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MINI-REVIEW

Current state and prospects of the phytosynthesized colloidal gold nanoparticles and their applications in cancer theranostics

Muhammad Ovais[1,2] · **Abida Raza**[2] · **Shagufta Naz**[3] · **Nazar Ul Islam**[4] · **Ali Talha Khalil**[1] · **Shaukat Ali**[5] · **Muhammad Adeeb Khan**[5] · **Zabta Khan Shinwari**[1,6]

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Abstract The design, development, and biomedical applications of phytochemical-based green synthesis of biocompatible colloidal gold nanoparticles (AuNPs) are becoming an emerging field due to several advantages (safer, eco-friendly, simple, fast, energy efficient, low-cost, and less toxic) over conventional chemical synthetic procedures. Biosynthesized colloidal gold nanoparticles are remarkably attractive in several biomedical applications including cancer theranostics due to small size, unusual physico-chemical properties, facile surface modification, high biocompatibility, and numerous other advantages. Of late, several researchers have investigated the biosynthesis and prospective applications (diagnostics, imaging, drug delivery, and cancer therapeutics) of AuNPs in health care and medicine. However, not a single review article is available in the literature that demonstrates the anti-cancer potential of biosynthesized colloidal AuNPs with detailed mechanistic study. In the present review article, we for the first time discuss the biointerface of colloidal AuNPs, plants, and cancer mainly (i) comprehensive mechanistic aspects of phytochemical-based synthesis of AuNPs; (ii) proposed anti-cancer mechanisms along with biomedical applications in diagnostics, imaging, and drug delivery; and (iii) key challenges for biogenic AuNPs as future cancer nanomedicine.

Keywords Phytonanotechnology · Colloidal gold nanoparticles · Cancer theranostics · Green synthesis · Nanomedicine

✉ Muhammad Ovais
movais@bs.qau.edu.pk

[1] Department of Biotechnology, Quaid-i-Azam University, Islamabad 45320, Pakistan

[2] National Institute for Lasers and Optronics, Pakistan Atomic Energy Commission, Islamabad 45650, Pakistan

[3] Institute of Biotechnology and Genetic Engineering, University of Agriculture, Peshawar 25130, Pakistan

[4] Department of Pharmacy, Sarhad University of Science and Information Technology, Peshawar 25000, Pakistan

[5] Department of Zoology, University of Azad Jammu and Kashmir, Muzaffarabad 13100, Pakistan

[6] Pakistan Academy of Sciences, Islamabad 44000, Pakistan

Introduction

Although tremendous progress has been made in the development of novel drugs and treatment strategies for cancer, it remains as the second principal cause of deaths in the world. The annual incidence rate of cancer is around 2.6 million cases/year (May 2014; Siegel et al. 2015). As indicated in the recent report by American Cancer Society (ACS), global burden of cancer will rise to 21.7 million new cases by 2030 (Society 2015). Nearly half of the cancer diagnosed people in the previous 5 years are from the developed regions (Bray et al. 2013). The incidence rate of cancer in the underdeveloped regions is expected to rise exponentially in the coming years and the reason being either non-availability of the treatment or non-affordability of the expensive cancer therapies (Bray et al. 2012; Farmer et al. 2010). Most recent report published on June 2016 by iMShealth Institute for Healthcare Informatics reports the growth of global cancer treatment market up to a record level of $107 billion in 2015, which is anticipated to reach $150 billion by 2020 (InformaticsIIfH 2016). Consequentially, there is an urgent need of global actions to complement the benefits of new treatments in developed regions and take measures to make the existing cancer treatments accessible in the developing and underdeveloped regions (Alwan 2010). Recent research has

made significant progress in underlining the mechanisms and specific risk factors of different types of cancer. Chemotherapy, radiation therapy, immunotherapy, photodynamic therapy, stem cell transplantation and vaccinations, and combination of these are the major cancer treatment strategies. Unfortunately, most of the conventional therapies not only are expensive but also bear severe side effects (Lim et al. 2011; Patra et al. 2008). Scientific reports validate that the use of market available chemotherapeutics results in various types of toxicities (Benkovicova et al. 2013; Cancer.net 2017; Deb et al. 2011; Papasani et al. 2012). Therefore, research on development of economically acceptable and effective treatment options that could target specific cancers without causing damage to the healthy tissues is of paramount importance. In the present context, nanobiotechnology can play a vital role in creating brighter horizons for cancer treatment and diagnosis.

Foreseeing the deficiency of a systematic review on the use of biogenic gold nanoparticles as potential cancer (i) therapeutic, (ii) diagnostic, (iii) imaging, and (iv) drug delivery agents, we designed this comprehensive review article. In the present article, we for the first time extensively elaborated the proposed anti-cancer mechanism of biogenic gold nanoparticles with a futuristic discussion on key advances and milestones achieved in taking biogenic gold nanoparticles to clinical phase for cancer theranostics.

Bridging nanotechnology, plants and cancer: a biointerface

Nanotechnology is the manipulation, control, and utilization of matter at the nanometer scale that includes atoms, molecules, and supramolecular structures. Biological cells possess built-in nanoscale functional components such as DNA that approximately possesses width of 2.5 nm and proteins that are about 1–20 nm; therefore, it was inevitable to apply nanotechnology to biology. As a result, the relatively new field of nanobiotechnology has emerged in life sciences (Jain 2008). Nanobiotechnology is already having an impact on the healthcare and pharmaceutical industries because of its wide range applications for drug discovery. The surge for nanobiopharmaceuticals has now been vigorously pursued. Nanobiotechnology has now been applied to effectively treat human cancers. Recently, metal nanoparticles (NPs) especially silver nanoparticles (AgNPs) and gold nanoparticles (AuNPs) were extensively used as a diagnostic and treatment option for cancer. Metal NPs are of considerable interest in the present era because of their attractive features at nanoscale that is attributed to its very high aspect ratio (Thakkar et al. 2010). Due to their size, shape, and unique thermal and optical features which are different than their macro-scaled counterparts, they are ideal for theranostic applications. NPs can be used to deliver the anti-cancer drugs to the specific site of tumor where they send out signals after the destruction of tumor cells (Jain 2008). Foreseeing the safety of NPs, many scientists have reported the use of naturally present materials for NPs synthesis. Therefore, the term "green nanotechnology" was tossed under the umbrella of green chemistry. Paul Anastas and John Warner of Environmental Protection Agency (EPA) USA established the 12 principles of green chemistry. With the purpose of reducing human health and environmental concerns, these principles are applied in design plus synthesis and use of NPs (Anastas and Warner 1998). With the increase in awareness among scientists and drawbacks of organic synthesis, a shift has been seen in the previous decade towards green synthesis. Among green synthesis methods, NP synthesis via plants is becoming increasingly popular (Ovais et al. 2016). Medicinal plants not only are the source of important biologically active chemical entities that can be used as anti-cancer drugs but also provide exciting strategies of treatment through eco-friendly synthesis of metal NPs. Plant-based production systems have smaller incubation time and therefore can easily be scaled up for commercial applications.

Significance and history of medicinal use of AuNPs

By nature, Au is a noble element, i.e., highly unreactive. It can retain its shape and shine for thousands of years as it is resistant to deterioration and tarnishing through chemical oxidation. Moreover, AuNPs have enormous biomedical applications due to their distinctive physico-chemical features (Bhat et al. 2013; Chen et al. 2013; Daniel and Astruc 2004; Dhas et al. 2014; Dykman and Khlebtsov 2011; El-Sayed et al. 2005; Giljohann et al. 2010; Karuppaiya et al. 2013; Mata et al. 2016; Mukherjee et al. 2015; Nath and Banerjee 2013; Patra et al. 2008). Specifically, their shapes like nanorods, nanostars, nanocages, and nanoshells exhibit localized surface plasmon resonant features that potentially make their applicability in oncology (Hirsch et al. 2003; Loo et al. 2004; O'Neal et al. 2004). AuNPs can rapidly accumulate at the tumor sites and can enter the cells faster than other small molecules. Recent research has indicated the effectiveness of gold NPs for the easy detection of malignant cells because of their bioconjugation property (Dreaden et al. 2011; Mukherjee et al. 2016; Mukherjee et al. 2012). AuNPs are now used as photothermal agent for cancerous cell detection and their thermal destruction (Ahmad et al. 2003; El-Sayed et al. 2006). The transport of the anti-cancer drugs can be significantly enhanced via the endocytosis of AuNP conjugate. Because of their flexibility, AuNPs can be fabricated and functionalized to have simultaneous diagnostic and therapeutic applications (Dreaden et al. 2011).

Synthesis platforms for AuNPs

There are various methods (chemical, physical, and biological) following bottom–up and top–down approaches for the synthesis of AuNPs (Fig. 1). The first scientific report indicating the synthesis of colloidal AuNPs was published in 1857 by Michael Faraday. He found the nanoscale gold by the aqueous reduction of gold chloride with phosphorus and later stabilized by carbon disulfide. Today, the chemical synthesis of AuNPs follows a similar pattern involving the reduction of Au-salts with the addition of ligands that are used for capping and hence aggregation is prevented (Arvizo et al. 2010; Faraday 1857; Noruzi 2015). However, the chemical means of synthesis of NPs are accompanied by certain disadvantages such as use of highly toxic chemicals during synthesis and generation of dangerous by-products (Kannan et al. 2006; Patra and Baek 2015). Similarly, physical means of synthesis require huge energy inputs and are highly expensive. On the contrary to chemical and physical means of synthesis of NPs, biological method provides an eco-friendly, non-toxic, economical, low input-high yield, and single-step option for the synthesis.

Biosynthesis of AuNPs via plant extracts: a novel approach

Biogenic AuNPs possess a definite advantage over the chemically synthesized NPs as they are less toxic and more biocompatible (Bhau et al. 2015). Various biological resources such as plants, fungi, bacteria, and algae are already used to effectively synthesize metal NPs (Islam et al. 2015b; Kitching et al. 2015; Singh et al. 2016; Thakkar et al. 2010). Systematic review of literature indicates that among green synthesis methods, plants have been used comprehensively for formulation of gold nanoparticles. Literature for 2000–2016 was thoroughly reviewed from various data bases like Google Scholar, ISI web of knowledge, and PubMed. The results, as summarized in Fig. 2, b, clearly indicates that phytosynthesis is the method of choice for scientists. Microorganisms need relatively lengthier incubation times for reduction of metal ions while phytochemicals can reduce metal ions quickly. Unlike microorganism-based synthesis, plant does not require any expensive downstream processing procedures. Using bacteria and fungi for synthesis of metal, NPs can raise some biosafety concerns; however, it is not the case with plants (Ahmad et al. 2003; Rath et al. 2014; Shankar et al. 2004).

Green synthesis of metallic NPs exploiting plants, including its optimization and applications, is introduced as latest filed known as “phytonanotechnology” (Singh et al. 2016). For plant-mediated green synthesis of AuNPs, extracts of the plant material (flower, fruit, leaves, roots, stem, etc.) are obtained that possess the necessary phytochemicals (alkaloids, terpenoids, phenols, and flavonoids). When the plant extract is dissolved in the aqueous solution of tetrachloroauric acid ($HAuCl_4$), a proposed two-step chemical reaction kick starts as graphically illustrated in Fig. 3. In step one, the phytochemicals reduce Au^{+3} into Au° while in the second step, agglomeration and stabilization result in the formation of colloidal AuNPs (Huang et al. 2007; Sheny et al. 2011). Although it is well established that the formation and stabilization of metallic NPs is due to the presence of phytochemicals in plant extract, the proper mechanism is still unclear and is highly dependent on the phytochemistry of plant extract (Iravani

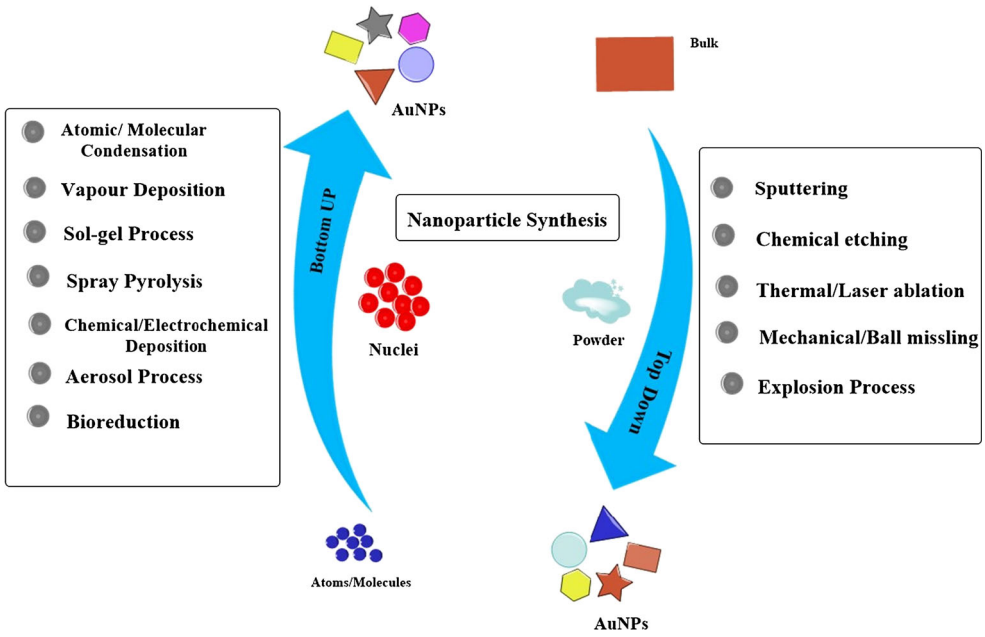

Fig. 1 Top–down and bottom–up approaches exploiting different physical, chemical, and biological methods for the synthesis of AuNPs

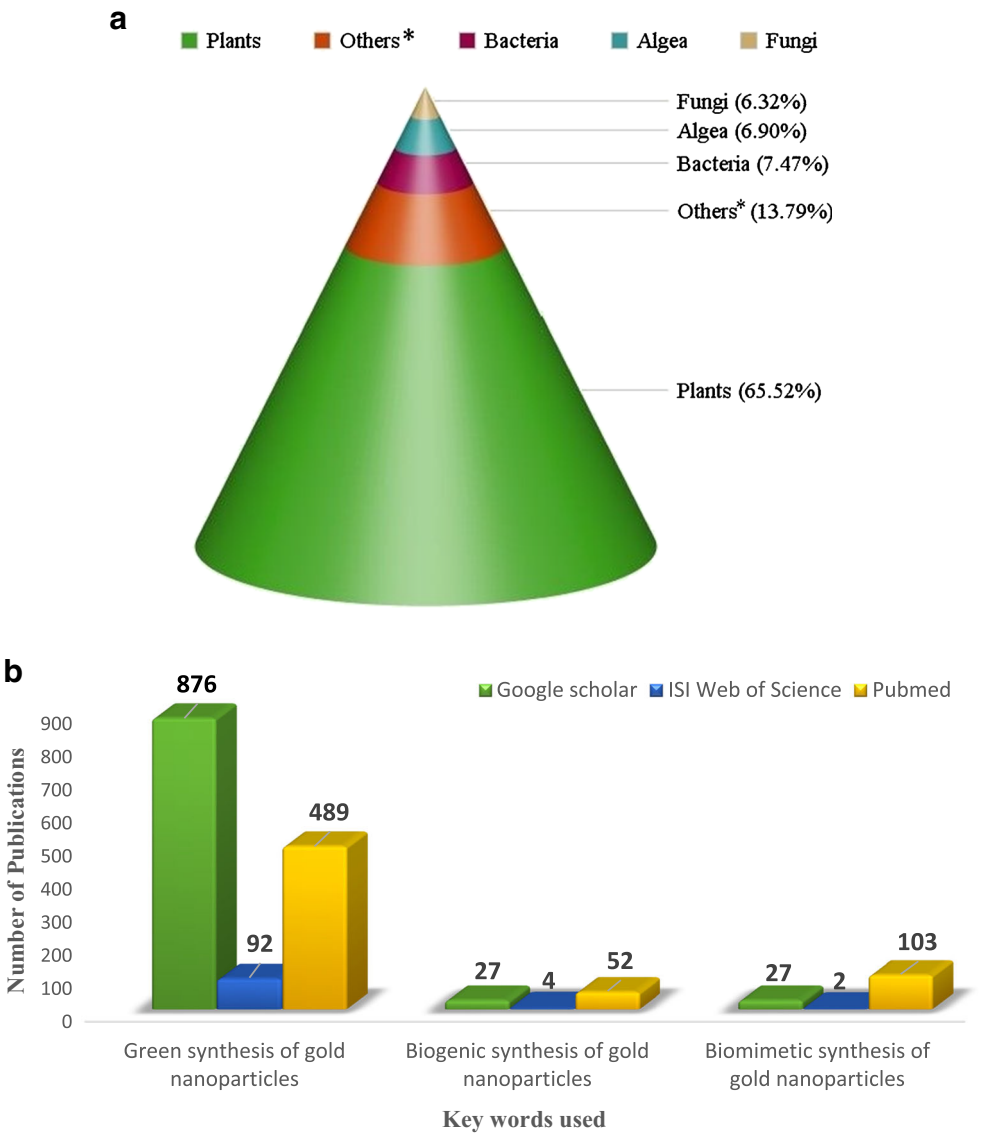

Fig. 2 **a** Literature published during 2000–2016 on green synthesis of AuNPs from various natural sources. *Asterisk* indicates vitamin C, chitosan, glycerol, starch, Ca-alginate, honey, sponge, diatoms, etc. **b** Search results of different keywords used for phytosynthesis of AuNPs (2000–2016)

2011; Lee et al. 2011; Shukla et al. 2008). Literature published on plant-mediated green synthesis proposes that aldehydes/ketones, polyphenolic/alcoholic compounds, and proteins might be the responsible candidates for Au^{+3} reduction and stabilization to AuNPs. Moreover, the conversion of metallic ions into NPs facilitated by low (12–22 kDa) and high molecular weight proteins (~150 kDa) present in plant extract is well established. It is very important to note here that the nature of plant has a central role in the mechanism followed for AuNPs formation. For example, in *Eclipta alba* leaf extract, both the low (~15 kDa) and high molecular (~150 kDa) weight proteins were responsible for AuNPs formation and stabilization (Mukherjee et al. 2012). While in case of *Olax scandens* leaf extract low molecular weight proteins (~12–15 kDa) and various phenolic compounds were responsible for synthesis and stabilization of AuNPs as demonstrated in Fig. 4 (Mukherjee et al. 2013). AuNP formation from $HAuCl_4$ is a case of redox reactions which involves electron transfer. Furthermore, the reduction of $HAuCl_4$ into AuNPs is also demonstrated by Newman et al. ($HAuCl_4 + 3NR_3 \rightarrow Au° + 3NR_3^+ + H^+ + 4Cl^-$) through free radical reactions (Newman and Blanchard 2006). The standardized reduction potential value of $Au^{3+}/Au°$ ($E°_{Au^{3+}/Au°}$) is 1.50 V, while that of $Ag^+/Ag°$ ($E°_{Ag^+/Ag°}$) is 0.80 V. The standardized reduction potential for acid/aldehyde, aldehyde/alcohol, quinone/phenol, and proteins are below 0.80 V, which clearly demonstrates the potent reduction potential of these phytochemicals (Bhaumik et al. 2015; Korchev et al. 2005).

Factors affecting biological synthesis of AuNPs

Factors which mostly affect sizes and shapes of NPs are substrate concentration, metal ion concentration, reaction time, temperature, reaction medium (acidic/neutral/basic),

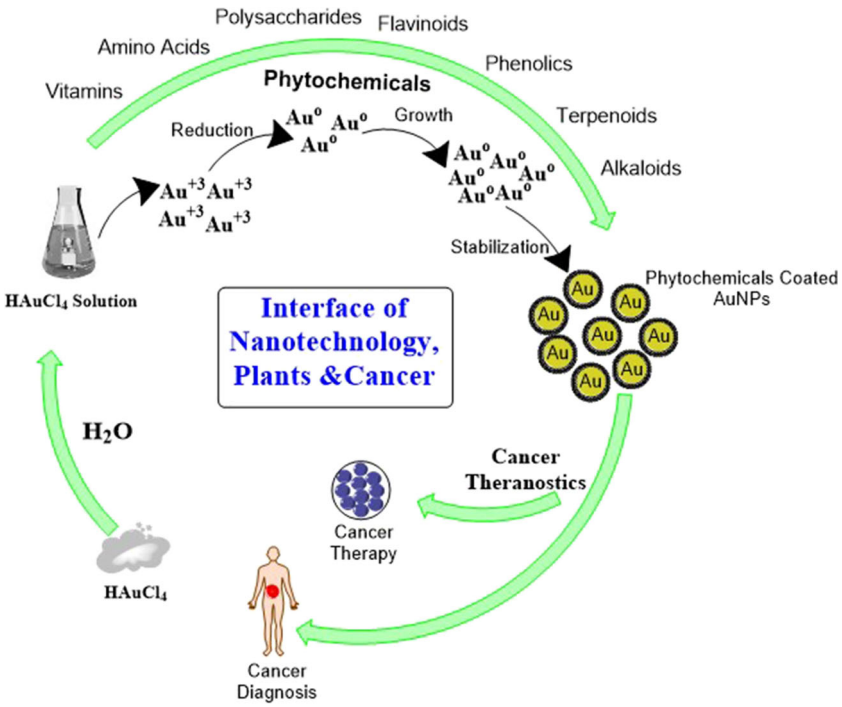

Fig. 3 General mechanism of plant extract-mediated synthesis and stabilization of AuNPs

isotonicity, and rarely on solvent or radiations. Concentration of substrate plays an important role for determining not only the optimized conditions but also the shapes and sizes of NPs. Lower concentrations of extract produced larger percentage

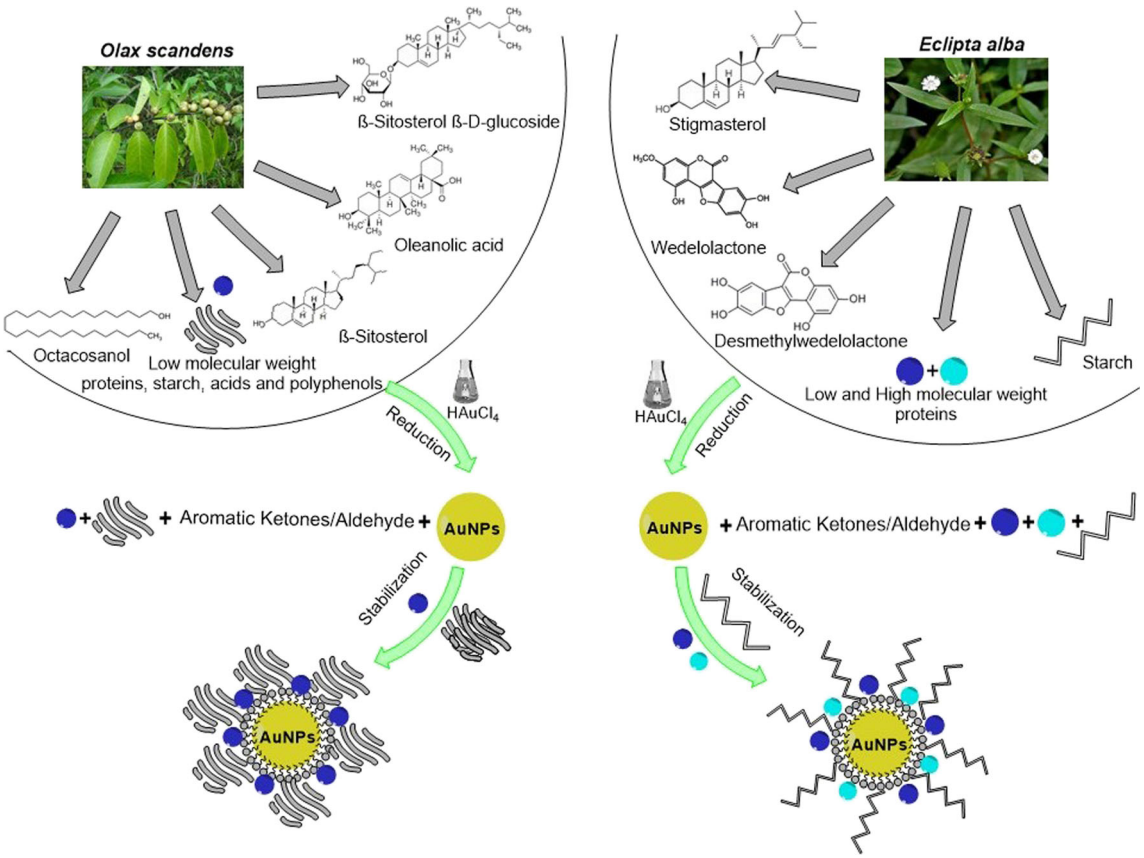

Fig. 4 The plausible mechanism for the formation and stabilization of AuNPs using *Olax scandens* and *Eclipta alba* leaf extract

of triangular and prismed masses as compare to hexagonal and spherical AuNPs (Chandran et al. 2006). Like extract concentration, metal ion concentration also has a vital role in sizes, shapes, morphology, and exploration of optimum conditions, but less attention and work have been directed to this aspect while generating biosynthetic AuNPs. Reaction time is also one of the major factors for the synthesis of AuNPs. Good reducing agents require shorter reaction times while poor reducing agents require longer reaction times. Studies have shown that with short reaction time, there is a tendency to get more monodispersed and spherical gold nanoparticles, while with high reaction time, the tendency is to obtain large triangular and hexagonal morophologies. (Kumar et al. 2012). Like other factors, temperature also plays an important role in the synthesis of AuNPs. Lower temperature is desired for fast reaction while for slow reactions; temperature is to be raised even up to 100 °C which is a boiling point of reaction medium (mostly water). pH also plays a vital role in the formation of stable nanoparticles and stabilization of redispersed nanoparticles (Das et al. 2015). Once the pH for the formation and stabilization is known, it is easy to use these AuNPs in different dosage forms. In case of solvents, normally water is used as the greener solvent for the synthesis of biogenic AuNPs but sometimes, when scientists are unable to synthesize these in water, then other solvents are used. In phytosynthesis of AuNPs, many scientists also have shown interest in the fraction of plant extract having high medicinal value (Mukherjee et al. 2013; Patra et al. 2015; Sadeghi et al. 2015).

Characterization of biogenic AuNPs

For proper characterization of phytosynthesized AuNPs the following techniques are exploited: ultraviolet–visible (UV–Vis) spectroscopy; transmission and scanning electron microscopies (SEM, TEM); X-ray diffraction (XRD); inductively coupled plasma atomic emission spectroscopy (ICP/AES); X-ray photoelectron spectroscopy (XPS); Fourier transform infrared (FTIR) spectroscopy; dynamic light scattering (DLS); and atomic-force microscopy (AFM).

The change in color of tetrachloroauric acid and plant extract solution to red or violet indicates the initial formation of colloidal AuNPs, which is further confirmed by the appearance of absorption band in the specific range by UV–Vis. AuNPs have absorption maximum in the range of 500–600 nm due to SPR phenomena. With the help of DLS technique, hydrodynamic average size of AuNPs along with their distribution pattern is determined (Brar and Verma 2011). TEM and SEM are major techniques exploited to measure the shape and size of synthesized biogenic AuNPs (AbdelHamid et al. 2013; Islam et al. 2015a). The functional groups attached to the surface of biogenic NPs responsible for its reduction and stabilization are identified by FTIR (Islam et al. 2016; Mukherjee et al. 2016). The conformation of zero-valent crystalline AuNPs formation and elucidation of its structural information is done by XRD technique. Moreover, it is important to note that XPS is especially useful for the identification of amorphous metallic NPs, as they cannot be characterized via XRD (Abdel-Raouf et al. 2013; Elia et al. 2014).

Biogenic AuNPs as cancer theranostics agents

Nanobiotechnology has huge impacts in the development of therapeutics, diagnostics, and drug delivery systems for various diseases (Parveen et al. 2012; Rizzo et al. 2013). Many researchers have recently demonstrated that the growth of cancer cells has been potentially reduced in a time and dose dependent manner after the treatment of plant-mediated green synthesized AuNPs. Full scheme of biogenic AuNP synthesis, optimization, characterization, and potential application as a cancer therapeutic and diagnostic agent is shown in Fig. 5. Studies have also shown the use of these biogenic AuNPs as photothermal agents for cancer therapy. Foreseeing the in vivo biocompatibility of AuNPs, Fazal and coworkers synthesized anisotropic biogenic AuNPs form cocoa seeds as potential photothermal agents for cancer therapy (Fazal et al. 2014). These AuNPs exhibit near infrared (NIR) absorbance in wavelength ranging from 800 to 1000 nm. Moreover, the nanoparticles were found to be biocompatible when tested on normal human cell lines. Various cancerous cell lines have been screened for phytosynthesized AuNPs and its nanoconjugates cytotoxic activity (Bhat et al. 2013; Chuang et al. 2013; Dhas et al. 2014; El-Sayed et al. 2005; Karuppaiya et al. 2013; Kuppusamy et al. 2016; Mukherjee et al. 2015; Mukherjee et al. 2012; Mukherjee et al. 2013; Nethi et al. 2014; Patra et al. 2015; Ramalingam et al. 2016; Rao et al. 2016). In Table 1, anti-cancer results along with optimized conditions for phytosynthesis of AuNPs are enlisted extensively from studies conducted in the previous decade.

Phytosynthesized AuNPs and cancer therapy: a mechanistic approach

The proposed mechanism for anti-cancer activity of biogenic AuNPs is associated with generation of reactive oxygen species (ROS) and oxidative stress, which induce the upregulation of caspase-3 and oxidation of glutathione (GSH) to glutathione disulfide (GSSG). Moreover, G2/M or sub-G1 cell cycle arrest has been proposed to induce apoptosis upon treatment with biogenic AuNPs, which may further help in elucidation of anti-cancer mechanism in depth. Key advances in proposed mechanisms for anti-cancer activity of biogenic AuNPs are graphically illustrated in Fig. 6 (Bell et al. 2013; Kajani et al. 2016; Kuppusamy et al. 2016; Ramalingam et al. 2016; Rao et al. 2016).

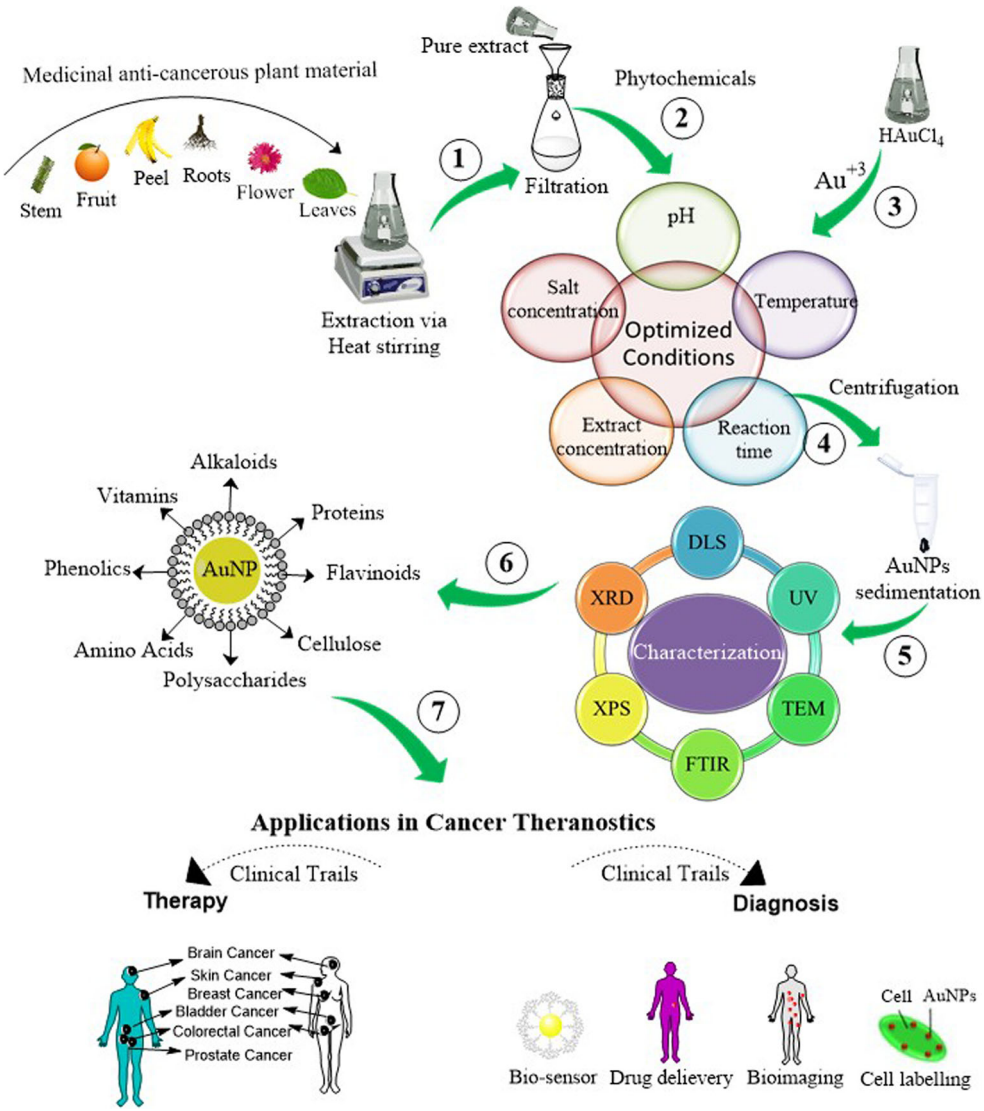

Fig. 5 Detailed scheme of AuNPs synthesis, optimization, characterization, and prospective use as cancer theranostics agent. In step 1, extract of wet/dry plant material is obtained via standard protocol. Steps 2 and 3 deal with the optimization of AuNPs synthesis by varying different reaction parameters. In step 4, AuNPs are obtained in the form of pellet by centrifugation of reaction mixture. Steps 5 and 6 deal with proper characterizations and elucidation of AuNP morphology, size, shape, functional groups attached, etc. In step 7, properly characterized and highly stable AuNPs are exploited for cancer theranostics

Generation of ROS and GSH oxidation

ROS generation has been associated with anti-cancer activity of many market available cancer drugs (Velayutham et al. 2005). In case of biogenic AuNPs, very few studies have validated the production of ROS upon treatment with cancer cells and proposed it to be one of the mechanisms for its anti-cancer activity. In one of the studies published by Mukherjee and coworkers, *Lantana montevidensis* leaf extract-mediated green synthesized AuNPs were demonstrated to produce ROS upon treatment with A549 cells (Mukherjee et al. 2015). Furthermore, the group has also validated that the uptake of biogenic AuNPs was less in A549 cells as compared to chemically synthesized AuNPs; hence, the generation of ROS may be due to the anti-cancer phytochemicals coating biogenic AuNPs and is not related to the uptake of AuNPs by cancerous cells. GSH is an anti-oxidant (non-enzymatic) which is responsible for the prevention of cell form ROS-mediated damage (Liu et al. 2011). Studies report that generation of ROS converts GSH to GSSG via oxidation process, which is regarded as one of the proposed mechanisms for anti-cancer activity of biogenic AuNPs (Mukherjee et al. 2014; Liu et al. 2011). Published literature overall proposes that generation of ROS and oxidation of GSH may be a proposed mechanism for anti-cancer activity of phytosynthesized AuNPs.

Sub-G1 and G0/G1 arrest and anti-cancer activity

Recently, researchers have demonstrated that cancerous cells treated with phytosynthesized AuNPs or its drug delivery system (DDS) undergo accumulation in sub-G1 phase or G0/G1 phase of cell cycle as compared to other phases (Beach et al. 2011; Chang et al. 2011; Mukherjee et al. 2016; Patra et al. 2015). Recent studies on A549 cells treated with doxorubicin

Table 1 Research studies reporting phytosynthesis of gold nanoparticles as potential cancer theranostics agent

Plant	Part used	Cancer cell line[a]	IC $_{50}$ value	Characterization			Optimal variables				References
				Particle size (nm)	Shape	Techniques used[b]	$HAuCl_4$ (mM)	pH	Temp (°C)	Incubation time	
Abelmoschus esculentus	Pulp	PBL, Jurkat	68.18, 8.17 μg/ml	14	Spherical	UV–Vis, DLS, TEM, XRD, FTIR	1	Neutral	Room	18 h	Mollick et al. (2014)
Achyranthes aspera Linn	Seed epi-cotyls	HeLa	25–30 μg/ml	9	Spherical, hexagonal, triangular	UV–Vis, SEM, XRD, FTIR	10	Neutral	Room	1 h	Alagar et al. (2014)
Argemone mexicana	Leaf	MCF-7	160 μg/ml (LD_{50})	Polydispersed	Spherical	UV–Vis, SEM, TEM, XRD, FTIR	1	Neutral	Room	Rapid	Varun and Sudha (2015)
Argemone mexicana	Leaf	HepG2	Dose dependent	Polydispersed	Spherical	UV–Vis, SEM, TEM, XRD, FTIR	1	Neutral	Room	Rapid	Sellappa et al. (2015)
Artabotrys hexapetalus	Whole Plant	MCF 7	2 μg/ml (MIC)	~30	Spherical	SEM, EDX	1	Neutral	Room	Rapid	Priya and Iyer (2015)
Barleria cristata	Leaf	HeLa	Dose dependent	40	Rod, round, triangular	UV–Vis, SEM, TEM, XRD, FTIR, DLS	1	Neutral	Room	Rapid	Baskar et al. (2016)
Bauhinia tomentosa	Leaf	HEp- 2	34.37 μg/ml	31	Spherical	UV–Vis, FTIR, SEM, XRD	1	Neutral	Room	Rapid	Mukundan et al. (2005)
Carica papaya	Leaf	MCF7, HepG2	Dose dependent	15–28	Spherical	UV–Vis, FTIR, SEM, TEM, XRD	1	Neutral	60	5 min	Muthukumar et al. (2016)
Catharanthus roseus	Leaf	MCF7, HepG2	250 μg/ml (GI_{50})	15–28	Spherical	UV–Vis, FTIR, SEM, TEM, XRD	1	Neutral	60	5 min	Muthukumar et al. (2016)
Camellia sinensis	Whole Plant	MCF 7	2 μg/ml (MIC)	~30	Spherical	SEM, EDX	1	Neutral	Room	Rapid	Priya and Iyer (2015)
Coriandrum sativum	Whole Plant	MCF 7	2 μg/ml (MIC)	~30	Spherical	SEM, EDX	1	Neutral	Room	Rapid	Priya and Iyer (2015)
Couroupita guianensis	Leaf	HL-60	5.14 μM	Polydispersed	Spherical, triangular, tetragonal, pentagonal	UV–Vis, SEM, TEM, XRD, FTIR	1	Neutral	Room	5 min	Geetha et al. (2013)
Couroupita guianensis	Flowers	HL-60	Dose dependent	7–48	Spherical, triangular, tetragonal, pentagonal	UV–Vis, FTIR, SEM, TEM, XRD	1	Neutral	Room	5 min	Geetha et al. (2013)
Curcuma pseudomontana	Rhizome	T47D	5–25 μg/ml	20	Spherical	UV–Vis, FTIR, SEM, TEM	1	Neutral	Room	30 min	Muniyappan and Nagarajan (2014)
Diospyros ferrea	Whole Plant	HepG2	Dose dependent	7–90	Spherical, rods	UV–Vis, FTIR, SEM	1	Neutral	Room	Rapid	Verrub (2015)
Gymnema sylvestre	Leaves	HT29	95 μg/ml	72.8	Spherical	UV–Vis, FTIR, SEM, TEM, XRD, EDX	1	Neutral	Room	Rapid	Arunachalam et al. (2014)
Gymnema sylvestre	Leaves	Hep2, HaCaT	Dose dependent	26	Spherical	UV–Vis, DLS, TEM, EDX, FTIR	1	Neutral	Room	30 min	Nakkala et al. (2015)
Hygrophila spinosa	Leaves	HeLa	45 μg/ml	50–80	Triangular, spherical	UV–Vis, DLS, EDX, FTIR, XRD	1	Neutral	Room	10 min	Koperuncholan (2015)
Lantana montevidensis	Leaves	A549, MCF-7, CHO, B16	Dose dependent	70.16	Spherical	UV–Vis, DLS, EDX, FTIR, XRD, TEM, ICP-OES, SDS-PAGE	1	Neutral	Room	~1 h 30 min	Mukherjee et al. (2012)
Mentha arvensis		MCF 7	2 μg/ml (MIC)	~30	Spherical	SEM, EDX	1	Neutral	Room	Rapid	

Table 1 (continued)

Plant	Part used	Cancer cell line[a]	IC_{50} value	Characterization			Optimal variables				References
				Particle size (nm)	Shape	Techniques used[b]	$HAuCl_4$ (mM)	pH	Temp (°C)	Incubation time	
	Whole Plant										Priya and Iyer (2015)
Mimusops elengi	Whole Plant	MCF 7	2 μg/ml (MIC)	~30	Spherical	SEM, EDX	1	Neutral	Room	Rapid	Priya and Iyer (2015)
Olax scandens	Leaves	A549, COLO 205, MCF-7	Dose dependent	5–15	Spherical, rod	UV–Vis, DLS, EDX, FTIR, XRD, TEM, ICP-OES, FCS, SDS-PAGE	0.1	Neutral	Room	25 min	Mukherjee et al. (2013)
Olea europaea	Leaves	K562	Dose dependent	20–100	Spherical	UV–Vis, DLS, FTIR, XRD, TEM	0.1	Neutral	Room	Rapid	Parida et al. (2014a)
Panax ginseng	Root	SiHa, CaSki	2 μM	16.2	Spherical	UV–Vis, DLS, FTIR, XRD, TEM	100	Neutral	Room	Rapid	Mukherjee et al. (2015)
Peltophorum pterocarpum	Leaves	A549, B16	0.65–5 μM	54.2	Spherical	UV–Vis, DLS, EDX, FTIR, XRD, TEM, ICP-OES, FCS, SDS-PAGE	0.1	Neutral	Room	Rapid	Mukherjee et al. (2016)
Phyllanthus amarus	Whole Plant	MCF 7	2 μg/ml (MIC)	~30	Spherical	SEM, EDX	1	Neutral	Room	Rapid	Priya and Iyer (2015)
Punica granatum	Fruit peel	MCF-7	250 ng/ml	70.90	Spherical	UV–Vis, FTIR, TEM	0.1	Neutral	Room	1 min	Gao et al. (2004)
Syzygium aromaticum	Fruit	SU-DHL-4	150 μM	12–20	Spherical	UV–Vis, DLS, FTIR, XRD, TEM	1	Neutral	Room	1 min	Parida et al. (2014b)
Syzygium aromaticum	Whole Plant	MCF 7	2 μg/ml (MIC)	~30	Spherical	SEM, EDX	1	Neutral	Room	Rapid	Priya and Iyer (2015)
Tabernaemontana divaricata	Flower	MCF-7	100 μg/ml	100	Spherical	UV–Vis, DLS, FTIR, TEM	1	Neutral	Room	Rapid	Preetam Raj et al. (2016)
Theobroma cacao	Cocoa	A431, MDA-MB231, L929, NIH-3T3	~200 μg/mL	150–200	Spherical, anisotropic	UV–Vis, FTIR, SEM, TEM, XRD, DLS	1	Neutral	37	15 min	Fazal et al. (2014)
Xanthan gum	Gum	A549	0.79 μg/ml (coated with doxorubicin (DOX))	15–20	Spherical	UV–Vis, DLS, FTIR, TEM	1	Neutral	80 °C	2 h	Pooja et al. (2014)
Zataria multiflora	Leaves	HeLa	100 μg/ml	10–42	Spherical	UV–Vis, DLS, FTIR, TEM	1	Neutral	Room	Rapid	Baharara et al. (2016)

[a] Cancer cell lines: MCF-7, human breast cancer (MDA-MB231), liver carcinoma (Hep-G2), cervical cancer (HeLa), lung cancer (A549), human promyelocytic leukemia cells (HL-60), human T cell lymphoma (Jurkat cell line), human T cell lymphoma (COLO 205), human colorectal adenocarcinoma (HT29), aneuploid immortal keratinocyte (HaCaT), Chinese Hamster Ovary (CHO), myelogenous leukemia (K562), SiHa, cervical cancer (CaSki), human B lymphocyte (SU-DHL-4), and epidermoid carcinoma (A431)

[b] Techniques used: UV–visible absorption spectroscopy (UV–Vis), X-ray diffraction (XRD), Fourier transform infrared (FTIR), energy-dispersive X-ray (EDX), dynamic light scattering (DLS), transmission electron microscopy (TEM), scanning electron microscopy (SEM), Atomic Force Microscope (AFM), X-ray photoelectron spectroscopy (XPS), inductively coupled plasma optical emission spectrometer (ICP-OES), sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), fluorescence correlation spectroscopy (FCS)

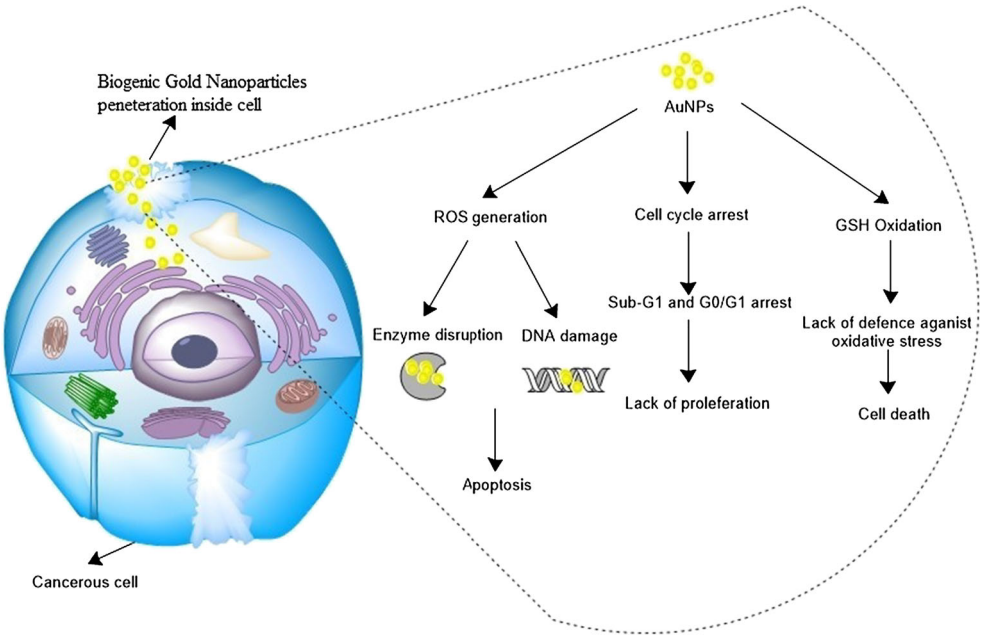

Fig. 6 Key recent advances in proposed mechanism for anti-cancer activity of biogenic AuNPs

(DOX)-coated phytosynthesized AuNPs from *Peltophorum pterocarpum* were found to be accumulated in G0/G1 phase as compared to cells treated with free DOX (Mukherjee et al. 2016). Furthermore, B16F10 cells treated with DOX-coated phytosynthesized AuNPs were found to be in high proportion in early sub-G1 phase, in comparison to cells treated only with free DOX. The same early sub-G1 phase arrest in B16F10 cells was demonstrated by phytosynthesized AuNPs from *B. monosperma* leaf extract (Patra et al. 2015). Overall, these studies validate that cell cycle regulation may have a vital role in induction of apoptosis plus rapid uptake and enhanced cytotoxicity of DOX coated phytosynthesized AuNPs as compared to free DOX. On the biases of these scientific reports, we propose that accumulation of cancerous cells in sub-G1 or G0/G1 phase upon treatment with biogenic AuNPs or its nanoconjugates may be responsible for its anti-cancer activity.

Apoptosis, upregulation of p53 protein and caspase 3 and 9 expression

Induction of apoptosis is highly correlated with anti-cancer activity of nanoparticles (Alabsi et al. 2012). Gold nanoparticles have induced apoptotic cell death in many cell lines including AGS cells, HeLa cells, MCF-7 cells, etc. (Chuang et al. 2013; Dhas et al. 2014; Selim and Hendi 2012). Mechanistic studies found that the action of gold nanoparticles is associated by apoptosis induction, which depends on cell type and cellular context (Chuang et al. 2013). In an experimental study, the toxic effects of biogenic AuNPs were examined by analyzing the inner structure of cells (nuclear damage) using DAPI staining. In this, the fluorescence part of control cells showed no damage in nuclei whereas cancer cells (HeLa cells) showed condensed and fragmented chromatin upon treatment of AuNPs (Dhas et al. 2014). Interestingly, nuclear fragmentation in cells after treatment of AuNPs was also observed (Kang et al. 2010). Overall, scientific studies validate that the induction of apoptosis via caspase 3 and 9 activation and downregulation of P53 protein may be a proposed mechanism for the anti-cancer activity of biogenic AuNPs.

Synthesizing biogenic AuNPs: a diagnostic approach in cancer

Fluorescent materials play an important role in many applied fields such as mineralogy, gemology, chemical sensors, fluorescent labeling, dyes, biosensors, and generally fluorescent lamps (Basabe-Desmonts et al. 2007; Gao et al. 2004; Matz et al. 1999). Very recently, Mukherjee and coworkers for the first time demonstrated the use of phytosynthesized AuNPs as diagnostic and therapeutic agents (two-in-one system) (Mukherjee et al. 2013). In their study on synthesis of AuNPs from leaf extract of *O. scandens*, they have found that not only the NPs were synthesized and stabilized by phytochemicals but also self-fluorescence ability was attained due to coating of fluorescence phytochemicals present in the leaf extract. Furthermore, the group confirmed that the red fluorescence shown by AuNPs was due to the phytochemicals of *O. scandens* and that fluorescence is also maintained after treatment with A549 and MCF-7 cells. Furthermore, Fazal and coworkers also have biosynthesized gold nanoparticles, which when tested by computed tomography (CT) proved to exhibit X-ray contrast (Fazal et al. 2014). A study by Chanda and coworkers also have reported the utilization of green synthesized cinnamon-coated gold nanoparticles as potential CT/

optical contrast-augmentation agents for cancer cells detection (Chanda et al. 2011). In future, biosynthesized AuNPs due to its self-fluorescence ability can be exploited as promising agents for diagnosis of cancer.

In-vivo drug delivery potential of biogenic AuNPs

As the phenomenon of multidrug resistance is increasing constantly and is becoming a limiting factor for the cancer treatment, the conjugation of drugs with gold nanoparticle-based drug delivery is being used to overcome this drug resistance (Zeng et al. 2014). Although chemically synthesized AuNPs have been exploited, to the best of our knowledge, only one study published by Mukherjee and coworkers has reported the in vivo biodistribution, toxicity, and drug delivery potential of phytosynthesized synthesized AuNPs and much is yet to be explored. Previously, this group has pioneered in the development of in vitro DDS from *Butea monosperma* leaf extract synthesized AuNPs for DOX (Patra et al. 2015). While in their latest study, for the first time, they have demonstrated the development of in vitro and in vivo DDS from *P. pterocarpum*-mediated green-synthesized AuNPs for DOX; the detailed scheme of the study is shown in Fig. 7. Furthermore, they have reported in vitro and in vivo anti-cancer activities of DOX-loaded DDS on A549 and B16F10 cancer cells and melanoma tumor mouse models, respectively. The results indicated that the uptake and release of free DOX were slow as compared to its nanoconjugated form while biosynthesized AuNP-PP-DOX conjugates showed better tumor regression ability compared to free DOX. Overall, the results of this novel in vivo study have set a roadmap for potential use of phytosynthesized AuNP-biased DDS as a cost-effective and alternate approach for cancer treatment in the near future.

Hurdles for biogenic AuNPs as future cancer nanomedicine

Due to outstanding physico-chemical properties of nanomaterials, they have many versatile applications like in targeted drug delivery, optical bioimaging, biosensors, cancer cells photothermolysis, immunoassays, etc. Though, the toxic nature of these NPs in various body parts should not be ignored. Proper screening of these nanomaterials for biosafety, long-standing toxicity, potential efficacy, interaction with immune system, and detailed in vivo pharmacokinetics study is very vital before moving to clinical trials. Key challenges faced by researchers for entrance of phytosynthesized

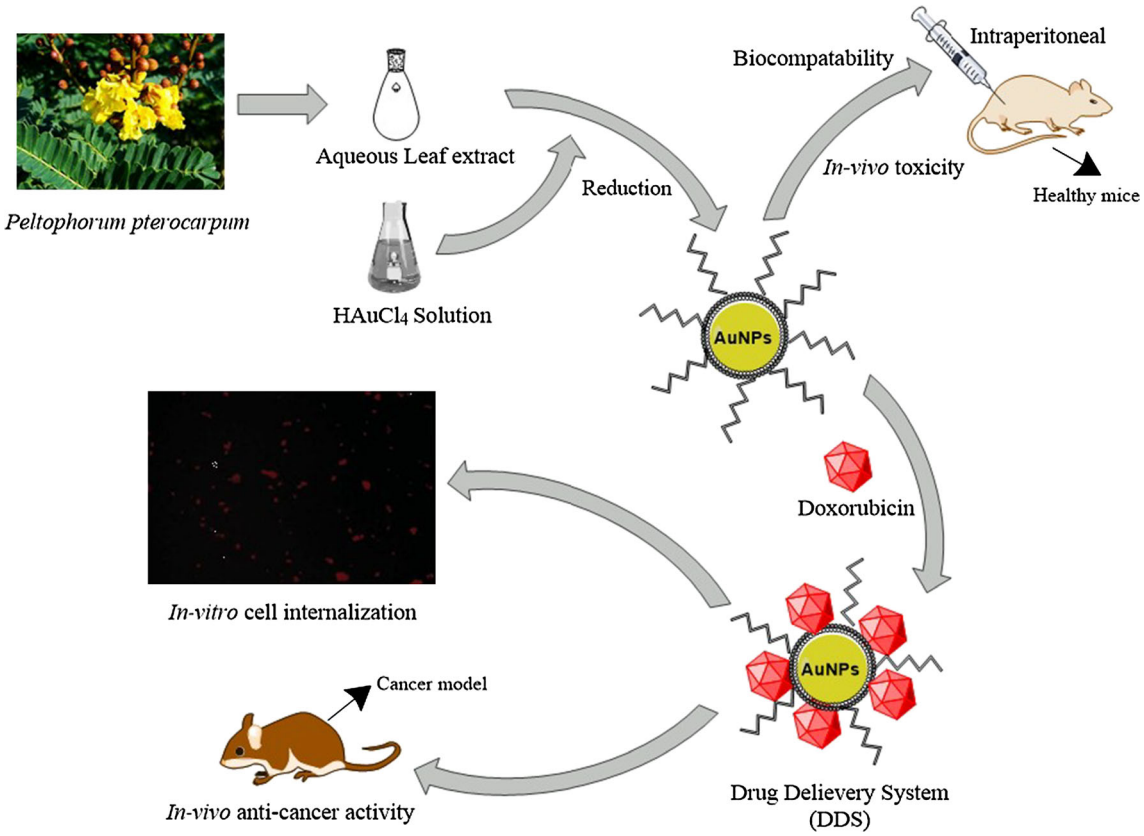

Fig. 7 Drug delivery system formulation using biogenic AuNPs synthesized via *Peltophorum pterocarpum* leaf extract and its in vitro and in vivo anti-cancer activities

AuNPs into clinical phase are (i) biodegradability and biocompatibility; (ii) dosage and route of admiration; (iii) uptake, retention, and clearance; and (iv) combinatorial approach with FDA-approved anti-cancer drugs (Arvizo et al. 2010; Bao et al. 2014; Wason and Zhao 2013). It is of paramount importance that the strategies acquired at lab-scale for the production of AuNPs should be feasible for industrial or large-scale production. Moreover, the conditions on which these nanoparticles/nanoconjugates are synthesized determine its effectiveness as potential nanomedicine, especially the ratio of plant extract and $HAuCl_4$, reaction time, pH, concentration of drugs, pressure, type of cross linker, etc. Recently, scientists have developed several drug delivery systems by exploiting different moieties to minimize accumulation of biogenic AuNPs in healthy body tissues ultimately resulting in tumor specific uptake (Mukherjee et al. 2016; Mukherjee et al. 2013; Patra et al. 2015). For effective uptake of nanomedicine, proper diffusion and penetration through the cell and tissue barriers are critical. Vital issues which are associated with intravascular delivery of NPs include (i) immune rejection, (ii) intestinal tissue penetration, (iii) release of drug via diffusing into cytoplasm, (iv) crossing endothelium to reach targeted sites, (v) possible entrance into nucleus, (vi) clearance in the liver and spleen, and (vii) receptor-mediated entry into cells (Barua and Mitragotri 2014). Beside their diverse applications, AuNPs are also associated with different types of toxicities to human health, which poses a serious challenge for their clinical implications**.** Many reports scientifically validate the acute or chronic in vivo toxicity of various metallic nanomaterials like copper, zinc, silver, platinum, and cerium (Aalapati et al. 2014; Triboulet et al. 2015). Although, Mukherjee and coworkers demonstrated biogenic AuNPs to be biocompatible and non-toxic in in vitro and in vivo experiments (Mukherjee and Patra 2016; Mukherjee et al. 2016; Mukherjee et al. 2013; Patra et al. 2009; Rengan et al. 2015). Once injected inside body, these NPs encounter body fluids and tissues ultimately form a corona around them due to active biomolecules. This protein corona and NPs complex should be studied in more detail as it is responsible for the ultimate variation of biological activities of these NPs in vivo (Corbo et al. 2016).

Authors concluding remarks and future prospects

The increase in the incidence of cancer and significant high market value, various limitations in the conventional therapy, high cost, and high toxicity of present nanomedicine has thrown a severe challenge to all the researchers to design and develop an alternative, biocompatible, eco-friendly, and cost-effective nanomedicine in a greener way. In this scenario, biosynthesized multifunctional gold nanoparticles are likely to revolutionize the face of nanomedicine in the next decade towards cancer theranostics. High biocompatibility and biodegradability have increased the utility of biosynthesized gold nanoparticles in cancer therapy. Low cost of green synthesized AuNPs has decreased the overall production cost in the large industrial scale. Utilization of plant-based bioactive molecules (capping, anti-cancer, fluorescence) has ended the requirement of external drugs or fluorescent labeling agents. All the results taken together, this comprehensive review article highlights the various cancer theranostics applications and detailed mechanisms of biosynthesized AuNPs. Finally, various factors including potential long-term toxicity study, biosafety, metabolic fate, immunogenicity, and pharmacokinetics and pharmacodynamics studies should be systematically examined in animal model before using these robust green gold nanoparticles in clinical trials.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with animals or human participants performed by any of the authors.

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