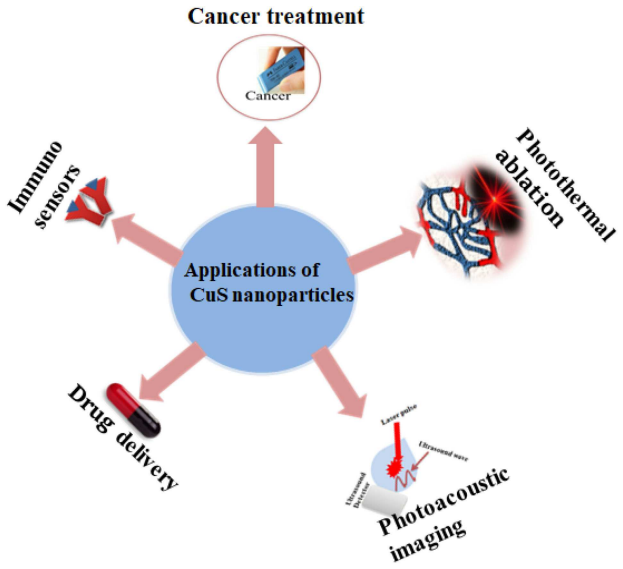

Fig. 5 *Biomedical applications of CuS NPs [93]*

shaped MnO_2 NPs formation [115]. However, theranostic potential of all these NPs is still needed to be evaluated.

3.3 Bismuth nanoparticles

Bismuth nanoparticles (Bi NPs) because of their properties such as small carrier effective masses, long Fermi wavelength, and small bond overlap energy have attracted the attention of researchers to evaluate their potential as theranostic agent. It has been revealed that Bi NPs can be used as radio sensitiser and as contrast agent for CT. Bi NPs has been developed as theranostic moiety with potential to be applied for dual modal CT/PA imaging and PTT for treatment of tumour [116]. Bi NPs with nanoscale spherical sponge morphology have been reported as potential agents for image-guided PTT against tumour [117]. Commonly used contrast agents for CT of GIT such as $BaSO_4$ suspension and iodinated molecules (meglumine diatrizoateare) can give false-positive results due to intrinsic insolubility and iodine hypersensitivity, respectively. Moreover, anatomy of GIT including complex loops and peristalsis also contribute to difficulty in diagnosis. Bi NPs are most appropriate candidates to be applied for CT visualisation of GIT that overcome all above-mentioned problems, in addition to that they offer low cost, biocompatibility, and high sensitivity [118]. In addition, Cu_3BiS_3 nanocrystals can serve as new generation of theranostics which has been reported with strong NIR absorbance and exhibits CT imaging response due to large X-ray attenuation coefficient of bismuth. Therefore, cancerous cells can be efficiently diagnosed and killed upon irradiation of NIR and X-ray [119]. Bi-gadolinium NPs are potential candidates for CT-guided radiotherapy with prolong circulation causing selective death of cancerous cells without damaging surrounding healthy tissues, thus providing more effective cancer therapy [120]. Spherical-shaped Bi NPs was from *Eclipta alba* with 40 nm size; however, theranostic potential of these NPs was not evaluated [11].

3.4 Silica (metalloid) nanoparticles

Silica nanoparticles (Si NPs) are novel prognostic biomarkers for cancer diagnosis and delivery of chemotherapeutic moiety to cancerous cells [121]. They are optically transparent, biologically inert, relatively non-toxic elements with surface modification properties. These properties make Si NPs an appropriate candidate for incorporation of various dyes such as polymethines,

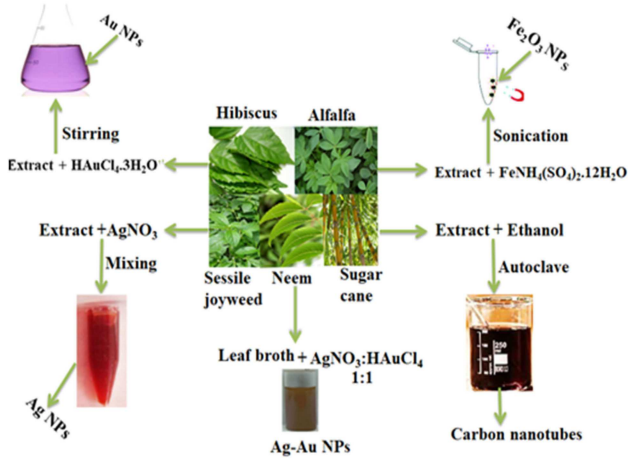

Fig. 6 *Schematic illustration of general fabrication process for plant-based green synthesis of nanoparticles [14, 17, 79, 130, 131]*

indocyanine green, Alexa Flour 750 etc. Moreover, incorporation of more than one moieties can be achieved by making mesoporus silica nanoparticles (MSNs) [122]. The presence of uniform pores, surface modification properties allow simultaneous incorporation of multiple moieties inside distinct domains including contrast agent for bioimaging, therapeutic agent, and a ligand that ensures targeted drug delivery thus acting as ideal candidate as theranostic agent [123]. MSNs ensure delivery of many hydrophobic drugs such as paclitaxel and camptothecin which if administered through intravenous route require large amount of organic solvents such as DMSO for solubility which may cause toxicity. The presence of silanol groups on MSNs make them soluble in aqueous environment and porosity provides increased surface area with high incorporation efficiency while surface modification property provides more strong control over holding and releasing drug molecules [124]. By taking advantage of surface modification property of MSNs, Cheng *et al*. have suggested a novel platform for their use as cancer theranostics [125]. Toxicity study on MSNs reveals that they are less toxic and do not cause any type of hypersensitivity and immunogenic sensitisation reactions [126]. Green synthesis of Si NPs is commonly carried out from rice husk but theranostic potential is still not evaluated. The waste material has been revealed as silica precursor [10]. More studies are required to explore and further develop Si NPs for clinical and diagnostics purposes.

4 Mechanism behind plant-based green synthesis of NPs

Phytoconstituents such as terpenoids, flavonoids, sugars, proteins, and alkaloids are responsible for reduction in metal ions resulting in NP formation. Terpenoids are organic polymers produced in plants exhibiting strong antioxidant potential. Eugenol is an important terpenoid responsible for reduction in metal ions. It has been revealed that breakdown of proton from the OH group of eugenol forms resonance structure having potential for further oxidation. It is followed by reduction in metal ions responsible for NP formation [127]. Flavonoids are polyphenolic compounds found in plants having potential to chelate and reduce metal ions. Tautomeric transformation of flavonoids from enol-form to keto-form release hydrogen atom that reduce metal ions and forms NPs [128]. Sugars are an important constituent found in plants that also assist in NP formation. It has been revealed that aldehyde group of sugar is oxidised into carboxyl group via nucleophilic addition of OH group which results in reduction in metal ions and NP formation. Proteins are another important class of phytoconstituents involved in NP formation. Amino acids that are building blocks of proteins contain binding sites for metal ions such as carboxyl group (aspartic and glutamic acid), nitrogen atom of imidazole ring (histidine), thiol (cysteine), thioether (methionine), hydroxyl (serine, threonine, tyrosine), carbonyl group (asparagine and glutamine) etc. Amino acids can also reduce metal ions such as hydroxyl group (tyrosine), carbonyl group (glutamine and asparagine), and thiol (cysteine) resulting in NP formation. General mechanism involved in plant-based NP formation is proposed as: (i) first of all reduction in metal ions takes place by the phytoconstituents followed by nucleation of reduced metal atoms that is called activation phase; (ii) during growth phase, small NPs adhere to form large size NP (Ostwald ripening); (iii) termination is the last phase during which NPs attain their shape [127].

5 General fabrication process for plant-based green synthesis of NPs

Green synthesis of metal NPs can be carried out in a single-step process. However, appropriate solvent system, environment-friendly reducing agent, and non-toxic stabilising agent should be selected for this approach [129]. Preparation of metal NPs through plant-mediated green chemistry approach is usually carried out by mixing plant extract that act as reducing agent and a metal precursor under suitable conditions as shown in Fig. 6. Hydrogen tetrachloroaurate (III) hydrate ($HAuCl_4{\cdot}3H_2O$) and sodium tetrachloroaurate (NaAuCl4) are used as gold precursor for synthesis of Au NPs. Reduction process takes place within 1–1.5 h that is indicated by the appearance of stable light violet or purple colour [9, 130]. In the case of IONPs, most commonly used iron precursors are iron (III) chloride hexahydrate ($FeCl_3{\cdot}6H_2O$) and ferric ammonium sulphate dodecahydrate $FeNH_4(SO_4)_2{\cdot}12H_2O$ etc. Appearance of black-coloured solution indicates the completion of reduction process [17, 54]. Preparation of TiO_2 NPs is carried out by using metatitanic acid $TiO(OH)_2$, titanium oxysulphate $TiOSO_4$, titanium teteraisopropoxide ($C_{12}H_{28}O_4Ti$) etc. as precursors of titanium which undergoes reduction by phytoconstituents under defined conditions. The completion of reduction process is indicated by the deposition of coalescent white crystals at the bottom of container [66–68, 70]. Silver nitrate $AgNO_3$ is a commonly used silver precursor for fabrication of Ag NPs and completion of silver reduction is indicated by reddish brown colour solution [79]. Green synthesis of carbon nanotubes can be carried out by autoclaving *Saccharum officinarum* as a carbon source until dark brown-coloured solution forms [14]. Plant-based green synthesis of NPs offers several attractive features as shown in Table 6.

6 Advantages offered by green synthesised NPs and toxicity concerns of theranostics

NPs of well-defined shape with desired characteristics are commonly prepared by chemical methods, but these methods are quite expensive and involve the use of chemicals that may pollute our environment and NPs produced by these methods may produce harmful effects on human beings [136]. Green synthesis is an alternative echo-friendly approach for synthesis of NPs that may be carried out by using plant extracts as well as microorganisms like bacteria and fungi. NPs produced by these methods are usually economical, biocompatible, and possess relatively low toxic effects on human health. Moreover, in contrast to chemical methods, there is no need to apply high pressure, temperature, and energy; and usually do not involve toxic chemicals [137]. Plants are considered as most appropriate platform for synthesis of NPs with naturally occurring phytoconstituents that act as capping and stabilising agents for synthesis of NPs [138]. Plant-mediated synthesis of NPs offer several benefits over microorganisms such as ease of improvement, less biohazards, elaborate process of maintaining cell culture, reduce the cost of microorganisms isolation, and their culture media.

Moreover, plant-mediated synthesis of NPs can be easily upgraded to industrial scale [136, 139, 140]. In the case of physical and chemical methods, it is sometimes challenging to prevent aggregation of NPs and to achieve stable NPs of desired shape and size while, green synthesised NPs have been reported to be more stable and can be reduced at faster rate when compared with other methods [3]. On the other hand, major drawback of synthesis of

Table 6 Features of plant-based fabrication of nanoparticles compared to traditional methods

Plant-based fabrication	Traditional methods	References
Plant-based CuO NPs were found to be more stable with less ion releasing capability and less toxic	engineered CuO NPs were more soluble, less stable with high ion releasing capability, and more toxic	[132]
Plant-based Ni NPs were found to be non-toxic and possessed magnetic property, good colloidal stability, better antioxidant, and antimicrobial potential.	Ni NPs synthesised through chemical methods did not possessed magnetic property and they were found to have poor colloidal stability, antioxidant and antimicrobial potential, and showed toxicity	[133]
plant-based TiO_2 NPs exhibited better dispersibility, stability, and smaller size resulting in enhanced therapeutic potential	chemically synthesised TiO_2 NPs were unable to exhibit equivalent dispersibilty, stability, and size resulting in poor therapeutic potential	[70]
green synthesised nanoparticles prepared from peanut shell exhibited the size range 10–50 nm, pharmacological potential similar to commercially available Ag NPs	peanut-based synthesis can be scaled up to large scale as it offers the same features as commercially available nanoparticles at low cost	[134]
plant-based synthesis of nanoparticles is a one-step process, safe to handle, offer minimum side effects, and plants are readily available	chemical syntheses of nanoparticles require toxic solvents, high energy, and produce many byproducts	[135]
plant-based nanoparticles have tested only in small number of biomedical applications and used only small-scale production. Therefore, this research area needs significant attention of researchers	nanoparticles synthesised through physical and chemical methods have been widely tested and applied for various biomedical applications	[127]

NPs using plants is varying chemical composition of plant extracts of same species collected from different geographical regions, thus sometimes making it challenging to produce reproducible results [139].

Although TNPs are being widely applied to treat and diagnose cancers, however, they may impart potentially toxic impact on human health due to different reasons. For example, raw materials (plant products) used for the synthesis of NPs should be tested for its toxicity or side effects. In addition, certain and small sized NPs have potential to penetrate cell membrane where they disturb normal cellular functions; mainly resulting in necrosis, cell degeneration, and apoptosis in Na^+–K^+ ATPase cell membrane [141]. Large amounts of bismuth oxide NPs are released in the atmosphere as a result of volcanic eruptions and are found associated with eco-toxic impacts [142]. Ag NPs possess strong antibacterial activity but unable to differentiate beneficial bacterial strains, which can eliminate environment-friendly bacteria; for example, nitrogen-fixing bacteria thus impeding plant growth and resulting in eutrophication of rivers and lakes [143, 144]. Ag NPs have been reported to deposit inside the testes and effect sperm cells imparting toxicity on male reproductive cells [145]. It has been revealed that Ag NPs become more toxic when stored for prolong time period [146]. They cause osmoregulation disturbances in fish by inhibiting basolateral activity inside gills [147]. Moreover, release of silver ions into the environment can result in bluish to grey skin and eye discoloration, kidney and liver damage, and respiratory and intestinal tract irritation [143]. In the case of IONPs, commercially available products such as Feridex and Resovist are biocompatible and non-cytotoxic. However, emerging studies have reported DNA damage, oxidative stress, and mitochondrial membrane dysfunction caused by SIONPs. Therefore, further studies should be conducted to ensure safety of these NPs [148]. TiO_2 NPs produce inflammatory responses, lung cancer, and productive and developmental toxicities in animals have been revealed, so further studies should be conducted to evaluate toxicity in humans [149]. Au NPs are biocompatible relatively less toxic and non-immunogenic [150]. Toxicity study has been carried out on MnO_2 NPs by using rats where they caused DNA damage in leucocytes, micronuclei, and chromosomal aberrations thus causing genetic damage and histopathological changes in the liver, kidney, spleen, and brain [151]. Cu NPs have been reported to cause increased DNA damage and oxidative DNA lesions when compared with control resulting in non-viable cells [152]. Si NPs cause cytotoxicity in human bronchiolar carcinoma derived cells imposing risk for lung cancer [153]. Therefore, appropriate precautions should be taken before introducing NPs as potential theranostic agents; especially those based on heavy metals [141].

7 Proteins and peptides as potential candidates for biomimetic synthesis of theranostic capable NPs

Protein and peptide-based biomimetic synthesis of NPs is another emerging approach that has achieved increasing attention by offering several unique features. NPs obtained from this approach can be applied for in vivo imaging and therapy, bio-sensing, and bio-labelling [154]. Bovine serum albumin is a commercially available protein that is most commonly applied for preparation of NPs. Gadolinium-based hybride NPs prepared from bovine serum albumin can be employed as effective blood pool contrast agents [155]. Paramagnetic gadolinium is also effective tool for MRI [156]. A wide variety of theranostic capable NPs have been prepared through this approach, i.e. QDs, Fe_2O_3 NPs, Cu NPs, MnO_2 NPs, Bi_2S_3 NPs etc. Protein-based synthesis of NPs offers several attractive features such as good stability, reproducibility, compatibility, minimum non-specific absorption, better pharmacokinetics, and green processing can be carried out at room temperature [157–159]. Peptides are products obtained after hydrolysis of proteins that are composed of three or more proteins linked through peptide bond. When compared with amino acids; peptides possess less molecular weight, clear structure, and composition. Peptides can be designed especially as they are more liable to change in sequence, thus providing opportunity to produce multifunctional NPs. Most commonly used peptide templates are CCY-based linear peptide, cyclopeptide while Glutathione and CLEDININE are some other peptides. Various types of NPs can be prepared by using peptides, i.e. Au NPs, Ag NPs, Cu NPs etc. Glutathione-based NPs offer several advantages such as better accumulation at tumour site, CT imaging, improved therapeutic efficiency, and increased renal clearance. However, peptides offer several limitations when compared with proteins such as non-human endogenousness, less bioactivity, and reaction efficiency [154, 160]. The exact mechanism involved behind protein or peptide-mediated NP synthesis is not completely explored; however, it has been revealed that proteins contain metal binding sites, i.e. N-terminal amine, Cys residues that help them in metal adherence. Proteins because of their enormous charged groups and molecular chain flexibility exhibit the confirmation of nanocages in basic environment, thus forming nanoclusters with metal ions. In the case of peptides, some functional groups such as phenolic group of tyrosine converts into phenoxide in basic environment which reduce metal ion to metallic NP [154].

8 Conclusion and future prospects

In the light of above discussion, we can conclude that NPs-based theranostics is promising approach to increase the quality of clinical care and treatment [161]. Synthesis and development of

NPs can be carried out using economical approach (i.e. plant-mediated synthesis of TNPs) which could provide stable TNPs of desired shape, physical, and chemical characteristics in a single-step process. Although green synthesis approach gained significant attention of researchers and a wide variety of plant extract-based NPs have been prepared and evaluated till now, still this research area need to be explored for the synthesis of more efficient theranostics. Further efforts are needed to optimise the reaction conditions for synthesis of bioinspired NPs and engineering of recombinant organisms and gene modification of plants in order achieve high amount of phytoconstituents such as proteins, enzymes, phenols that are natural capping and reducing agents present in plants. Productivity of plants to prepare NPs can be further improved by exploring the pathways involved in NP synthesis and heavy metal accumulation and detoxification. Plants can also produce complex nanohybrides. It has been revealed that bimetallic synthesis of NPs with Au core–Ag shell can be carried out by using Neem (*Azadirachta indica*) leaf broth [131]. Moreover, *Brassica juncea*-mediated trimetallic Au–Ag–Cu NP synthesis has also been reported [162]. However, still there is an intense need to further explore the potential of plants to produce complex nanomaterials. Some toxic impacts of TNPs have been revealed; therefore, further studies should be conducted to investigate underlying mechanisms of toxicity and to establish appropriate dose in order to get maximum therapeutic benefits with least side effects. In the view of above discussion, we can conclude that green synthesised nanomaterials can appear as potential therapeutic and diagnostic agents in near future, but currently, it is inceptive and needs intensive efforts to overcome all the research gaps.

9 References

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