



# Phytosynthesized nanoparticles as a potential cancer therapeutic agent

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## Abstract

Plants are the well-known sources for the hyper-accumulation and reduction of metallic ions. Analysis of various plant extracts has justified the presence of different types of phytochemicals that possess the stabilization and reduction functionalities of precursors to form nanoparticles. Such characteristics make plants as an attractive source for synthesizing eco-friendly nanoparticles (NPs) with potentially less toxicity to the body. Recently, phytosynthesized nanoparticles have been explored for targeted inhibition and diagnosis of cancer cells without affecting non-cancerous healthy cells. The aim of this review is to discuss the characteristic performance of NPs synthesized from various plant sources for the diagnosis and inhibition of cancer. The mode of action of phytosynthesized nanoparticles for anti-cancer applications are also discussed.

**Keywords** Phytosynthesis · Nanoparticles · Nanomedicine · Anticancer · Cancer diagnosis

## Introduction

Cancer is a non-communicable disease, which is characterized by rapid and continuous division of cells (Jeevanandam et al. 2020b). It is the world's second causative factor of deaths, with an estimate of 606,880 mortality in the USA alone, until June 2019 (Siegel et al. 2019). The International Agency for Research on Cancer (IARC) reported about 18.1 million new cases and 9.6 million deaths in 2018. One out of every six women and one out of every five men throughout the world tend to develop cancer during the course of their life span (Bray et al. 2018). Cancer is a chronic disease that usually exhibit complications in the later stages or revealed via tedious early stage diagnosis. Early diagnosis will increase the chance of effective treatment and management

of this deadly disease. Annually, about 2.6 million cases of cancer is diagnosed (Siegel et al. 2015), and according to the American Cancer Society (ACS), the incidence of cancer will rapidly increase to 21.7 million new cases in 2030 (Agarwal et al. 2017). In the past 5 years, 50% of the diagnosed cancer cases belonged to developing countries (Bray et al. 2012) and it has been attributed to the poor, misdiagnosis of cancers and lack of appropriate treatment with high cost of management and cancer theranostics (Bray et al. 2012). Both diagnosis and treatment are essential in reducing the complication of cancer among patients. In 2016, a report by iMShealth Institute for Healthcare Informatics stated a record level for worldwide market of cancer therapeutic drug (\$107 billion USD) in 2015 and is predicted to increase up to \$150 billion in the year 2020 (Wise 2016). Even after spending a massive budget to produce an effective cancer theranostic agent, cancer is still considered as a deadly disease which is the causative factor for several deaths, and the risk of increasing cancer cases is still intensifying, especially in the developing countries (Mahmoud and Moneer 2017). The situation is more severe in the low and middle-income countries, wherein around 75% of cancer-related deaths occur and is found to increase rapidly. Inevitably, serious global concerns are required to harmonize the remuneration of new treatments and diagnostic strategies to be accessible by all the cancer patients in underdeveloped and developing world (Shah et al. 2019). Thus, it is necessary to develop a

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diagnostic and therapeutic method that is highly effective and low cost to eradicate cancer throughout the world.

Amongst all different types of cancers, the incidence rate of lung, female breast, and colorectal cancers are the top-most in terms of cancer deaths. There are several treatment strategies available such as surgery, chemotherapy, radiation, immunotherapy, and hormonal therapy. Although these practices are regularly employed in the hospitals to date, they are associated with several mild to severe side-effects (Jeevanandam et al. 2019c). Likewise, the diagnostic techniques of cancers that are widely in practice are tissue biopsy, micro-imaging and histopathology assay (Abbaci et al. 2014). However, these methods are usually limited to minimum tissue extent and may lead to rapid neoplastic alterations, cancerous cell proliferation and growth of cancerous metastatic cells. In case metastatic cancer spread to other tissues, it is extremely difficult to target the individual neoplastic cells by conventional chemotherapeutic or surgical techniques (Mudali et al. 2020). Furthermore, surgical removal of cancer tissues may also lead to damage and removal of healthy cells along with cancerous neoplasms (Sudhakar 2009). Thus, existing techniques for the diagnosis and treatment of cancer cannot reach neoplastic cells at the minimum level of individual cells (Mallidi et al. 2011). However, imaging agents based on nanoparticles, in contrast, offer the potential to reach the target site effectively and to the highest degree that enhances tumor detection using conventional scanning technologies, such as Positron Emission Tomography (PET), Computed Tomography (CT) scan, and Magnetic Resonance Imaging (MRI) (Devaraj et al. 2009; Lee et al. 2008). Moreover, imaging at the nanoscale platform equips the physicians to treat and diagnose cancers more accurately compared to traditional techniques such as Raman spectroscopy, Multimodal Imaging and Photo-Acoustic Tomography (PAT) (Brigger et al. 2012). Thus, nanoparticles are under extensive research to offer innovations in cancer diagnostic and treatment modalities.

Nanotechnology is a multidisciplinary field, which involves diverse areas of research ranging from engineering to physics, chemistry, biology, and medicine (Pal et al. 2019). For several years, it has been exploited in every aspect such as manufacturing of nanodevices, nanotherapeutics, nanoelectronics and engineered biological structures (Pal et al. 2017). Briefly, nanoparticles (NPs) are formed by assembling atoms or small group of molecules or breaking down of large materials in the nano regime (1–100 nm in diameter) (Jeevanandam et al. 2018). Although synthesized from bulk or micromaterials, nanoparticles possess distinct durability, higher surface to volume ratio, conductivity and other functional biocompatible properties. NPs can be synthesized by physical, chemical and biological methods. Numerous literature suggested that physicochemical synthesis of NPs are costly and also hazardous to the environment

(Andra et al. 2019; Jeevanandam et al. 2020a). Contrarily, the nanosized particle formation by biological means is a much better approach owing to their advantages in reducing the limitation of physical and chemical approaches (Jeevanandam et al. 2019a). NPs synthesized by biological methods are non-toxic, easy to scale up with consistent unique shape, dimension and composition (Asiya et al. 2019; Deepak et al. 2019). These properties of the nanoparticles are vital in the end user application of nanoparticles. The synthesis of NPs via chemical approaches require distinct reducing agents such as sodium borohydride (NaBH<sub>4</sub>), sodium citrate, tollens reagent and stabilizing agents to produce definite sized particles (Wong et al. 2019). Recently, emphasis is also being given to the development of new strategies for ease in synthesis, less time consuming and affordable fabrication of nanosized particles. The increasing applications of chemicals in NPs synthesis causes inhalation problems, which can easily damage the lungs and cause many other fatal diseases (Mossman et al. 2007). The use of precursor materials, detergent, and stabilizer during synthesis of NPs creates the cytotoxicity and many adverse effects to the human health (Wiesner et al. 2006). These issues can be addressed via integrating green and eco-friendly methods in nanoparticles synthesis. Biosynthesis approaches have significance in emphasizing the making of the NPs synthesis route as clean, safe, eco-friendly, and to delineate the current gap of physical and chemical methods of synthesis.

Biological sources including fungi and bacteria are most commonly used for the synthesis of nanoparticles (Sonar et al. 2017) which is high cost and time consuming process. In case of microbial synthesis of NPs, pathogenic and saprophytic microbes such as *E. coli* are used that can cause serious health issues. However, phytosynthesized NPs are devoid of such risks and safer for health concerns (Rahul et al. 2015). Moreover, the plant-based NP fabrication approach does not demand any costly procedures, in contrast to microbial synthesis of NPs. Thus, medicinal plants are the source of anticancer phytochemicals that are recently studied and declared as an excellent source for producing natural NPs with negligible hazards and require a short time for large-scale production (Nasrollahzadeh et al. 2015b; Ovais et al. 2017). Therefore, phytosynthesized nanoparticles are proposed and valued as highly beneficial for commercial applications. In recent times, the interest of researchers has been shifted towards phytosynthesized nanoparticles due to the increasing menace of organic synthesis and upcoming research studies pronouncing plants as safer sources. Nanoparticles such as gold (Au), copper (Cu), silver (Ag), palladium (Pd), titanium (Ti), zinc (Zn) and iron (Fe) are widely synthesized via plant extracts as sources and possess tremendous applications in the biomedical field (Nasrollahzadeh and Sajadi 2015, 2016a; Ovais et al. 2016). Interestingly, nanoparticle-based approaches such as bio-imaging, cancer

cell inhibition ability and photo-thermal therapy is now focused by researchers for cancer theranostics. Especially, phytosynthesized nanoparticles, including gold and silver are employed for the visualization of tumors and assess them at cellular level (Ovais et al. 2016, 2017). Therefore, phytosynthesis of nanoparticles is the top priority and a matter of interest for the scientific community in the current era. Among plant-based NP synthesis approach, plant extracts from leaves, roots, fruits and seeds are particularly promising due to their safe in use, low cost and easily available (Mamatha et al. 2017; Nasrollahzadeh and Sajadi 2016b; Sadeghi and Gholamhoseinpoor 2015). In phytosynthesis, several organic as well as inorganic phytochemicals such as flavonoids and alkaloids are found to be useful in the formation of NPs (Sajadi 2021). The characteristic of a phytosynthesized NPs, depends on the phytochemistry of plants and these phytochemicals will be a beneficial factor in altering the properties of NPs (Rath et al. 2014). Thus, this article discusses the fabrication of NPs synthesized from different plant sources and their application in the inhibition and diagnosis of cancer. In addition, the mechanism of diagnostic and anticancer effects of phytosynthesized nanoparticles is also discussed.

## Phytosynthesized nanoparticles

In recent times, synthesis of NPs has been achieved using exclusive phytochemical extracts from plant sources in their live, dead or inactive form (Husen and Siddiqi 2014). Several metabolites from plant such as tannins, phenols and alkaloids are essential for the formation of nanoparticles by reducing metal ions. The challenge in its widespread application is the varying composition of polyphenolic and phytochemical compounds in various plant species (Rahul et al. 2015). Thus, it is necessary to devise a method, in which optimized and controlled quantity of phytochemicals can be produced to obtain the desired product with a higher reproducibility rate, in lesser time and cost. Hence, it is predicted that quantification and isolation of phytochemicals using plant tissue culture technique can be beneficial in producing significantly dynamic nanoparticles. Furthermore, the application of extract or biomass from plants has been identified as more consistent and eco-friendlier for nanoparticle fabrication (Andra et al. 2019). The major merits of phytochemical extracted from plants in the synthesis of NPs include (i) wide accessibility, (ii) safety, (iii) low cost, (iv) rapid synthesis rate, (v) ease in large scale synthesis and (vi) better morphology and dimension control of nanoparticles. These meritorious properties have inspired numerous researchers to identify distinct species of plants for the synthesis of NPs. Literature suggest that several plant species possess excellent ability to accumulate metals, that are

intracellularly reduced into nanoparticles (Vijayaraghavan and Ashokkumar 2017). The *Medicago sativa* and *Brassica juncea* are well-known metallophytic plants with the capability to collect and form nanosized gold (Au) from aqueous  $\text{KAuCl}_4$  precursor as demonstrated by Bali and Haris (2010). The metal was stored as NPs in distinct plant parts including vascular tissue, epidermis and cortex, however, mostly present in parenchyma cells and xylem (Bali and Harris 2010). The NPs of 5–10 nm were formed in *B. juncea* and 10–20 nm in *M. sativa*, respectively. The mechanism of synthesis involves in live plants involves the nucleation of crystal via interaction, evolution, and coagulation consistent with the well-known Turkevich method of AuNPs synthesis. Apart from this, a lot of attention has been directed towards the plant utilization with effective phytoremediation of heavy metals to synthesize nanosized metallic particles. For the first time, Gardea-Torresdey et al. (2003) reported the synthesis of nanosized silver (AgNPs) and gold particles formation within live *Medicago sativa* (alfalfa) plants via respective metal uptake (Gardea-Torresdey et al. 2003, 2002). Characterization by X-ray absorption spectroscopy and TEM confirmed the internalization and accumulation of gold and silver NPs. However, the intracellular fabrication of nanosized metallic particles is tedious and requires expensive processes to recover them from the plant biomass and thus, very few reports have been found in the literature. So far, *Sesbania drummondii* (Sharma et al. 2007), *Chilopsis linearis* (Gardea-Torresdey et al. 2005), *Triticum aestivum* (Armendariz et al. 2004b), and *Avena sativa* (Armendariz et al. 2004a) were used for the intracellular production of distinct metallic NPs. Furthermore, the critical limitation of intracellular approach is the reducing and stabilizing functional group variations in distinct plant parts that are essential for nanosized particle formation (Dauthal and Mukhopadhyay 2016). Nowadays, the extracellular route for the synthesis of NPs has opened a new avenue as an alternative to intracellular NPs synthesis, due to the ease in downstream and scaling up processes. Nevertheless, it is demanding to replicate nanosized particles with definite uniform dispersity and reliable surface morphology due to the fluctuating composition and structure of phytochemicals. Furthermore, the existence of impurities with wastes from agriculture or biomasses of plant is high, at all times. So, the critical aspects of plant-mediated synthesis involve a specific phytochemicals (extract) obtained from a specific part or the whole living plants. Literature evidence suggested that focus of researchers is now diverted towards fabrication of NPs of noble metals such as gold, platinum (Pt), silver and palladium (Pd). These nanoparticles are categorized under valuable metals and are broadly utilized in nanomedicine and nanobiotechnology. The phytosynthesized nanoparticles can be classified into metal, oxides of metal, polymer, carbon and nanocomposites, based on the type of precursor

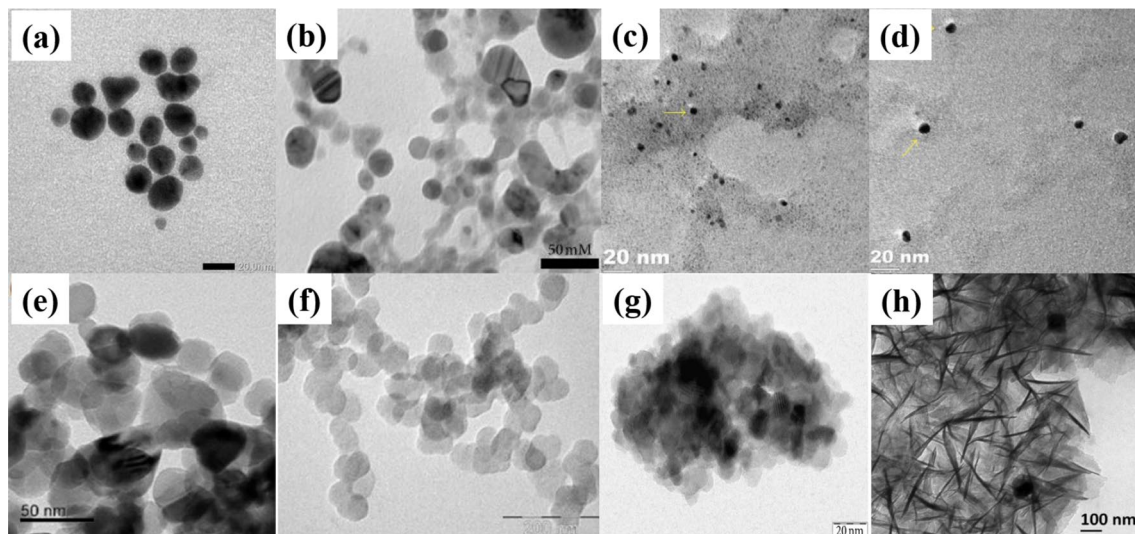
used and nanoparticles formed. Figure 1 shows the TEM micrographs of various nanoparticles synthesized from the phytochemical extracts of different plants.

### Metallic nanoparticles

Numerous metallic nanoparticles such as Ag, Au, copper, zinc oxides, platinum and cobalt have been synthesized from either whole plants or their extracts. Gold is a noble element by nature and hence highly unreactive. AuNPs have attracted substantial attention from various research groups in the field of phytochemical mediated synthesis of nanoparticles, due to their several applications in nanoelectronics, drug delivery, catalysis and nanodevices. AuNPs have several properties such as, resistant to deterioration, tunable surface plasmon resonance (SPR) and exceptional physiochemical properties (El-Sayed et al. 2005). Moreover, they are monodispersed, have enhanced surface area to volume ratio, and easy to functionalize with any biomolecules such as antibodies, nucleic acids, proteins and peptides. In general, the reduction of auro chloric acid ( $\text{HAuCl}_4$ ) into ruby red color AuNPs via conventional citrate reduction or polyol method confirms the formation of nanosized gold particles (Ovais et al. 2017). Shankar et al. (2003) carried out the first experiment on the biosynthesis of nanosized metallic particles via phytochemical extract of geranium leaves. The extracts of plants were proven to possess ability to form nanosized gold particles of various morphologies. It has been suggested in the study that the existence of terpenoids in the

plant extract may be accountable for gold ions reduction into nanosized gold. Recently, similar studies also demonstrated the synthesis of AuNPs using phytochemicals from lemon grass (Shankar et al. 2005) and *Azadirachta indica* leaves (Shankar et al. 2004). Vimalraj et al. (2018) synthesized AuNPs by utilizing aqueous phytochemicals from *Mangifera indica* seed as a reducing material in one step method. TEM studies revealed the spherical morphology of the synthesized NPs and the biocompatibility assessment of these 46.8 nm sized particles indicated the non-toxicity of AuNPs towards mesenchymal stem cells. The in vitro analysis results emphasized the anti-angiogenic properties of these nanoparticles with supreme biocompatibility, thereby useful in several biomedical and pharmaceutical applications.

*Glycyrrhiza uralensis* is a medicinal plant, which is well reported for its hepatoprotective effects. The root extracts of *G. uralensis* was used for the rapid biogenic fabrication of nanosized silver and gold particles (Huo et al. 2018). The reduction of  $\text{HAuCl}_4$  and silver nitrate, lead to the formation of Au and Ag and the X-ray diffraction (XRD) data showed the FCC phase formation in both nanoparticle samples with an optimum crystallite size of 12.25 nm and 8.01 nm, respectively. Moreover, AuNPs were also synthesized using *Dracocephalum kotschy* leaf extracts and are systematically characterized via various analytical instruments. The synthesized AuNPs displayed 11 nm sized spherical shaped dimension and enhanced anti-choline esterase ability (Dorosti and Jamshidi 2016). Likewise, Desai et al. (2018) synthesized nanosized photoluminescent gold particles with excellent



**Fig. 1** Transmission Electron Micrograph (TEM) of various nanoparticles synthesized from plant extracts. **a** Gold nanoparticles from *Polyscias scutellaria* (Reproduced from Yulizar et al. 2017), **b** Silver nanoparticles from *Impatiens balsamina* (Reproduced from Arinonang et al. 2019), **c** Platinum nanoparticles and **d** Palladium nanoparticles from *Gloriosa superba* (Reproduced from Rokade et al. 2018),

**e** Zinc oxide nanoparticles from *Costus pictus* (Reproduced from Suresh et al. (2018a; b), **f** Iron oxide nanoparticles from plantain peel extract (Reproduced from Herlekar et al. 2014), **g** Copper oxide nanoparticles from *Saraca indica* (Reproduced from Prasad et al. 2017b) and **h** Magnesium oxide nanoflowers from *Rosmarinus officinalis* (Reproduced from Abdallah et al. 2019)



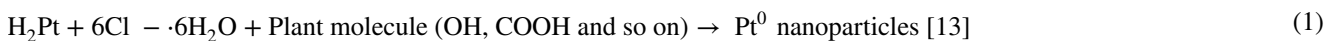
antioxidant and catalytic potential by reducing  $\text{HAuCl}_4$  with kokum fruit extract. The photoluminescence property of the AuNPs demonstrated a broad excitation at 311 nm and an emission at 455 nm. Also, the nanosized gold particles exhibited significant dose-mediated activity of scavenging DPPH radicals (Desai et al. 2018). The Euphorbiaceae family plants contain highly active constituents, i.e., euphol, is found in *Euphorbia tirucalli* (Avelar et al. 2011). Lunardi et al. (2018) synthesized AuNPs using dried euphol latex as nanoparticle formation agents. The synthesis was performed under microwave irradiation without solvents of organic nature to yield eco-friendly nanoparticles (Lunardi et al. 2018). Similarly, *Origanum vulgare* contain numerous phytochemicals namely, flavonoids, essential oils, phenolic acids, and anthocyanins in their leaves and flowering stems. Benedec et al. (2018) used different concentrations of *Origanum vulgare* extracts to reduce gold ions and fabricate biocompatible AuNPs. The cytotoxicity assays revealed that AuNPs synthesized from the biogenic source were less toxic towards normal human dermal fibroblast cells (Benedec et al. 2018). Furthermore, the *Croton Caudatus Geisel* plant is widely distributed in South East Asia, and it is utilized for numerous human disease therapy. Recently, Kumar et al. (2019) extracted phytochemicals from those plants and utilized for the fabrication of AuNPs and proposed that the oxygen atom of flavonoids was accountable for the biogenic formation of nanosized particles. The AuNPs yielded were spherical in morphology with 20–50 nm in size and the ability to scavenge free radicals disclosed that the phytochemicals extracted from *C. caudatus* possess extreme reducing power. These AuNPs also exhibited excellent in vitro proliferative efficacy and microbial cell inhibition activity (Kumar et al. 2019). In an experiment performed by Rajan et al. (2014), *Garcinia combogia* fruit extracts were employed for the fabrication of anisotropic and spherical nanosized gold. The morphology of the synthesized AuNPs were proved to be depended on the reaction temperature and the amount of *Garcinia combogia* fruit extract used in the chemical reaction (Rajan et al. 2014). A similar type of experiment was steered by Islam et al. (2015), where the leaf extract of *Pistacia integerrima* was used for ion reduction into nanosized gold particles. The presence of hydroxy and carboxylic groups in polyphenols was proposed to be accountable for gold ions decrement to form nanosized gold particles, while polyphenols are anticipated to be the functional group to control the size of obtained nanosized particles at distinct pH and extreme temperatures. Furthermore, Dhamecha et al. (2015) synthesized 72–85 nm sized gold nanoparticles via *Pterocarpus marsupium* extract under various synthesis conditions, such as pH, stirring rate and temperature. The study showed that the synthesis parameters did not have any remarkable effect on morphology; however, the stability was significantly affected. The in vitro stability analysis revealed

that the nanosized gold particles were stable (except at low pH), and highly biocompatible (Dhamecha et al. 2016c). Similarly, nanosized gold particles were fabricated using *Nepenthes Khasiana* aqueous extract and its stability was evaluated in 2% of bovine serum albumin, human serum albumin, 0.2 M of histidine, cysteine, 5% of sodium chloride, and acidic solution. The study showed that the synthesis parameters and the morphology of the gold nanoparticles played a major role on stability, and the nanoparticles were unstable in sodium chloride and the acidic solution (Dhamecha et al. 2016a). These studies partly support that the presence of phytochemicals as functional group in nanoparticles, along with the synthesis parameters, is highly significant in maintaining stability of the nanoparticles under in vitro conditions.

Silver nanoparticles (AgNPs) are another exclusive group of metallic nanoparticles, which are phytosynthesized via a wide variety of plant species. Generally, AgNPs synthesis in solution requires three main components, namely, (i) metal precursor, i.e., salt of silver (ii) a material with reducing ability, and (iii) a functional group material to stabilize and control the size of nanosized particles and to avoid aggregation. Generally, materials with reducing property namely ascorbic acid, alcohol, borohydride, sodium citrate and hydrazine compounds are used for AgNPs fabrication. Apart from physicochemical synthesis approach of AgNPs, there is much attention towards a plant-mediated synthesis of AgNPs. Recently, parts of plants and their metabolites have been efficaciously utilized for the effectual biogenic fabrication of AgNPs (Husen and Siddiqi 2014; Nasrollahzadeh et al. 2015a). Ahmed (2016) fabricated nanosized silver particles via extracts of *Azadirachta indica* (neem) leaves with reducing property for transforming ions of silver to AgNPs. The synthesized AgNPs were homogeneous and spherical, and the presence of a surface plasmon resonance band revealed the formation of AgNPs. The average particle size was approximately around 34 nm as evidenced from dynamic light scattering (DLS). The synthesis of nanoparticles required only 15 min for silver ion transformation into silver nanoparticles without any toxicity. The existence of ion reducing biomolecules such as polysaccharides and proteins in the plant extracts were proposed to be accountable for silver nanoparticle formation (Chung et al. 2016). *Cleome viscos* plant extracts were successfully used for the biological silver nitrate reduction into silver ions and subsequent formation of AgNPs (Lakshmanan et al. 2018). Also, several reports emphasized the fabrication of AgNPs using a variety of phytochemicals from diverse plant species, such as *Butea monosperma* (Patra et al. 2015), *Cucurbita maxima* (Nayak et al. 2015), *Achillea Biebersteinii* (Baharara et al. 2015) and *Alternanthera sessilis* (Lalitha 2015). Similar to gold nanoparticles, several studies have demonstrated that the type of phytochemicals, synthesis parameters and

conditions can significantly affect the stability and biocompatibility of phytosynthesized silver nanoparticles (Jadhav et al. 2015, 2016).

Apart from AuNPs and AgNPs, nanosized platinum particles are generally utilized for catalytic speeding up of reactions in industries and in widespread biomedical as well as pharmaceutical applications. Certain platinum nanoparticles have been utilized in numerous medical applications with non-metals as bimetals, alloys or nanosized core-shell clusters (Bhattacharya and Mukherjee 2008). However, reports on phytosynthesis of platinum nanoparticles are significantly scarce as compared to silver and gold nanoparticles. The synthesis of platinum nanoparticles leads to the reaction as shown in Eq. (1).



The first plant mediated nanosized platinum particle fabrication was performed via extracts of *Diopyros kaki* leaves and aqueous solution of  $\text{H}_2\text{PtCl}_6 \cdot 6\text{H}_2\text{O}$  as precursor. It is noteworthy that the 90% of platinum ions were converted into NPs at 95 °C and > 10% concentration of leaf broth (Song et al. 2010). Similar type of synthesis was performed by Dobrucka (2016) using *Fumariae herba* extract to yield hexagonal and pentagonal shape of the platinum NPs (Dobrucka 2016). Furthermore, Kumar et al. (2013) fabricated platinum NPs via plant extracts of *Terminalia chebula* and the high performance liquid chromatography (HPLC) results revealed that polyphenols are responsible for the decrement of  $\text{Pt}^{+4}$  ions into  $\text{Pt}^0$ .

The phytosynthesis of copper nanoparticles (CuNPs) was also widely reported, due to their applications in sensor, antimicrobial and catalysis field. Several plant species such as *Cappariou zeylanica* leaf broth (Saranyaadevi et al. 2014), *Ocimum sanctum* leaf extracts (Kulkarni and Kulkarni 2013; Patel et al. 2016), aqueous extracts of *Syzygium aromaticum* (cloves) (Subhankari and Nayak 2013) and the leaf extracts of *Vitis vinifera* (Angrasan and Subbaiya 2014) were used as CuNPs formation agents. Nagar and Devra (2018) developed a rapid and green convenient nanosized copper particle fabrication method using salts of cupric chloride and leaf extracts of *Azadirachta indica*. The phytosynthesized CuNPs were highly crystalline and cubical with a size of 48 nm and stable for 2 months due to elevated zeta potential (− 17.5 mV) at 4 °C. This study claimed that the metal ion decrement into metallic nanoparticles is rapid, compared to the microbial extract mediated nanoparticle fabrication.

## Metal oxide nanoparticles

Metal oxides nanoparticles are significant in biomedical fields, due to their stability as compared to their

corresponding elemental forms (Cifuentes et al. 2019). The conventional synthesis approach of metal oxide nanoparticles includes sol-gel, force hydrolysis and electrochemical techniques. However, the disadvantages associated with the chemical synthesis, such as involvement of toxic chemicals, paved the way for the eco-friendly synthesis of metal oxide nanoparticles (Nasrollahzadeh et al. 2015c, 2016).

Nanosized iron oxide ( $\text{Fe}_3\text{O}_4$ ) particles have potential applications in diagnosis and therapy of several diseases. Izadiyan et al. (2018) synthesized  $\text{Fe}_3\text{O}_4$  using the *Juglans regia* husk extracts and the results suggested that the obtained iron oxide nanoparticles are smaller in size, compared to the co-precipitation method. Furthermore, studies have shown that the biogenic nanosized iron oxides are non-

toxic towards normal cell, even at high concentration (below 1000  $\mu\text{g}/\text{mL}$ ). In addition, the phytosynthesis of  $\text{Fe}_3\text{O}_4$  was also performed using the leaf extracts of *Artemisia vulgaris* (Kouhbanani et al. 2018) and fruit extracts of *Couroupita guianensis* (Sathishkumar et al. 2018). Likewise, Prasad (2016) synthesized  $\text{Fe}_2\text{O}_3$  nanoparticles from the garlic vine leaf extracts via  $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$  as precursor. The octahedral shaped 18.22 nm sized particles were attained, and nanoparticles' stability was ascribed to the existence of biomolecules in the plant extracts as evidenced via thermogravimetric analysis (Prasad 2016). In another study, irregular shaped  $\text{Fe}_2\text{O}_3$  nanoparticles were obtained from the leaf extracts of *Ocimum sanctum* with a size of 20–47 nm. The decrement was proposed to be due to the existence of proteins and phenols in the extract (Balamurugan et al. 2014).

Zinc oxide nanoparticles has gained attention due to its wide benefits in optics, electronics, drug distribution, cancer and diabetic cell inhibition applications (Pal et al. 2015). The United States Food and Drug Administration (USDA) has enlisted zinc oxides nanoparticles as 'generally recognized as safe (GRAS)' metal oxide (Pulit-Prociak et al. 2016). Even though, nanosized ZnO is utilized for biomedical and pharmaceutical applications, the challenge of toxicity is yet to be resolved. Due to the increasing popularity of biosynthesis approaches, several studies have been performed to synthesize ZnO NPs using plant parts. The most common protocol to synthesize ZnO nanoparticles via plant extracts is the utilization of zinc nitrate or zinc sulphate as precursor and boiling the mixture at the desired temperature. Optimization is usually performed considering the concentration of plant extracts, incubation temperature, and reaction time. (Agarwal et al. 2017) Generally, plants such as *Anisochilus carnosus* (Anbuvarannan et al. 2015), *Plectranthus amboinicus* (Fu and Fu 2015) and *Vitex negundo* (Ambika and Sundrarajan 2015) belongs to family Lamiaceae have been

utilized for nanosized ZnO particle fabrication, due to presence of specific nanoparticle stabilizing phytochemicals. Recently, Chung et al. (2015) demonstrated an eco-friendly and inexpensive method for ZnO nanoparticles fabrication using hydro extracts of *Eclipta prostrata* leaves. The TEM images of the synthesized nanoparticles revealed that their optimum size is  $29 \pm 1.3$  nm with distinct morphologies (Chung et al. 2015). Hence, the design of phytosynthesized nanoparticles has specific significance in biomedical applications, especially in nanomedicine.

Titanium oxide (TiO<sub>2</sub>) nanoparticles exhibited a unique surface chemistry and have broad applications in textiles, papers, energy, and food industries, similar to other metal oxides (Abd El-Nasser et al. 2020). Mostly, TiO<sub>2</sub> nanoparticles are synthesized via chemical approaches such as micro emulsion, sol–gel methods and hydrothermal crystallization requires elevated temperatures and toxic chemicals. Hence, the formation of nanosized TiO<sub>2</sub> particles by eco-friendly approach is the need of the hour. Sundrarajan and Gowri (2011) synthesized TiO<sub>2</sub> nanoparticles with the leaf extract of *Nyctanthes arbortristis* (Night-flowering Jasmine) using titanium tetra-isopropoxide (TTIP) as precursors. The SEM micrograph revealed that the synthesized nanoparticles are uniform, spherical and crystalline in nature with 100–150 nm in size. Moreover, Santhoshkumar et al. (2014) synthesized TiO<sub>2</sub> nanoparticles using leaf extracts of *Psidium guajava*. The 32.5 nm sized particles displayed effective antibacterial activity against several bacterial species (Santhoshkumar et al. 2014). By following the similar procedure, several researchers synthesized nano TiO<sub>2</sub> powders by utilizing phytochemicals from the plants such as *Azadirachta indica* aqueous leaves extract (Sankar et al. 2015), extract of *Murraya koenigii* leaves (Suganya et al. 2013), aqueous phytochemical extracts of *Solanum trilobatum* leaves (Rajakumar et al. 2014) and *Citrus reticulata* (orange) peel extract (Rao et al. 2015).

## Nanocomposites

The increased knowledge and understanding in the synthesis of nanoparticles has enabled researchers to synthesize a newer class of hybrid nanoparticles consisting of two or three types of nanocomponents (Pal et al. 2013). They have superior qualities owing to their nanometer size and physicochemical properties, when compared to the traditional composite materials (Hatamifard et al. 2015; Pal 2019). Nanosized core–shell particles contain a nanosized material at the centre and other components surrounding central core that are made of distinct biphasic nanomaterials (Gawande et al. 2015). The nanosized particle surface can be altered with the biological moieties such as proteins, antibody, peptides and aptamers for several purposes, including sensing and targeted drug distribution. Literatures suggested that during

the synthesis of nanoparticles if the particles are not capped, the hydrophobic surface of NPs will interact with each other and form agglomerated nanoparticles (Khatami et al. 2018a). This agglomeration phenomenon could be addressed using natural protecting biomolecules. The biomolecules obtained from the plant extracts are surface immobilized over nanosized particles during their formation and results in increased stabilized nanoparticles. Prasad et al. (2017a, b) developed a low cost biogenic approach for the formation of spherical and 16–20 nm sized oxides of magnetic iron particles supported with nickel via leaf extracts of *Moringa oleifera* as stabilizing and capping material. Similarly, Venkateswarlu et al. (2015) synthesized 50 nm sized oxides of iron-silver core–shell particles with improved magnetism and excellent bacteria inhibition ability using stem extracts of *Vitis vinifera* as reducing and capping agent (Venkateswarlu et al. 2015). A similar type of Au/Ag nanocomposite from the dried tuber of *Dioscorea bulbifera* (Ghosh et al. 2015), Au–PD from the leaf extracts *Cacumen platyclade* (Zhan et al. 2011) and Fe<sub>3</sub>O<sub>4</sub>–SiO<sub>2</sub> nanoparticles from the leaf extracts of green tea (Sharma and Tapadia 2016) were synthesized and demonstrated potential application in various fields.

Several studies have shown that plant mediated synthesized nanoparticles possess various significant functional properties, similar to nanoparticles synthesized from chemicals. Huang et al. (2020) reported that nanoparticles synthesized from plant biomass have active functional groups to provide excellent optical properties such as photoluminescence. Likewise, Bhoir and Chawla (2016) showed that silver nanoparticles fabricated using mint extracts possess excellent mechanical strength, opacity and ultraviolet light transmittance property. Kombiah et al. (2016) demonstrated that zinc-iron oxide nanoparticles synthesized from *Hibiscus rosa-sinensis* plant have superior photoluminescence and magnetic properties at room temperature, compared to conventional combustion methods. Plant extract-mediated synthesis of nanoparticles are known for their biological properties such as bioavailability (Shinde et al. 2019), biocompatibility (Ovais et al. 2018) and non/less toxicity (Nasrollahzadeh et al. 2014; Vasantharaj et al. 2019). The unique properties of phytosynthesized nanoparticles depend on various factors including extraction method, solvent used for extraction, existence and quantity of phytochemicals, and biochemical interactions between phytochemicals and precursors, which eventually affects the size, shape, morphology, surface charge and functional groups present in the synthesized nanoparticles (Sajadi et al. 2016). Even though, all the aforementioned properties may be incorporated into chemically synthesized nanoparticles, the use of toxic chemicals in the synthesis process contributes to the toxicity of the nanoparticles in environmental

and biomedical applications (Jeevanandam et al. 2020a). These factors make phytosynthesis approaches more promising for biomedical applications. Table 1 presents a summary of phytosynthesized nanoparticles from several plant extracts.

## Phytosynthesized nanoparticles with cancer cell inhibition property

Recently, numerous researchers have diverted their attention on the application of nanotechnology in cancer theranostics (Shewach and Kuchta 2009). Different types of nanoparticles are being synthesized via conventional chemical

**Table 1** Phytosynthesized nanoparticle from various plant extracts

Nanoparticles	Plant	Plant parts	Size (nm)	Shape	References
Silver nanoparticles	<i>Acacia nilotica</i>	Gum	10–78	Spherical	Yeasmin et al. (2017)
	<i>Acorus calamus, Moringa oleifera, and Cucurbita maxima</i>	Petals	21–57	Spherical and rectangular	Nayak et al. (2015)
	<i>Ceropegia thwaitesii</i>	Leaves	20–100	Spherical	Muthukrishnan et al. (2017)
	<i>Panax ginseng</i>	Leaves	10–20	Spherical	Castro-Aceituno et al. (2016)
	<i>Ficus retusa</i>	Leaves	15	Spherical	Zayed et al. (2019)
	<i>Euphorbia hirta</i>	Leaves	2.9–206.3	Spherical	Selvam et al. (2019)
	<i>Gossypium hirsutum</i>	Stem	20–100	Spherical	Vanti et al. (2019)
	<i>Callistemon citrinus</i>	Aerial parts	29	Spherical	Larayetan et al. (2019)
	<i>Cressa cretica</i>	Leaves	15–22	Spherical	Balasubramanian et al. (2019)
Gold nanoparticles	<i>Dillenia indica</i>	Fruit	5–50	Spherical	Sett et al. (2016)
	<i>Peltophorum Pterocarpum</i>	Flower	5–40	Spherical	Balamurugan et al. (2016)
	<i>Ocimum tenuiflorum</i>	Flower and leaf	20	Spherical	Rao et al. (2017)
	<i>Azadirachta indica</i>				
	<i>Nepenthes khasiana</i>	Leaves	50–80	Spherical	Bhau et al. (2015)
	<i>Panax notoginseng</i>	Whole plant	100	Spherical	Wang et al. (2019)
	<i>Lonicera japonica</i>	Flower	10–40	Spherical	Patil et al. (2019)
	<i>Bursera serrata</i>	Fruit	10	Spherical, triangular and tetragonal	Bag (2019)
Zinc oxide Nanoparticles	<i>Rhizopus oryzae</i>	Protein extracts	20	Spherical	Das et al. (2012)
	<i>Cassia fistula</i>	Plant	5–15	Crystalline	Suresh et al. (2015)
	<i>Heritiera fomes</i>	Leaves	40–50	Spherical	Thatoi et al. (2016)
	<i>Sonneratia apetala</i>				
	<i>Boswellia ovalifoliolata</i>	Bark	20	Spherical	Supraja et al. (2016)
	<i>Pongamia pinnata</i>	Leaves	100	Spherical	Sundrarajan et al. (2015)
	<i>Allium sativum, Allium cepa and Petroselinum crispum</i>	Leaves	14–70	Hexagonal	Stan et al. (2015)
	<i>Passiflora caerulea</i>	Leaves	70	Spherical	Santhoshkumar et al. (2017)
	<i>Stevia rebaudiana</i>	Leaves	10–90	Rectangular	Khatami et al. (2018b)
Copper Oxide Nanoparticles	<i>Aloe vera</i>	Leaves	20	Spherical	Kumar et al. (2015)
	<i>Punica granatum</i>	Peels	40	Spherical	Ghidan et al. (2016)
	<i>Gloriosa superba L</i>	Leaves	5–10	Spherical	Naika et al. (2015)
	<i>Pterospermum acerifolium</i>	Leaves	100–250	Oval	Saif et al. (2016)
	<i>Tinospora cordifolia</i>	Leaves	6–8	Spherical	Nethravathi et al. (2015)
	<i>Moringa Oleifera</i>	Leaves	16–20	Spherical	Prasad et al. (2017a)
Ni/Fe <sub>3</sub> O <sub>4</sub>	<i>Moringa Oleifera</i>	Leaves	16–20	Spherical	Prasad et al. (2017a)
Au–Ag	<i>Antigonon leptopus</i>	Leaves	10–60	Spherical	Ganaie et al. (2016)
Au–Pd	<i>Cacumen Platycladi</i>	Leaves	7.4 ± 0.8	Spherical	Zhan et al. (2011)
Au/Ag	<i>Diopyros kaki</i>	Leaves	50–500	Spherical	Song and Kim (2008)



synthesis approaches, such as citrate reduction and polyol methods, and studied for their anticancer activity and or for therapeutic drug distribution to the cancerous cells. Nanoparticles with anticancer properties and efficacy in reaching target sites are used as a novel alternative to conventional cancer treatment modalities which are characterized with various side effects on normal healthy cells (Yesilot and Aydin 2019). Till date, several microorganisms, including bacteria, fungi and yeast, have been utilized to fabricate nanoparticles with potential anticancer ability. Moreover, nanoparticles have not only been synthesized from microbes, even seaweeds (Sanaeimehr et al. 2018), algae and dried waste grass (Khatami et al. 2018c) have also been employed. In addition, plants are explored to a large extent due to their simple, non-elaborative, cost-effective and facile approach in synthesizing nanoparticles with biocompatibility (Barabadi et al. 2017). Thus, extracts of plants have the capability of reducing metal ions, and has been extensively under evaluation since the nineteenth century. Considering all the significant aspects of green synthesis, this type of approach has been widely used for various biomedical applications. This section of the review discusses the plant mediated synthesis of nanoparticles and their significance in cancer therapeutics and strategies adopted for inhibition of the growth of cancer cells.

### Metallic nanoparticles with anticancer property

Nanosized metallic nanoparticles, such as nano silver and gold particles, gained substantial attention in recent times for cancer theranostics, due to their striking characteristics at nano-regime, that has been ascribed to its enhanced aspect ratio. Plant mediated approaches for nanoparticles are increasingly popular due to ease in scaling up and downstream process for commercial applications (Ovais et al. 2017). In addition, plants with medicinal properties are the significant source of bioactive chemical entities with anticancer ability and offer exhilarating cancer treatment tactics via ecofriendly fabrication of nanosized metallic particles. Numerous scientists have described the utilization of biological extracts for nanoparticle fabrication by anticipating nanosized particles' safety, which has led to the emergence of green nanotechnology.

Silver has been traditionally used in several medicinal drugs due to its excellent antimicrobial (Ali et al. 2020) and anticancer activities (Gomathi et al. 2020). Since bulk silver exhibits potential antimicrobial property, their nanosized counterparts have been extensively studied to demonstrate excellent inhibition property against pathogenic microbes (Boateng and Catanzano 2020). Thus, various nano forms of metals, particularly silver and magnesium, are employed to contribute additional benefits to drug formulations for disease treatment (Chandran et al. 2019; Jeevanandam et al.

2015, 2019b). Several cancer-related studies have been performed using AgNPs synthesized from plants as compared to other metallic nanoparticles. AgNPs acts on cancer-affected cells via caspase and mitochondrial pathway-mediated apoptosis. Moreover, these nanoparticles are also highly biocompatible and show higher efficiency in cytotoxic activity against cancer cells (Ovais et al. 2016). Furthermore, AgNPs were produced via hydro extract of *Salacia Chinensis* bark and evaluated against different cancer cells such as liver (Hep G2), lungs (L-132), pancreas (MIA-Pa-Ca-2), breast (MDA-MB-231), oral (KB cells), prostate (PC-3), and HeLa cancer cell lines ( $IC_{50} = 5-15 \mu\text{g/mL}$ ). These phyto-synthesized nanoparticles (40–80 nm) from the reduction of silver nitrate were characterized and reported to be stable. Cytotoxicity of these AgNPs was investigated towards normal fibroblasts ( $\geq 95\%$  of cell viability) and blood erythrocytes ( $< 3\%$  of hemolysis), wherein the results demonstrated negligible toxicity to the cells. Moreover, the study served as a potential proof that the phytosynthesized AgNPs can be efficiently applied for cancer treatment as compared to the traditional therapies (Jadhav et al. 2018). Selvan et al. (2018) also attempted to synthesize AgNPs via aqueous extracts of garlic, turmeric and green tea. Phytochemical analysis showed the existence of various biochemicals in the extracts, which served as capping and reducing mediators for obtaining nanosized silver particles. The antioxidant effectiveness of NPs was studied through various scavenging assays such as 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) cation, 2,2'-diphenyl-1-picrylhydrazyl (DPPH), p-nitrosodimethylaniline (p-NDA), hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) and dimethyl sulfoxide (DMSO). The synthesized AgNPs displayed excellent concentration-dependent (2, 5, 10, 25, 50 and 100  $\mu\text{g/mL}$ ) cancer cell inhibition ability after 48 h, compared to the standards such as rutin and ascorbic acid. The anticancer activity of NPs was also studied in vitro using different cancer cells, such as MCF-7, HeLa, Hep-2, A549 cells and normal human dermal fibroblasts (NHDF) cell line. The cytotoxic assay result of AgNPs synthesized using turmeric extract demonstrated remarkable results for antioxidant and anticancer assays as compared to the other plant extracts (Selvan et al. 2018). Likewise, Mousavi et al. (2018) assessed nanosized silver particles synthesized using extracts of *Artemisia turcomanica* leaves. In this study, they investigated the apoptosis induction in cancerous gastric cells (AGS) and also compared the cancer cell inhibition potential with commercially available nano silvers. Improved programmed cell death was detected, while treating cells with the phytosynthesized AgNPs compared to those not treated with NPs ( $p < 0.001$ ). The study revealed that the phytosynthesized AgNPs induced significant apoptosis (95%) and showed a time- and dose-mediated cytotoxic and anticancer effect against AGS cells compared to the commercial chemically synthesized AgNPs (84%). A

similar biogenic AgNPs (0.04 and 0.08 mg/mL) was synthesized using *Saccharina japonica* extract, and their cytotoxicity effect was examined in HeLa cells, revealing their excellent anticancer efficiency via sulforhodamine B (SRB) assay (~20–40% cytotoxicity towards cancer cells) (Sreerkanth et al. 2016). Sarkar and Kotteeswaran (2018) phyto-synthesized AgNPs using hydro extracts of *Punica granatum* (pomegranate) leaves, and the cancer inhibition ability was investigated using HeLa cell lines. The proliferation reduction potential of the nanosized particles was evaluated via MTT assay, and the  $IC_{50}$  was reported to be 100  $\mu\text{g}/\text{mL}$ . Lactate dehydrogenase (LDH) assay also showed that a 100  $\mu\text{g}/\text{mL}$  dosage of the nanoparticles exhibited 50% cytotoxicity, and the cancer cell inhibition efficiency of the phytosynthesized nanosized particles was demonstrated via DNA fragmentation assay.

AgNPs have not only been synthesized from whole plant extracts, but also from tissue cultured explants. This approach for the synthesis of NPs has received a positive response, due to their eco-friendly approach. Recently, callus extracts of particular plants have been employed as it requires a shorter period to grow, when compared to the plants and also can secrete secondary biochemical metabolites that are necessary for the nanoparticle formation. The first report of using callus for nanosized silver particle fabrication was by Mude et al. (2009), where they synthesized 60–80 nm sized spherical AgNPs from callus extracts of papaya (*Carica papaya*) (Mude et al. 2009). Later, Satyavani et al. (2011) utilized callus of *Citrullus colocynthis* extracts for AgNP fabrication. Herein, the anticancer activity was evaluated against human HEP-2 carcinoma cells of epidermoid larynx using different assays. The synthesized spherical shaped AgNPs (31 nm) were found to exhibit a dose-mediated (500 nM) side-effects in the cell line (50%). Additionally, LDH assay showed that an increased level of LDH was significantly observed than the control. In yet another assay, AgNPs treated cells showed double-strand breaks exhibiting apoptosis and cellular DNA fragmentation (Satyavani et al. 2011). Interestingly, Huang et al. (2019) synthesized AgNPs using reducing agents obtained from callus extracts of *Chlorophytum borivilianum* L. (Safed Musli) plants. The NPs were fabricated by exposing nitrates of silver to the methanolic extracts of callus, wherein the change in yellow color to brown showed the bio-reduction and development of nanosized particles. The well-characterized AgNPs were studied for their cytotoxic property against the cancerous human HT-29 colon cells via MTT assay ( $IC_{50}$  at AgNPs concentration of 500  $\mu\text{g}/\text{mL}$  after 24 h is 254  $\mu\text{g}/\text{mL}$ ) and validated their potential application for cancer treatment in the future (Huang et al. 2019).

Apart from AgNPs, AuNPs have found their utility in several biomedical applications. They have been utilized extensively in industries and in biological fields for

detection and therapy purposes. Although AuNPs can be efficiently synthesized using chemical approaches, other methods such as biological preparations have their own unique advantages. Physico-chemical approaches are push and involve elevated energy inputs, and thus scientists have diverted their focus towards biological methods which are eco-friendly, cost-effective and biocompatible (Ovais et al. 2017). Recently, gold NPs are fabricated by utilizing various natural sources, such as microbes and plants, of which plant extracted AuNPs have found their place in several anticancer studies and have gained wide attention in cancer treatment. Wu et al. (2019) stated nanosized gold particle formation via plant extracts of *Abies spectabilis*. The well-characterized nanoparticles were studied for anticancer, cell migration and apoptosis activities in bladder cancer (T24) cells. The synthesized AuNPs displayed dose-dependent cytotoxicity (1 to 25  $\mu\text{g}/\text{mL}$  for 24 h), while the other assays showed up regulation of Beclin-1, Bax and caspase 3, and down-regulation of Bid and Bcl-2 genes (Wu et al. 2019). In another study, biogenic AuNPs were synthesized by incubating salts with the phytochemicals to obtain curcumin-based, AuNPs coated with curcumin, turmeric, quercetin and Paclitaxel. The obtained NPs were assessed for anticancer activity in various cancerous breast cells and the cytotoxicity studies exposed that the combination of these synthesized NPs (5  $\mu\text{M}$  concentration) shows significant toxicity in cancerous cells of MCF-7 and MDA-MB-231. Moreover, when the nanoparticles were tested in normal human embryonic kidney (HEK) 293 cells, they did not show any signs of toxicity either alone or in combination (Vemuri et al. 2019). In another study, flowers of *Lonicera japonica* were used for the synthesis of AuNPs and evaluated for cancer cell inhibition ability (95%) in cancerous cervical cells. The presence of several biochemical metabolites such as alkaloids and phenolic compounds is proposed to be a contributing factor for the formation and anticancer activity of nanoparticles (Patil et al. 2019). Other nanosized metallic particles, such as zinc and copper have also been synthesized using plant sources. Recently, it was established that nanosized zinc sulphide particles can be synthesized using *Stevia rebaudiana* plant extract. Biochemical metabolite glycoside was used as the bioreducing agent in nanoparticle formation and exhibited excellent cytotoxicity ( $IC_{50} = 400 \text{ mg}/\text{mL}$  for 24 h) against cancerous MCF-7 cells (Alijani et al. 2019). Similarly, floral extracts of *Quisqualis indica* were used to fabricate CuNPs by Mukhopadhyay et al. (2018) via copper acetate as a precursor. The cytotoxicity potentials of the CuNPs were investigated by MTT and LDH assay on B16F10 melanoma cells ( $IC_{50} = 102 \text{ }\mu\text{g}/\text{mL}$  after 24 h), revealing that the phytosynthesized CuNPs demonstrated a significant decrease in tumor growth in mice bearing B16F10 melanoma tumor.

## Anticancer nanosized oxides of metal particles

Metal oxides are extremely utilized in biomedical applications, especially in cancer therapeutics. Sisubalan et al. (2018) synthesized nanosized oxides of cerium ( $\text{CeO}_2$ ) and Zn particles using *Rubia cordifolia L* leaf extracts. These nanoparticles were studied for their biomedical activity towards MG-63 cells of osteosarcoma by MTT assay. Overall, this study revealed the anti-proliferative activity (~70–80%) of nanosized ZnO and  $\text{CeO}_2$  particles (50  $\mu\text{g}/\text{mL}$ ) towards osteosarcoma cells by producing exceptional levels of ROS, thus underlining the role of green synthesis. Likewise, Prashanth et al. (2018) fabricated nano ZnO powders via solution combustion approach. In this study, the group synthesized nano ZnO particles using lactose and phytochemicals extracted from *Melia azedarach*, *Indigofera tinctoria* and *Abutilon indicum*. Anticancer activity was evaluated in cancerous Calu-6 (58–112  $\mu\text{g}/\text{mL}$ ) and DU-145 (34–103  $\mu\text{g}/\text{mL}$ ) cells, wherein the bio-synthesized nanosized oxides of zinc particles showed significant activity with enhanced biocompatibility (Prashanth et al. 2018). Besides, ZnO nanoparticles were fabricated via leaf extracts of *Tecoma castanifolia* plant to identify their ability to inhibit bacteria and cancerous cells. The  $\text{IC}_{50}$  value of the nanoparticles in cancerous A549 cells was found to be 65  $\mu\text{g}/\text{mL}$ , which indicated their enhanced anticancer ability (Sharmila et al. 2019). Furthermore, Sanaeimehr et al. (2018) synthesized ZnO nanoparticles from phytochemical extracts of the algae *Sargassum muticum* to assess its cell inhibition properties towards cancerous HepG2 cells of human liver. The findings from the assay using trypan blue dye confirmed that the ZnO NPs (175  $\mu\text{g}/\text{mL}$ ) possessed a concentration-dependent cytotoxicity in liver cancer cells (55.5%) and the MTT assay showed a time- and dose-dependent cancer cell inhibition ability. Also, ZnO nanoparticles synthesized from aqueous extracts of *Sargassum muticum* have been treated on murine cancer cell lines (Namvar et al. 2015). The nanoparticles demonstrated various levels of cytotoxicity in various cancerous murine cell lines such as 4T1 ( $\text{IC}_{50} = 21.7 \pm 1.3 \mu\text{g}/\text{mL}$ ), CRL-1451 ( $\text{IC}_{50} = 17.45 \pm 1.1 \mu\text{g}/\text{mL}$ ), CT-26 ( $\text{IC}_{50} = 11.75 \pm 0.8 \mu\text{g}/\text{mL}$ ) and WEHI-3B ( $\text{IC}_{50} = 5.6 \pm 0.55 \mu\text{g}/\text{mL}$ ). They did not show cytotoxicity against healthy 3T3 mouse fibroblasts. The nanosized ZnO particles also mediated diverse morphological alternations, apoptotic cell cycle population block, and apoptotic protein stimulation towards cancer cells. Additionally, Namvar et al. (2014) demonstrated the fabrication of biogenic magnetic nanosized iron oxide particles ( $\text{Fe}_3\text{O}_4$  MNP) using the aqueous extracts of brown *Sargassum muticum* seaweed containing

functional active groups for effective nanoparticle formation. The in vitro cancer cell inhibition ability of these nanoparticles was confirmed using human Jurkat leukaemia cells ( $\text{IC}_{50} = 6.4 \pm 2.3 \mu\text{g}/\text{mL}$ ), cancerous HeLa ( $\text{IC}_{50} = 12.5 \pm 1.7 \mu\text{g}/\text{mL}$ ), MCF-7 ( $\text{IC}_{50} = 18.75 \pm 2.1 \mu\text{g}/\text{mL}$ ) and HepG2 ( $\text{IC}_{50} = 23.83 \pm 1.1 \mu\text{g}/\text{mL}$ ) liver cells. An exceptional minimum inhibitory concentration ( $\text{IC}_{50}$ ) value was observed at 72 h after  $\text{Fe}_3\text{O}_4$  MNPs treatment. Cell cycle evaluation also suggested a substantial increment in  $\text{Fe}_3\text{O}_4$  MNPs accumulation in cells at sub-G1 phase, which confirmed apoptosis induction by the magnetic nanoparticles.

Apart from ZnO and  $\text{CeO}_2$ , nanosized oxides of copper particles (CuO nanoparticles) have also been synthesized by utilizing phytochemical extracts. In a particular study, phytochemicals of *Azadirachta indica* was utilized for the nanosized CuO particle fabrication and their anticancer ability was evaluated through in vitro molecular methods. The uptake of copper ions inside the cancer cells led to ROS and eventually results in apoptosis and DNA fragmentation. Interestingly, in vivo evaluation was also carried out in a Balb/C breast tumor mice model and observed that the biogenic CuO NPs caused reduction of the cancer cells and increased mean survival time of mice. It was also observed that CuO NPs altered the pro-inflammatory cytokine level and pro-apoptotic protein expressions (~68% increased expression of P38, caspase 3 and caspase 8) to be beneficial as a better anticancer agent (Dey et al. 2019). Furthermore, CuO NPs have been proposed for its widespread use in emerging anticancer applications. Gopinath et al. (2016) synthesized CuO NPs by extracting phytochemicals from the dried fruits of *Tribulus terrestris* and studied their anticancer potential. MTT assay was performed using normal human mesenchymal stem and adenocarcinoma AGS cell lines to study anticancer activity, wherein the NPs were found to be safe for stem cells (100  $\mu\text{g}/\text{mL}$  nanoparticle concentration = ~80% cell viability) while showing significant toxicity towards cancer cells (100  $\mu\text{g}/\text{mL}$  nanoparticle concentration = 17.1% cell viability) (Gopinath et al. 2016). In another study, nanosized CuO particles were fabricated via phytochemicals extracted from black bean and studied their ability to disrupt the mitochondrial structure in cancer cells along with inhibiting their proliferation (0.5 and 1 mg/mL of CuO NPs inhibits ~70% of Hela cell after 24 h) (Nagajyothi et al. 2017). In addition, Ezhilarasi et al. (2016) used *Moringa oleifera* plant extract to study their antibacterial and anticancer activities and the MTT assay results in HT-29 cells provided ample evidence about the anticancer ability of nickel oxide (NiO) nanoparticles (1000 g/mL nanoparticle concentration leads to 7.6% cell viability) (Ezhilarasi et al. 2016). In an interesting study, un-doped tin

oxide and cobalt-doped tin oxide were synthesized from the aqueous *Clerodendrum inerme* extract using solution combustion synthesis method. The synthesized 30 and 40 nm cobalt-doped tin oxide nanoparticles were proved to possess effective anticancer activity against MCF-7 ( $IC_{50} = 18.15 \pm 1.0 \mu\text{g/mL}$ ) and Ehrlich ascites tumor cells (Tumor volume =  $1.2 \pm 0.65 \text{ mL}$ ) (Khan et al. 2018).

### Anticancer nanocomposites

In recent times, nanocomposites have been synthesized via phytochemicals extracted from plants to act as better anticancer agents without side-effects on noncancerous cells. In an interesting study, graphene-based nanocomposites were prepared and used to demonstrate its ability in treating cancer. Graphene and graphene-based nanocomposites are usually utilized in several industrial-based applications such as the development of sensors, energy storages and catalysts. The group synthesized eco-friendly and simple, nanosized silver-graphene oxide composites utilizing plant extracts of *Tilia amurensis* (5–25  $\mu\text{g/mL}$  nanocomposite dose), evaluated their anticancer efficacy against cancerous ovarian A2780 cells and the results demonstrated reduced cell viability ( $IC_{50} = \sim 12.5 \mu\text{g/mL}$ ) (Gurunathan et al. 2015). Similarly, rGO–Ag (reduced graphene oxide–silver) nanocomposites were prepared using *C-phycocyanin* and evaluated for their anticancer ability by adding cisplatin (Cis). The anticancer efficacy in HeLa cells was studied by different assays and stress markers by treating the cells in combination with Cis and rGO–AgNPs. Cytotoxicity assays demonstrated a dose-dependent decrement in the viability of cells, when incubated with Cis, GO, rGO, AgNPs, and rGO–AgNPs (Dose = 0.1–6  $\mu\text{g/mL}$  and  $IC_{50} = \sim 1.5 \mu\text{g/mL}$ ), and the inhibition of cells were more significant when used in combination. Moreover, the study also demonstrates the expression of genes related to apoptosis such as pro-apoptotic, anti-apoptotic, and autophagy with a polymerase chain reaction in real-time. The findings revealed pronounced effects on the expression of apoptotic and autophagy genes when treated in combination. Thus, it emphasized the potential of rGO–AgNPs nanocomposites in promoting cytotoxicity, apoptosis, and autophagy in cervical cancer cells and are proposed as a strong agent in cancer treatment (Yuan and Gurunathan 2017). Biogenic approach for the fabrication of nanosized gold–silver–indium–reduced graphene oxide composite was demonstrated using *Piper pedicellatum* leaf extracts. The inhibitory assay using  $\alpha$ -glucosidase showed that the nanosized composites had exceptional potential to inhibit PC3 cells ( $IC_{50} = 0.178 \pm 0.01 \mu\text{g/mL}$ ) than nanosized graphene oxide particles and are non-toxic towards healthy epithelial RWPE-1 and prostate cells (Saikia et al. 2018).

### Other novel nanoparticles

In a recent study, core–shell  $\text{Fe}_3\text{O}_4/\text{Au}$  nanoparticles were synthesized by a green route using husk extracts of *Juglans regia* (walnut) in two-step co-precipitation method. These NPs of size  $6.08 \pm 1.06 \text{ nm}$  was tested for their anticancer activity using colorectal HT-29 cancer cell line and the results demonstrated a significant toxic effect in cancer cells ( $IC_{50} = 235 \mu\text{g/mL}$ ), compared to non-cancer cell line (Izadiyan et al. 2019). Another study highlighted the efficacy of  $\text{Fe}_3\text{O}_4\text{-}\gamma\text{-Fe}_2\text{O}_3$  structured core–shell magnetic nanoparticles that are synthesized via phenolic phytochemical extracts of *Vanilla planifolia* and *Cinnamomum verum* as capping and reducing agents. The 10–14 nm sized core–shell magnetic nanocomposites were studied for their efficacy in hyperthermia mediated inhibition of BV2 microglial cells. The particles were used as heating element in the hyperthermia experiment and were proven to be valuable in persuading cell death after 30 min at a temperature of  $46^\circ\text{C}$ . Hence, these types of novel magnetic nanocomposites are proven to be an active hyperthermia material with potential cancer treatment ability in the future (Ramirez-Nuñez et al. 2018). Table 2 lists a summary of phytosynthesized metallic nanoparticles towards cancer cells.

### In vitro and In vivo studies

Several therapeutic strategies have been established and used for the treatment and complete eradication of cancer from the patient's body. However, the success rate of each strategy is less and may lead to toxicity in patients, which is a critical limitation. Apart from existing conventional treatments, novel strategies such as RNAi nanotechnology have emerged, which show a ray of hope to tackle cancer more effectively than conventional methods. Nanoparticles namely metals (titanium, iron, gold, copper and silver), metal oxides (ZnO, CuO, Iron oxides), polymers and other hybrid nanoparticles synthesized from biological sources, especially plant extracts, have potential in tackling cancer as described in the previous sections. Phytosynthesized nanoparticles have been evaluated using MCF-7 cells (Şahin et al. 2018), HT-29 cells (Ezhilarasi et al. 2016), B16F10, MCF-7, HNGC2, A549 (Patra et al. 2015) and H1299 cells (He et al. 2016b) to reveal and compare in vitro anticancer activity. In vitro studies using these cell lines serve as an initial screening option to eliminate nanoparticles that are toxic towards normal and healthy cells (Dhamecha et al. 2015).

Apart from in vitro studies, in vivo animal models have been developed and studied for anticancer activity as well, although the review of literature for in vivo studies are limited. CuO NPs fabricated via *Azadirachta indica* plant leaf extracts were studied for their in vitro as well as in vivo anticancer efficiency via breast cancer Balb/C



**Table 2** Cancer cell inhibition ability of phytosynthesized metallic nanoparticles

Nanoparticles	Plant	Plant synthesis source	Anticancer activity	Cytotoxicity (IC <sub>50</sub> )	Anticancer mechanism	References
Silver nanoparticles	<i>Artemisia tournefortiana</i>	Aerial parts	HT29 cell line	40.71 µg/mL	ROS mediated programmed cell death	Baghbani-Arani et al. (2017)
	<i>Nigella arevensis</i>	Leaf extract	Non-small cell lung (H1229), MCF-7 cells	10 µg/mL	Cancer cell specific intracellular proliferation inhibition mechanism	Chahardoli et al. (2017)
	<i>Matricaria chamomilla</i>	Leaf extract	A549 cells	42.44 µg/mL	Apoptosis via DNA damage	Dadashpour et al. (2018)
	<i>Ligustrum ovalifolium</i>	Fruit extracts	Ovarian cancer (A2780 and A2780-Cis cells)	7 and 14.04 µg/mL, respectively	Functional group mediated inhibition of cancer cell growth	Moldovan et al. (2018)
	<i>Indoneesiella echioides</i>	Leaf extracts	Lung cancer (A549)	30 µg/mL	Nanoparticle-mediated cell shrinkage, cell growth retardation, cytoplasmic condensation and membrane blebbing	Kuppurangan et al. (2016)
Gold nanoparticles	<i>Gossypium hirsutum</i>	Leaf extracts	Lung cancer (A549)	40 µg/mL	Nanoparticle-mediated loss of membrane integrity, cytoplasmic condensation and cell clumping	Kanipandian and Thirumuran (2014)
	<i>Nigella sativa</i>	Oil from seed	Lung cancer (A549)	28.37 µg/mL	Nanoparticle-mediated nuclear morphology changes	Manju et al. (2016)
	<i>Genipa americana</i>	Fruit extract	A549 and HeLa cells	NA	Surface modified nanoparticles with extract with antioxidant property inhibits cancer cell growth	Kumar et al. (2016a)
	<i>Cassia roxburghii</i>	Leaf extracts	HepG2, HeLa and MCF-7 cells	30 µg/mL (HepG2), 50 µg/mL (MCF-7 and HeLa), respectively	Interact with phosphorus moieties of DNA and inhibit enzyme function	Balashammugam et al. (2016)
	<i>Abies spectabilis</i>	Aerial parts	Bladder cancer (T24 cells)	20 µg/mL	Lipid peroxidation, DNA damage and cell migration inhibition	Wu et al. (2019)
<i>Dunaliella salina</i>	Whole biomass	MCF-7 cells	NA	Late and early apoptosis phase at 24 h and 48 h of nanoparticle exposure	Singh et al. (2019)	

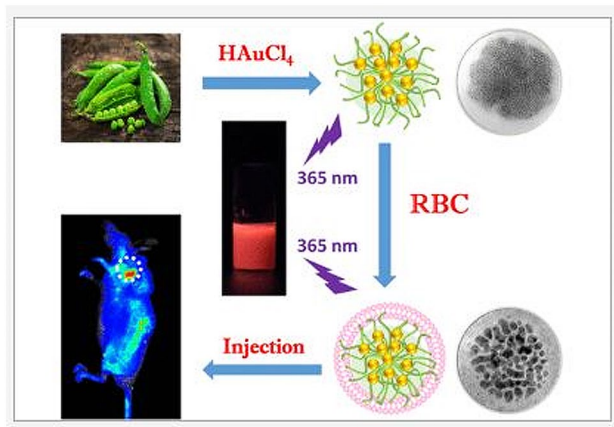
Table 2 (continued)

Nanoparticles	Plant	Plant synthesis source	Anticancer activity	Cytotoxicity (IC <sub>50</sub> )	Anticancer mechanism	References
	<i>Albizia amara</i>	Leaf Extracts	African green monkey kidney (Vero)	72.28 µg/mL	Free radical scavenging property inhibit membrane bound proteins and enzymes	Balsubramani et al. (2017)
	<i>Hibiscus sabdariffa</i>	Leaf and stem	Embryonic human kidney (293)	NA (LD <sub>20</sub> = 2 ng/mL)	Interacts with DNA and damages nuclear periphery	Mishra et al. (2016)
	<i>Rhus chinensis</i>	Plant gull	Hep3B	150 µg/mL	DNA damage and caspase-dependendt apoptosis	Patil et al. (2017)
	<i>Cassia auriculata</i>	Leaf	Prostate (LNCap- FGC)	10 µg/mL	ROS mediated DNA damage	Parveen and Rao (2015)
Zinc oxide Nanoparticles	<i>Tecoma castanifolia</i>	Leaf extract	A549 cells	65 µg/mL	Free radical scavenging property mediated cell damage	Sharmila et al. (2019)
	<i>Costus pictus D. Don</i>	Leaf extract	Daltons lymphoma ascites (DLA) cells	50 µg/mL	Functional group mediated cancer cell inhibition	Suresh et al. (2018b)
Copper Oxide Nanoparticles	<i>Tribulus terrestris</i>	Fruit extracts	Human adenocarcinoma AGS cell lines	-	Apoptosis and necrosis due to metabolism disruption	Gopinath et al. (2016)
	<i>Phaseolus vulgaris</i>	Bean extract	HeLa cells	0.5 and 1 mg/mL	Apoptotic cascade mechanism causing mitochondria and nucleus damage	Nagajyothi et al. (2017)
	<i>Azadirachta indica</i>	Leaf extract	MCF-7 and HeLa cells	21.56 and 24.74 µg/mL	Induce apoptosis via caspase and TNF-α signaling pathway activation	Dey et al. (2019)
Nanocomposites (Hydronan/zinc oxide)	<i>Sargassum muticum</i>	Aqueous extract	PANC-1, CaOV-3, COLO-205, and HL-60 cells	10.8 ± 0.3, 15.4 ± 1.2, 12.1 ± 0.9, and 6.25 ± 0.5 µg/mL	Activation of caspase, reduction of DNA content and chromatin condensation	Namvar et al. (2016)

mice model. The in vitro cytotoxicity analysis via MTT assay showed that the  $IC_{50}$  value of the resultant CuO NPs against MCF-7 (breast) and Hela (cervical) cancer cell lines were 21.56 and 24.74  $\mu\text{g/mL}$ , respectively. The synthesized CuO NPs showed 73.55% reduction in the tumor volume and improved the mice persistence time by altering pro-inflammatory cytokine levels up to 70.47% after treating the mice with 1000  $\mu\text{g/kg}$  of mice's body weight. Thus, in vivo model can be beneficial for studying the application of phytosynthesized NPs in cancer therapeutics and in preclinical toxicity analysis of these NPs towards normal cells (Dey et al. 2019). Similarly, Dhamecha et al. (2016a, b, c) synthesized doxorubicin (Dox) loaded nano-gold particles and evaluated their anticancer activity for the treatment of chemically induced fibrosarcoma in a mice model. The study showed 81% of tumor suppression by the gold nanoparticles (2.5 mg/kg), when compared to free Dox (48% of tumor suppression), and were reported to be highly safe for use with less toxicity and high biocompatibility (Dhamecha et al. 2016b). In another study, an in vivo model was developed using cells with Ehrlich ascites carcinoma (ESC) and treated with phytosynthesized un-doped tin oxide and tin oxide doped with cobalt nanoparticles. The NPs demonstrated better in vivo activity of inhibiting MCF-7 ( $IC_{50}$  value =  $18.15 \pm 1 \mu\text{g/mL}$ ) and ESC cell growth ( $48.99 \pm 0.65 10^6/\text{mL}$  of tumor cell count), respectively, compared to standard cancer drugs (Khan et al. 2018). Moreover, He et al. (2016a, b) developed an in vivo tumor xenograft model using H1299 cells in severe combined immunodeficient (SCID) mice. The phytosynthesized AgNPs of concentrations between 5–8  $\mu\text{g/mL}$  showed anticancer activity against lung cancer and effectively suppressed the tumor ( $IC_{50} = 5.33 \pm 0.37 \mu\text{g/mL}$ ). The findings demonstrated the cancer inhibition ability of nanosized silver particles with enhanced potential in chemoprevention and chemotherapy of cancerous lung cells, specifically for intervention in the early stage (He et al. 2016b). However, there is no proper regulatory firm, standard repositories or protocols to study the anticancer activity via standard methods and deposit those data for future research, which is a major limitation in commercializing these anticancer nanoparticles. Besides, unstable nanoparticles with no control of particle size distribution and shape/morphological uniformity are some additional limitations of phytosynthesized nanoparticles. Some of these limitations can be addressed using biopolymeric formulation or capping agents. Phytosynthesized nanoparticles are mostly less toxic and highly biocompatible compared to chemically synthesized nanoparticles and are useful for biomedical applications. This enables the functional bioactive molecules encapsulated within the nanoparticles to exhibit anticancer ability at the highest level (Jeevanandam et al. 2020a).

## Phytosynthesized nanoparticles for cancer diagnosis

Phytosynthesized nanoparticles are extensively used to diagnose prostate, gastrointestinal and hepatic cancers. These biogenic nanoparticles can act as bioimaging or biosensor agent to effectively diagnose cancer without any side-effects to patients due to their enhanced biocompatibility. Furthermore, phytosynthesized nanoparticles are used to detect biomarkers of cancer existing as a naturally occurring gene, molecule or a characteristic representing cancer complication (Chinen et al. 2015). There are few literatures available to prove the biosensor application of phytosynthesized nanoparticles for the detection of cancer cells. This can be attributed to the inefficiency of these nanoparticles to be incorporated in biochips, which upon continuous detection of cancer cells may lead to heat generation and disintegration of functional phytochemicals in its surface (Ohnishi et al. 2013). Thus, phytosynthesized nanoparticles are predominantly under extensive research in bioimaging applications, especially as a contrast agent, to locate the cancer cells in patients. Chanda et al. (2011) fabricated gold nanoparticles using phytochemicals of cinnamon such as starch, linalool, catechin, trans-cinnamaldehyde and epicatechin. The resultant nanoparticles are ~ 13 nm in diameter, homogeneously spherical shaped with narrow size distribution and long-term stability. Furthermore, these nanoparticles possess ability to internalize into human prostate cancer PC-3 and breast cancer MCF-7 cells and released detectable photoacoustic signals, which is beneficial as photoacoustic contrast enhancement agent to locate cancer cells via computational tomography images (CT) (Chanda et al. 2011). Likewise, Mukherjee et al. (2013) demonstrated the synthesis of gold nanoparticles using the phytochemicals extracted from the leaves of *Oxalis scandens*. The synthesis approach resulted in 5–15 nm sized spherical particles, 18–55 nm sized rod-shaped particles, 30–55 nm sized dumbbell shaped particles, 30–100 nm sized triangular and 15–35 nm sized hexagonal nanoparticles. Furthermore, these nanoparticles possess ability to internalize into A549 lung cancer, COLO205 colon cancer and MCF-7 breast cancer cell lines to exhibit bright red fluorescence along with anticancer ability, which is beneficial to evaluate the location of cancer cells for effective diagnosis (Mukherjee et al. 2013). Similarly, cocoa extract powder was used to fabricate spherical, anisotropic, 150–200 nm sized gold nanoparticles. These nanoparticles possess excellent internalization ability in epidermoid A431 carcinoma, triple negative MDA-MB-231 breast cancer, murine L929 and mouse NIH 3T3 fibroblast cells. Furthermore, the nanoparticle exhibited anticancer ability against cancer cells



**Fig. 2** Gold nanocluster hybrid synthesized using pea protein lysate, Reproduced with permission from ©American Chemical Society (Li et al. 2018)

via photoablation method and are less toxic to fibroblasts. In addition, these nanoparticles showed high contrast efficiency to be a contrast agent, when exposed to X-ray, which will be useful to locate the cancer cells via CT images (Fazal et al. 2014).

Recently, Li et al. (2018) utilized pea protein lysate for the fabrication of luminescent gold nanocluster hybrid, coated with red blood cell membrane to improve their blood compatibility, as shown in Fig. 2. The gold nanocluster was around ~10 nm size, spherical shaped with uniformity, whereas the gold nanocluster-protein hybrid is below 100 nm in size. This complex nanoclusters exhibited excellent internalization in the *in vivo* mouse model and showed superior fluorescence property to classify tumor and normal cells via real time near-infrared fluorescence images. Other than gold, carbon dots were also recently gaining interests among researchers to be synthesized using phytochemicals, as they exhibit excellent fluorescence property. Vandarkuzhali et al. (2017) recently fabricated carbon dots with a quantum yield of 48% using phytochemical extracts obtained from pseudo-stem of banana. The result carbon dots were 2–3 nm in size with a narrow distributed hydrodynamic diameter of 2.5 nm. These nanosized dots exhibited fluorescence property based on their binding nature with iron and thiosulfate ions. Furthermore, these carbon dots easily internalize into breast cancer MCF-7 and cervical cancer HeLa cells with ability to act as fluorescent probe for classifying cancer and normal cells via multi-colors such as green, blue and red. In addition, these nanodots possess high photostability, water solubility, less toxicity, cell membrane permeability and good compatibility to be useful as a potential bioimaging agent (Vandarkuzhali et al. 2017). Moreover, Song et al. (2016) fabricated hollow cobalt–platinum alloy nanoparticles using plant polyphenols such as

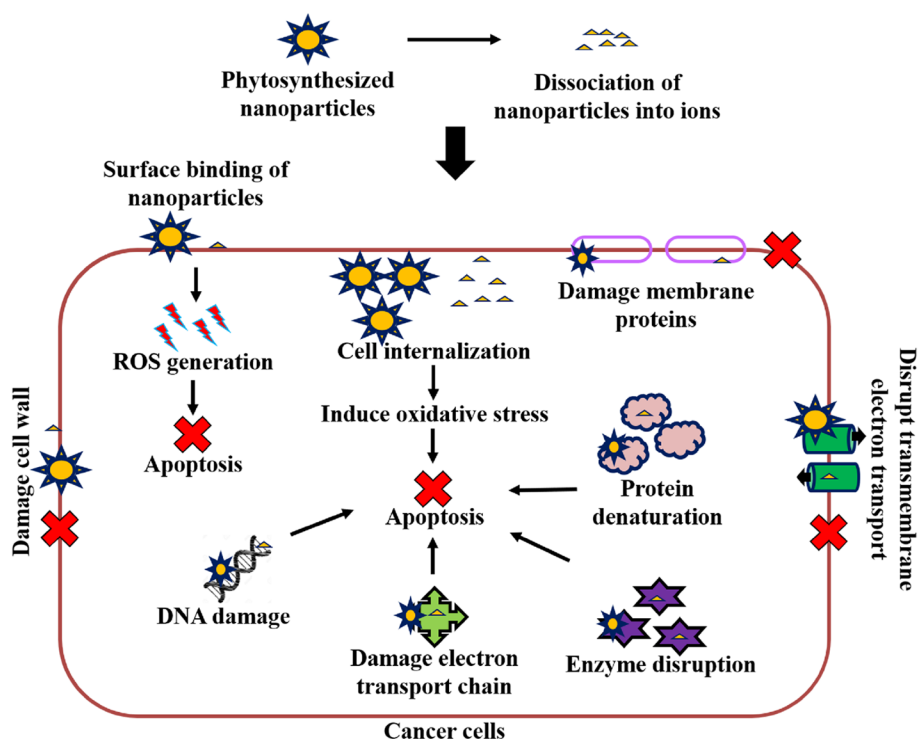
tannic acid and epigallocatechin gallate as a supporting agent. The alloys fabricated using tannic acid were 20 nm in size with 3 nm of thickness, whereas epigallocatechin gallate-mediated synthesis yielded ~9.6 nm sized particles, which further reduced to 6.6 nm after the addition of ellagic acid. These nano-alloys were injected in mice models and are demonstrated to possess ability for effectively internalization into cancer cells with high  $T_2$  relaxation property, which is beneficial to classify cancer location via magnetic resonance imaging (MRI) scans. In addition, they also possess excellent fluorescence property to classify cancer and normal cells via photoacoustic images (Song et al. 2016). However, there exist certain glitches such as long-term stability of phytosynthesized nanoparticles in cancer environment and its long circulation time, hinders their efficiency to compete with chemical synthesized nanoparticle, which must be addressed in the future studies.

### Mechanism of anticancer activity and cancer detection by phytosynthesized nanoparticles

There are numerous studies that focused on evaluating the anticancer ability of phytosynthesized nanoparticles. However, the exact mechanism is yet to be identified as different nanoparticles exhibited distinct mechanisms, based on the phytochemical content and their interaction of cancer cells. Figure 3 shows a schematic representation of various mechanisms exhibited by phytosynthesized nanoparticles against cancer cells to inhibit their growth. It is noteworthy that the phytosynthesized nanoparticles show enhanced anticancer ability, compared to chemical synthesized counterparts, as the phytochemicals are coated or bind as functional groups in the nanoparticles. Such phytochemicals will act as anticancer agents along with nanoparticles, which increases the intensity of apoptosis (programmed cell death) in cancer cells (Husen 2019). The phytosynthesized nanoparticles exhibits anticancer ability in two ways, either by binding to the surface or via cellular internalization (Andra et al. 2019). Some nanoparticles dissociate into its ionic states in the body fluid upon administration, due to low stability (Lee et al. 2016), whereas stable nanoparticles reach the targeted cancer cells (Tietze et al. 2015). The dissociated ions in the body fluid also perform anticancer activity but with less specificity towards cancer cells. Thus, unstable nanoparticles in body fluids are nanoencapsulated or nanoformulated to increase their stability (Hu et al. 2018). The primary mechanism in the inhibition of cancerous cells is the formation of reactive oxygen species (ROS) by nanoparticles. The ROS will be formed on the surface to damage cell membrane or nanosized particles can internalize into the cells and form ROS to disrupt cell membranes from inside



**Fig. 3** Anticancer mechanism of phytosynthesized nanoparticles. The schematic drawing demonstrates two possible anticancer mechanism exhibited by the majority of phytosynthesized nanoparticles. The first anticancer approach is the direct inhibition of cancer cell by the nanoparticles either by damaging cell wall and membrane protein; disrupting transmembrane electron transport; and generating reactive oxygen species (ROS) to facilitate apoptosis. Smaller nanoparticles may also enter into the cancer cell, generate ROS, induce oxidative stress, and disrupt DNA, electron transport chain, enzymes and protein to facilitate cancer cell apoptosis. The second approach is the dissociation of nanoparticles into ions and delivers anticancer activities by the standalone nanoparticle ions

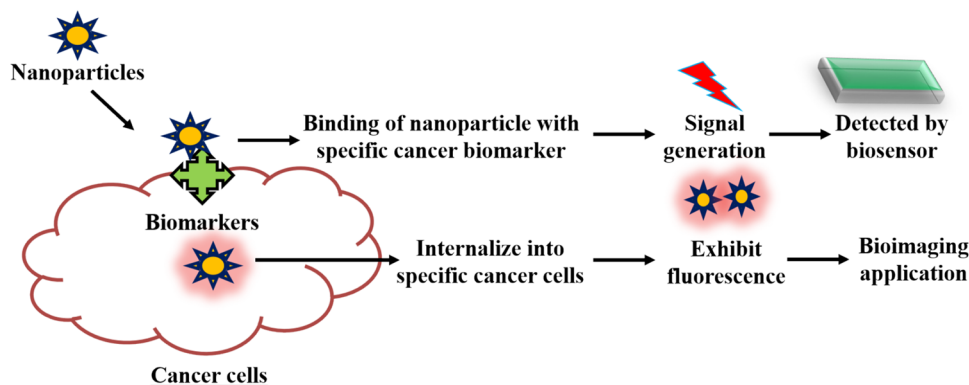


(Zhu et al. 2016). Phytosynthesized nanoparticles may also lead to membrane protein damage and transmembrane electron transport disruption, upon binding to the cancer cell surface and cause specific cancer cell apoptosis (He et al. 2016a; Zhang et al. 2018).

The main advantage of using phytochemicals for the formation of nanoparticles is to ease the internalization of them into the cancer cells (Yang et al. 2018). Internalization of nanoparticles into cancer cells may lead to increased oxidative stress and elevated osmotic pressure, which will be responsible for apoptosis (Morry et al. 2017). The internalized nanoparticles may also bind with cell organelles (Ghosh 2019), DNA (Sundaramoorthy et al. 2016), electron transport chain (He et al. 2016a), enzymes (Nosrati et al. 2018) and proteins (Hasegawa et al. 2015) to disrupt them and lead to programmed cell death. It is noteworthy

that all these mechanisms are possible to be responsible for cancer cell inhibition by nanoparticles. Thus, antagonistic and synergistic mechanism is the two classes of anticancer approaches that can be exhibited by phytosynthesized nanoparticles. In antagonistic approaches, only a specific type of the above mentioned mechanisms will be accountable for the cancer cell inhibition ability of nanosized particles (Zhu et al. 2017), predominantly cell wall disruption upon nanoparticles' interaction with the cancer cell surface. However, in synergistic approaches, involves a combination of two or more of the above mentioned mechanisms to inhibit cancer cell growth using nanoparticles (Thapa et al. 2017). Furthermore, nanoparticles are attracted towards the cancer cells either via electrostatic force (Revia and Zhang 2016) or they may disintegrate, and the ions may enter into cells via ion channels (Othman et al. 2016). In spite of several

**Fig. 4** Mechanism of cancer diagnosis using phytosynthesized nanoparticles for biosensors and bioimaging applications. The nanoparticles may either bind with specific cancer biomarker to generate an exclusive signal to be detected by the biosensor or internalize into the cancer cell to exhibit fluorescence that can be detected for bioimaging applications



reports on the anticancer mechanism of nanoparticles, extensive research is required to specify and standardize them to improve their anticancer ability in the future.

The mechanism of cancer diagnosis revolves around two main applications, either bioimaging or biosensors, as shown in Fig. 4. Nanoparticles with their enhanced ratio of surface area to volume can accommodate several biomolecules as receptors to detect a wide variety of cancer biomarkers. In addition, when nanoparticles are combined with biosensors, it is highly sensitive to even minute changes in their surface and rapid in delivering signals to the sensors. Thus, phytosynthesized nanoparticles coated with specific receptors are critical in the rapid detection of cancer biomarkers in biofluids, which includes sweat, blood and urine with high sensitivity and without any toxic reactions to humans and the environment (Kuang et al. 2017). Moreover, nanoparticles exhibit excellent fluorescent properties, which is proved to be enhanced by synthesizing them using phytochemicals and the existence of plant extracts as functional active groups in those nanoparticles (Wu et al. 2016). When these nanoparticles are tagged with specific receptors of cancer biomarkers, they bind to cancer cells, internalize via tagged receptors and exhibit fluorescent property, which will be highly beneficial in imaging specific cancer cells (Chinen et al. 2015). Moreover, conventional fluorescent dyes can also be encapsulated with phytosynthesized nanoparticles for targeted delivery into cancer cells without causing damage to non-cancerous cells (Chansaenpak et al. 2018). The same mechanism is used in the cancer diagnosis via MRI (Kumar et al. 2016b), PET (Ovais et al. 2017), CT (Ovais et al. 2016) and infrared-based (Chen et al. 2016) bioimaging approach.

In recent times, theranostic (detection and inhibition) mechanism of nanoparticles are widely explored and are considered as the future of cancer treatment. Here, the nanoparticles will possess both cancer detection and inhibition properties. Such novel nanoparticles will be coated with biomolecular receptors to bind with specific cancer biomarkers, either give signals for biosensors or bioimaging of cancer cells to locate and detect the type of cancer and its location. Upon diagnosis, the encapsulated or coated phytochemicals or drugs is released into the cancer cells to exhibit the anticancer mechanism, as mentioned earlier, for the inhibition of cancer cell growth. Magnetic nanoparticles are widely used in these types of multipurpose cancer treatment modalities. Magnetic nanoparticles can be remotely driven inside the patient's body to reach the target site via magnetic force, and this is beneficial to obtain MRI images of cancer types for diagnosis. After diagnosis, the release of the drug can be programmed and executed via external magnetic field depending on the effectiveness of drug and cancerous cell growth (Gobbo et al. 2015; Yang et al. 2017). Thus, phytosynthesized magnetic nanocomposites will be highly beneficial in the future as a multipurpose cancer drug

to be utilized as theranostic agent to cure cancer. Recently, Kesavan et al. (2018) fabricated a novel an iron oxide-drug nanocage theranostic nanocomposites using plant derived saponins as bio-surfactants for targeted chemotherapy of cancer via magnetic responses (Kesavan et al. 2018), which showed the potential of phytosynthesized multipurpose nanocomposites in the future of cancer treatment.

## Future perspective and outlook

Currently, phytosynthesized nanoparticles and nanocomposites have been demonstrated for the inhibition of cancer cell growth in preclinical lab research with various mechanisms of action proposed. Opportunities exist for some of these early demonstrations to make it to the clinical level. In future, phytosynthesized nanocomposites with the ability to inhibit multiple cancer types will play a major role as cancer therapeutic agent. Furthermore, dendrimer-based nanoforulations, which possess ability to accommodate various nanoparticles will be beneficial in the theranostic applications against cancer cells. (Asadi et al. 2018) Furthermore, phytochemicals with anticancer ability are encapsulated or coated on nanoparticles to deliver them at the target cancer cell type to effectively inhibit their growth (Ling et al. 2019). Moreover, the enhanced interaction of nanoparticles with cancer cells will be highly beneficial in cancer treatment modalities such as hyperthermia and nanocryosurgery. These nanoparticles specifically bind to cancer cells, which will be beneficial in avoiding damage in the non-cancerous cells and elevate the disruptive potential in cancer cells, via external heat treatment and cryosurgery (Ramirez-Nuñez et al. 2018; Yuan et al. 2017). In addition, certain noble nanosized metallic particles have surface plasmon resonance (SPR) properties, which is essential for photodynamic and photothermal cancer treatments (Erdogan et al. 2019; Song et al. 2016). Recently, numerous literatures are available on the immobilization of aptamers on the surface of nanoparticles. Such immobilizations will help nanoparticles in detecting biomarkers of specific cancer cells, bind with them and exhibit improved anticancer activity. Thus, aptamer with phytosynthesized hybrid nanocomposites will be highly useful in the targeted cancer cell attachment to cause programmed cell death, without affecting the growth of normal cells (Liu et al. 2016).

It is noteworthy from the previous sections that phytosynthesized nanoparticles are extensively employed in the diagnosis of both common and rare cancer types. Mostly, these phytosynthesized nanoparticles are employed as theranostic agents to avoid side-effects to the environment as well as patients. Nanoparticle based biosensors are now included in several personalized diagnosis methods, which allows the patients to diagnose themselves. Smart watches and smart

phones play a major role in these types of personalized disease diagnosis, including cancers. These phytosynthesized nanoparticles can be included in the implantable biosensors or biochips, which can detect the emergence and spread of cancer cells in patients. Furthermore, the details can also be sent to physicians via smart phones for continuous monitoring of cancer progression, without being present in the hospitals. Moreover, it is possible to detect multiple cancer types via nanosensors and bioimaging approaches which will play a significant role in the future of cancer diagnosis. In spite of this widespread research, there is limited information on preclinical and clinical trials of these phytosynthesized nanoparticles for cancer theranostics. Since several researchers have proposed various methods to evaluate the anticancer activity of nanoparticles, it is high time to form a regulatory body to standardize the assays used to evaluate the anticancer activity of nanoparticles. Furthermore, the phytosynthesized nanoparticles that are evaluated via these standard methods have to be enlisted in a standard repository and made available to researchers to catalyze the process of developing novel anticancer nanomedicines.

## Conclusion

Phytosynthesized nanoparticles show promising anticancer and in vitro cancer detection properties. Moreover, their bioavailability, less toxicity and biocompatibility make them a promising candidate for cancer treatment and diagnosis. However, their stability and dispersibility characteristics require improvements to enable wide-spread cancer theranostic applications. Furthermore, the idea of incorporating smart biosensors such as bioaffinity ligands (including aptamers and antibodies) and biochips with nanoparticles may improve the future of personalized theranostic approaches for cancer. In addition, the standardization of procedures to estimate cancer cell inhibition ability of nanoparticles and enlisting them in a standard repository will advance research into phytosynthesized nanomedicine.

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## Compliance with ethical standards

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

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