



Green Synthesized Silver Nanoparticles using Plant Extracts as Promising Prospect for Cancer Therapy: A Review of Recent Findings

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Abstract

Background: Silver nanoparticles are the leading in biomedical applications such as antioxidant, anticancer, antiviral, antidiabetic and antimicrobial because of their biocompatibility and stability. The activities of AgNPs synthesized using plant extracts is significantly improved due to phytochemical coating. The aim of this review is to explore the anticancer activity of AgNPs synthesized via plant extracts.

Methods: Anticancer activity of AgNPs very recently synthesized via different plant extracts was studied against various human cancer cells using 3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay in the papers explored in this review.

Results: The test results indicated that the explored nanoparticles displayed a considerable anticancer activity with excellent selectivity towards the cancer cells. Almost all the nanoparticles also displayed concentration dependency in their anticancer activities. The excellent selectivity of the nanoparticles is due to biocompatibility of silver and the phytochemicals from the plant extracts that cape their surface.

Conclusion: Green synthesized AgNPs via plant extracts already fulfilled one of the highest requirements in their excellent selectivity. Their concentration dependent activity needs serious attention as long term usage may lead to different side effects. Further investigations especially on the molecular level mechanism of the AgNPs may help in enhancing their potential and minimize the dose for their application as anticancer agents.

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Keywords: Silver nanoparticles; Plant extracts; Green synthesis; Anticancer activity; Apopticity; MTT assay.

Introduction

Nanotechnology is a bright hope for various problems in numerous fields, involving fabrication, depiction, operation and application of structures via maintaining the nanoscale shape and size [1]. Nanoparticles may be metal or non-metal based in an elementary state [2]. Metallic nanoparticles are among

the leading classes of nanoparticles with versatile applications in chemical, electronic, medicinal and pharmaceutical sciences [3]. Silver nanoparticles (AgNPs) are emerging as the most considered of all metallic nanoparticles for practicable nanomaterial production and applications [4-7].



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Nanoparticles can be synthesized conventionally via physical and chemical methods [8-11]. However, these methods are not in preference due to their high cost and energy consuming as it needs high temperature and pressure; releasing toxic chemicals to the environment [12-14] as well as involving complicated process with inadequate yield. As a result, the search for sustainable, eco-friendly, cost wise, good yielding and viable method, producing green nanoparticles has attracted high research interest in the last decade [15-18]. The most promising method adopted to overcome the conventional method related problems is biological synthesis (green approach) which uses natural products from algae, microbial (fungi and bacteria), plants and animals for production of harmless metallic nanoparticles [19-25]. Although it is green approach, nanoparticle fabrication using microbial has a complication due to some drawbacks such as aseptic culture surroundings preservation, low quantity product and costly. But, plant mediated synthesis of nanoparticles is found to be advantageous by far due to its harmless reagents, mild conditions which makes its process easier; large-scale production and broad spectrum of biological activities [26-30]. Consequently, the development of plant mediated synthesis methods significantly attracted researchers globally [31-34] due to its potential in producing stable nanoparticles with versatile applications. It is also reported that phytochemicals in the plant extracts such as flavonoids, alkaloids, steroids, saponins, carbohydrates and proteins play a dual role, acting as both capping and reducing agents in the process of nanoparticles fabrication with different compositions and morphologies via green approach [35-40]. Furthermore, the phytochemicals from plant extracts are able to be inserted or attached on the outer surface of the nanoparticles in their development process, which is critical in their biological applications like antimicrobial and anticancer [41,42].

Besides, the green synthesis of nanoparticles using plant materials gives an opportunity to adjust their size and shape by varying the quantity of the plant extract and metal ions [43,44]. This is one of the most critical advantages of this approach as shape and size are basic nanoparticles performance determining factors [45]. The foremost problem of this method is the fluctuation of phytochemical contents of the plant extracts as a result of climatic and seasonal alterations, affecting the development of sustainable procedures as well as the reproducibility of the nanoparticles and their applications [46]. There are also other factors affecting stability and quantity related cases, making the approach not well established [47].

Silver nanoparticles are in a great demand due to their exclusive and distinctive properties including high stability and conductivity [48] with showing remarkable flexibility [49]. Their unique optical, electrical, thermal, high electrical conductivity and biological properties are making them to be used in diverse fields [50-52]. Green synthesized silver nanoparticles were found to be quite potent of all others in medicinal applications [53], showing superb biomedical properties [54]. The aggregation problem of silver nanoparticles due to their high surface energy is efficiently avoided in plant mediated synthesis approach, in which the capping agents surround the particles, stabilizing the dispersions of metal colloidal through electrostatic and steric effects [55-57].

Cancer is an abnormal growth of tissue or cells exhibiting uncontrolled division autonomously, leading to a progressive increase within the number of cell divisions [58]. Although the

cause of cancer is doubt, genetics related disorders (5-10 %), lack of balanced diet, lack of physical exercise, definite infections, smoking, environmental pollution are among suggested factors leading to development of cancer [59]. Cancer is a major worldwide health problem with a rapidly increasing mortality rate every year [60], which makes it the second deadly disease next to cardiovascular diseases [61]. The existing cancer treatment modalities such as immunotherapy, chemotherapy, surgery, and radiotherapy [62] are not matching with the mortality rate and expansion problems of the disease because of their variety of limitations and toxicity. Hence, the need for developing new classes of potent therapies with efficient drug releasing method to deliver a harmless drug at the targeted site is tremendous. Nanoparticles are widely considered to be potential candidates for this as their *in vitro* apoptotic pathway stimulating ability have been shown, indicating their anticancer effects [63].

Silver nanoparticles synthesized by plant extract mediation have been showing promising anticancer activities against a variety of carcinoma cells [64,65]. The green synthesized silver nanoparticles perform their anticancer activity by reducing the proliferation of carcinoma cells via arresting cell cycle [66]. However, there is a limitation regarding the cytotoxicity information of metallic nanoparticles [67-69]; the inertness of Ag NPs is decreased in aqueous environment [70, 71] which may increase the cell-specific cytotoxicity concern. Hence, addressing this critical concern may enhance the probability of Ag NPs to be used as efficient targeted chemotherapy for cancer treatment. In view of these observations, we plan to explore the anticancer activity of Ag NPs synthesized recently via plant extract supported approach.

Plant extract mediated synthesis of silver nanoparticles

Plant extract mediated synthesis of silver nanoparticles has been considered as one of the most suitable approach for its easy scale-up, pollution less, and inexpensiveness advantages [72]. Biocompatibility of silver [73, 74] and the involvement of plant biomolecules in its nanoparticles synthesis make it a genuine candidate for various biological applications [75]. The plant extracts prepared from seeds, needles, roots, fruits, and aerial parts of the plants are rich in phytochemicals such as polyphenols, catechins, flavones and terpenoids [76-78]. These secondary metabolites are used for Ag nanoparticles synthesis through acting as reducing, capping and stabilizing agents. The whole process is suggested to have three fundamental steps (nucleation, growth/development and capping) [79,80].

The mechanism for synthesis of Ag nanoparticles via plant extracts is not established although the mechanism for reduction of Ag^+ to Ag can be described by considering the functional groups of the phytochemicals [81]. For instance, flavonoids which are a large family of polyphenols act as reductants by releasing their reactive hydrogens via tautomerization, transforming the phenolic form to keto-form and changing Ag^+ to Ag atom [82]. This indicates that the hydroxyl groups are the major role playing functional groups of the phenolic compounds in the reduction of silver cation [83]. The functional groups also enhance the stability of the nanoparticles by covering the metallic core to stay longer without altering their shape and size [84].

Hence, the concentration of the phenolic compounds in the extracts determines the quality of the nanoparticles formed in terms of size, shape and stability. As the concentration of the secondary metabolites varies between the plants, plant selec-

tion is critical in synthesizing nanoparticles via this method.

In addition to acting as capping and reducing agents in the synthesis of the metallic nanoparticles, the phytochemicals of the plant extracts also enhance their biological applications such as antibacterial, antifungal, antiviral, antioxidant and anticancer [85-87].

Factors influencing plant extract mediated synthesis of nanoparticles

Nanoparticle synthesis using plant extracts with the required stability and applications depend on several factors such as solution pH, temperature, reaction time and plant extract quantity.

The solution pH

The pH of a solution medium in which the syntheses of the nanoparticles take place is vital to fabricate stable nanoparticles in adequate quantity. The size and shape of nanoparticles which are critical in their applications as well as the kinetics of their formation is influenced by solution pH [88]. The nucleation centres formation is directly related to pH that influences all size, shape and rate of formation of the nanoparticles. The enhancement of nucleation centre formation increases the metal cations reduction by the functional groups of the phytochemicals from the plant extracts, supporting the formation of nanoparticles [89]. Smaller particle size regular shaped silver nanoparticles are formed in alkaline reaction medium (pH 8), which increases the electron donating ability of the phytochemicals through their OH- groups due to formation of AgO^- and AgO for better reduction of the silver cation and stability of the nanoparticles [90, 88]. This is also related to the ability of solution pH to the electrical loads of the secondary metabolites in plant extracts [91].

Plant extracts quantity

The volume of the plant extract is another major factor determining the fabrication of nanoparticles. It is reported that the quantity of the extract affects both the efficiency of the production and shape of the nanoparticles as the degree of production is usually enhanced with the quantity [92,93]. This makes plant extract volume optimization critical for effective fabrication of nanoparticles.

In synthesizing silver nanoparticles, the phytochemicals reducing Ag^+ ions to Ag atoms are obtained from the extracts and there is an optimum quantity at which the nanoparticles are formed to the best size, stability and quantity [90].

Temperature

Temperature of the reaction medium is another critical factor determining the fabrication of stable nanoparticles in adequate quantity.

The activation energy desired for starting a chemical reaction is usually obtained from temperature supply. Temperature also increases the kinetic energy of reactants for their enhanced molecular collision forming the desired products quickly [94, 95]. Increasing temperature catalyses the formation of the nanoparticles via increasing the formation of nucleation centres, [96] due to rapid reduction of metal cations [90]. Furthermore, raised temperature leads to formation of stable and smaller sized nanoparticles [97].

Silver and gold nanoparticles synthesis at different temperature showed high quantity of plant extract is required for the

reduction of the cations [98]. It is also reported that the absorbance of the nanoparticles increase with temperature [99], indicating high concentration of the synthesized nanoparticles. However, the temperature should be maintained in the range of 30-100°C as the phytochemicals decompose at higher temperature, interfering the critical reduction process.

Reaction time

The time required for interaction of metallic salts with the secondary metabolites of the plant extracts has also its own critical role in combination with other factors such pH, light exposure, temperature, nucleophilic potential of the biomolecules and volume of the extract for efficient synthesis of nanoparticles. Plant extract mediated synthesis is a one step easy approach and takes a shorter time than even other biological approaches such as microorganism supported synthesis [100]. However, reports indicated that the sharpening of peaks increases with increasing of contact time in Ag nanoparticles synthesis [101], leading to efficient production [102]. Like other factors, a reaction time also affects the size and shape of nanoparticles [103,104].

Anticancer activity

The potential of silver nanoparticles synthesized via plant extract mediation as anticancer is reported [105,106]. Although the mechanism of the activity is not well understood, it is suggested that the nanoparticles anticancer activity is via oxidative stress and inflammation formed due to ROS, causing DNA damage and mitochondrial dysfunction leading to carcinoma cells death [107]. The silver nanoparticles synthesized using plant extracts showed excellent selectivity by attacking cancer cells than normal cells [108,109], which is due to the presence of the biocompatible secondary metabolites [110,111].

Their less toxicity is the main reason behind considering them as potential candidate for cancer therapy. Recently, silver nanoparticle synthesized using various plant extracts are showing excellent anticancer activity.

Anticancer activity of silver nanoparticles synthesized using *Hypericum Perforatum L.* aqueous aerial part extracts was investigated against Hela, Hep G2, and A549 cells by 3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay. The green synthesized nanoparticles showed good anticancer activity by significantly decreasing the viability of the carcinoma cells. The high activity of the nanoparticles might be associated with the phenolic compounds on their surface which acted as capping agents upon synthesis in addition to shape and size of the nanoparticles [112]. The richness of the coating with phenolic metabolites is related to the medicinal plant *Hypericum perforatum* [113], which is rich in phytochemicals, making it a potent herb for treating series diseases like cancer and AIDS [114-117].

Silver nanoparticles synthesis by microwave-assisted green approach using banana leaf extract and its anticancer activity was carried out against A549 and MCF7 cell lines. The synthesized AgNPs exhibited excellent anticancer activity even at low concentration although the activity was enhanced with increasing concentration [118]. The strong activity of the product is attributed to the high Reactive Oxygen Species (ROS) stimulating ability of the AgNPs that disturbs metabolic and physiological process, leading to cell death [119]. The promising activity of the product makes it another potential candidate for the development of silver based cancer nanodrug.

Silver nanoparticles synthesized using *Mangifera indica* seed aqueous extract showed a dose dependent anticancer activity against HeLa and MCF-7 cancer cells after investigation via MTT assay. The newly synthesized nanoparticles also showed good specificity towards carcinoma cells as it was found that the sample has decreased cell viability against fibroblast normal cells, which indicates their less cytotoxicity towards normal cells [120]. The good anticancer activity of silver nanoparticles is attributed to its physicochemical interaction with the cancer cells that leads to biomolecules damage via releasing of ROS activate Caspase 3, induced DNA fragmentation and membrane leakage, finally leading to carcinoma cells death. There might be electronic interaction in which Ag^+ takes electrons from DNA to enhance oxidative stress via increasing ROS fabrication and cause cell death [121,122].

The anticancer potential activity of silver nanoparticles produced using *Heliotropium bacciferum* extract as capping and stabilizing agent was evaluated against breast (MCF-7) and colorectal (HCT-116) by three assays including MTT, comet, and scratch. The product showed excellent potential with IC_{50} of 5.44 and 9.54 g/mL for MCF-7 and HCT-116 respectively, which is associated in its potential to increase the production of ROS than the control [123]. The enhanced ROS production might be due to the electron withdrawing by Ag^+ from the biomolecules including DNA to make them free radicals and cause oxidative stress for the death of the cancer cells. The dependency of AgNPs cytotoxic activity on the types of cells is reported [124], distortion and morphological loss was observed on the MCF-7 and HCT-116 carcinoma cells after treatment with the synthesized nanoparticles [123]. Although the product showed excellent potential as anticancer, the activity is concentration dependent and modifications are required before using as anticancer therapy to minimize the concentration as it can lead to toxicity if applied for long time.

Silver nanoparticles were synthesized using *Carica papaya peel* extract and evaluated as anticancer against MCF-7 and Hep-2 cells using MTT assay. The synthesized nanoparticles showed good activity with better activity against MCF -7 cell line ($IC_{50} = 35.19$) than HEP -2 cell line ($IC_{50} = 83.06$) [125]. The good anticancer activity of the AgNPs is likely to be supported by phytochemicals from the plant extract which is rich in secondary metabolites including flavonoids, phenols and tannins, also enabling it a good antioxidant [126].

Novel silver nanoparticles formulated by the support of *Zingier officinale* leaf extract were tested as an anticancer against human pancreatic carcinoma such as AsPC-1, PANC-1, and MIA PaCa-2 via MTT assay. The activity was found to be dose dependent, but with very good cell viability. This makes the nanoparticles potential candidates for cancer therapy and can go to clinical trials after making some modifications to enhance its potential [127]. The integrative antioxidant potential of the synthesized AgNPs with the phenolic metabolites from the plant are suggested to be the likely factors behind the good anticancer activity, the plant phytochemicals also playing the cancer cell specificity role of the product. Antioxidants including silver nanoparticles minimize metastasis via removing free radicals [128].

Das et al. reported anticancer activity of green synthesized silver nanoparticles via *Cocos nucifera L.* fruit extract against HepG2 cells.

The product showed a considerable activity ($IC_{50} = 15.28$),

which could be related to their entering to the cells as a result of their smaller size and cause DNA destruction via immunological and electrostatic responses, leading to cancer cell death lastly [130-133].

Anticancer activity of novel silver nanoparticles synthesized using the residues of Chinese herbal medicine extract was studied against HCT116, HepG2 and HeLa cell lines by MTT assay. The synthesized nanoparticles exhibited a very good anticancer activity by significantly decreasing the cell viability in dose dependent manner, while the best activity was shown against HepG2 cells. The product also showed a comparable activity with AgNPs synthesized with other medicinal plants [134] which make the product a promising candidate for cancer treatment.

A one step up approach of green synthesis was used for AgNPs synthesis in which a di-methyl flubendazole compound isolated from *Carica papaya* leaf extract supported the synthesis. The anticancer activity of the product was evaluated against HepG2, MCF-7 and A549 cell lines using MTT assay, while Vero cells were used as control [135]. The synthesized nanoparticles showed a promising anticancer activity with the most activity against HepG2 cells. The activity difference against the carcinoma cells might be related to morphological change responses against AgNPs treatment, leading to differences in cell shrinkage, and fragmentation which leads to apoptosis difference [136]. The whole activity of the nanoparticles goes to increasing oxidative stress agents and reduction of antioxidant producers, thereby up regulating proapoptotic gene expression with down-regulating antiapoptotic gene expression oppositely [137,138]. The one step forward synthesis of AgNPs from an isolated compound is emerging and may replace the role of crude extracts as the nanoparticles from isolated compounds showed better biological applications [139]. Isolation of biomolecules from plant extracts may enhance the reducing and capping ability of the most potent biomolecules for more efficient nanoparticles fabrication via minimizing interferences due to computation from others in the crude extract. This also enhances their biological applications including anticancer and must be encouraged for better search of potent cancer drugs. The di-methyl flubendazole based AgNPs is an efficient candidate to develop a phytochemical dependent cancer therapy.

Anticancer activity of AgNPs photosynthesized using *P. frutescens* leaf extract was studied against human colon cancer (COLO205) and prostate adenocarcinoma (LNCaP). The product showed dose dependent activity against both carcinoma cells.

The better activity was observed against LNCaP, which indicates more morphological changes due to the exposure to the synthesized AgNPs that leads to accumulation of apoptotic bodies [140].

Padalia and Chanda reported synthesis of silver nanoparticles using *Ziziphus nummularia* leaf extract with their anticancer activity against HeLa cells, breast cells and fibroblast normal cells by MTT assay where Mitomycin C was used as a positive control. The green synthesized nanoparticles demonstrated a concentration dependent activity as the cell viability decreased with increasing dose of AgNPs. The higher cytotoxic activity was observed against HeLa cells than breast cells with a very good specificity towards carcinoma cells. *Ziziphus nummularia* is a potent medicinal plant found in Arabian countries and rich in secondary metabolites such as flavonoids, alkaloids, saponins, glycosides, and essential oils [142,143]. The leaf of this plant is used treat various diseases including diabetes, microbial infec-

tions, skin diseases, wounds and pain [144-149]. The secondary metabolites are the agents of the medicinal potential and their presence in the nanoparticles as capping agents is helpful in enhancing the anticancer potential as well the specificity of the nanoparticles. Further investigations are required to minimize the concentration of the nanoparticles at which it can be potential drug for cancer treatment.

Murugesan et al reported *Gloriosa superba* aqueous tuber extract based synthesis of AgNPs and studied its anticancer activity against human lung cancer cell line (A549) by MTT assay. The product showed excellent anticancer activity although it is dose dependent. The synthesized nanoparticles brought morphological change on the carcinoma cell, thereby decreasing cell proliferation and accumulation apoptotic cells for the death of the cells. The product is quite potent to be used as cancer drug, but the unclear mechanism of its action needs further investigation.

Green approach was used to synthesize AgNPs using *Ocimum americanum* aqueous leaf extract for checking its anticancer activity against A549 lung cancer cells using MTT assay. The fabricated nanoparticles displayed a considerable concentration dependent activity with excellent biocompatibility [151]. The high anticancer activity of the product might be associated with the apoptosis inducing mediated cell death *via* enhancing oxidative stress in caspase-mediated and mitochondrial-dependent pathways [152,153]. The biocompatibility of the AgNPs makes it potential candidate for cancer treatment with a modification enhancing its efficiency [151].

Solanum incanum leaf extract supported synthesis of silver nanoparticles was done and its anticancer activity was evaluated against HepG2, MCF-7 and normal Vero cells using MTT assay. The product exhibited a significant anticancer potential against the carcinoma cells although it is dose dependent [154]. The considerable activity might be attributed to mitochondrial damage based increment of ROS [155], related to minimization of Adenosine Triphosphate (ATP) in the carcinoma cells treated with the sample [156]. This process causes cell apoptosis due to DNA damage and protein denaturation initiated by entering Ag^+ the cytoplasm [157].

Eriobotrya japonica leaf extract was used to biologically synthesize silver nanoparticle for its anticancer activity investigation against MCF-7 and HeLa cells by MTT assay. The green synthesized AgNPs potentially induced apoptosis started by stimulation of caspase-3 [158] to cause Bcl2 down-regulation and Bax and p53 proteins down-regulation, indicating a very good anticancer activity. The displayed potential manifests the high probability of the fabricated product to be used for treatment of different types of cancers [159].

Cytotoxic activity of silver nanoparticles synthesized via green synthesis using *Rhizophora apiculata* aqueous leaf extract was evaluated against HeLa cancer cells and HEK-293 normal cells. The fabricated AgNPs displayed a dose dependent activity. The anticancer activity of the product against HEK-293 cells was a triple to that of HeLa cells which indicates a high morphological difference between the carcinoma cells in their response to the sample as well as specificity of the nanoparticles to cancer cells. The mechanism of the action which is not well established yet needs further action, which can also show a way for concentration minimization for efficient usage of the product as a cancer nanomedicine [160].

Silver nanoparticles were biologically synthesized from the leaf extract of *eucalyptus camaldulensis* for its evaluation as anticancer against A549, HT29 and MDA-MB-231 cells using MTT assay. The fabricated nonmaterial showed a considerable anticancer potential with MDA-MB-231 found to be more susceptible to the green synthesized AgNPs. The mechanism of the product at molecular level requires further investigation to be effectively applied as anticancer therapy [161].

Al-Nuairi et al. reported synthesis and anticancer activity of green synthesized silver nanoparticles via *Cyperus conglomeratus* root extracts against MCF-7 carcinoma cell and fibroblast normal cells using MTT assay.

The green product showed a very good anticancer activity with excellent selectivity to the investigated cancer cell [163]. The selectivity is related to high absorption of AgNPs by the cancer cells due to their high rate of proliferation and abnormal metabolism [165,166]. The excellent selectivity of the fabricated AgNPs makes it a very potential candidate, as selectivity is among the critical requirements for cancer drugs [163].

Hence, the product may go for clinical trials after some modifications regarding its potential enhancement for less quantity usage in cancer therapy.

Caesalpinia pulcherrima aqueous leaf extract was used to biologically synthesize AgNPs for its anticancer evaluation against HCT116 cell line *via* MTT assay. The synthesized AgNPs showed good anticancer activity [166], which might be associated with cell shrinking, coiling, chromatin condensation related cell quantity minimization, non-adherence and membrane blebbing due to treatment with AgNPs [167]. The other suggested mechanism is the usual apoptosis that leads to the opening of mitochondrial membrane opening and allows cell membrane disruption as a result of ROS production due to the influence of AgNPs, activating the apoptotic signals inside the cells [168]. *Caesalpinia pulcherrima* is a common medicinal plant used to treat various diseases including cancer, so identifying, isolating and preparing a silver nanoparticle with anticancer phytochemical may produce a potential therapy.

Anticancer activity of AgNPs synthesized *via* *Ruta graveolens* leaf ethanol extract was tested HeLa and HepG2 cell lines using MTT assay and compared with the extract. The extract showed a considerable anticancer activity against HepG2 cell [169], while the AgNPs showed a promising activity against both cell lines. *Ruta graveolens* is a common medicinal plant traditionally used for treating different diseases and as flavoring agent due to its high flavonoid content. Its anticancer property is also associated with the flavonoids, which have apoptotic-inducing property due to oxidizing activity that enhances ROS production and cause oxidative stress [170]. The plant extract inhibits the growth of rat normal cells, showing its cytotoxicity to normal cells, but its silver nanoparticles stimulated the normal splenic cells. Anticancer activity of the AgNPs is better by far than the extract, which might be related to different factors like synergic effect due to interaction between the secondary metabolites of the extract and the Ag^+ , and smaller size enabling easy penetration through the cell walls to disturb metabolic and physiological processes and lead to cell death [171,172].

Synthesis of silver nanoparticles in which *Cucumis propheta-rum* aqueous leaf was used as capping and reducing agent was for evaluation of anticancer activity against A549, MDA-MB-231, HepG2, and MCF-7 using MTT assay. The biosynthesize AgNPs

showed dose dependent activity with the highest anticancer activity shown against MCF-7 [173]. This indicates the huge potential the product has especially to treat breast cancer, but further investigations are required to use it as nanomedicine for cancer treatment.

A green approach was employed for synthesis of silver nanoparticles using *Fumaria parviflora* leaf extract for its anticancer activity evaluation against human breast cancer (MDA-MB-468) cell lines by MTT assay. The fabricated AgNPs showed a considerable activity which increased with the concentration of the product and it also displayed high selectivity [174].

The concentration dependency of the activity's strength might related to the suggested mechanism of silver nanoparticles, in which Ag⁺ is released from colloidal biogenic AgNPs to the cancer cells [175]. This also depends on the pH of medium as there is high releasing of Ag⁺ in acidic medium [176]. The strong anticancer activity and selectivity towards cancer cells makes the product very potential candidate for development of cancer defending and remedying nanodrug.

Cytotoxic activity of silver nanoparticles synthesized via green synthesis *Teucrium polium* leaf extract was evaluated against HeLa cancer cells and HEK-293 normal cells using. The product displayed a very strong anticancer activity which might be due to integrative action of the secondary metabolites flavonoids and polyphenols capped at the surface and nano-sized silver particles [177]. This is another potential candidate for the search of silver based nanomedicine.

Synthesis of silver nanoparticles via *Eucalyptus camaldulensis* leaf extract and its anticancer activity against A549, HT29 and MDA-MB-231 cancer cell lines was reported. The anticancer activity was investigated using MTT assay and the activity of the AgNPs was compared with the extract. The fabricated AgNPs displayed a very high activity against all the cancer cells and higher activity the plant extract. The plant extract showed good anticancer activity and its best activity came against MDA-MB-231 cancer cell line. Thus, better understandings of molecular level mechanistic actions are required from further investigations for usage of the product for cancer therapy [178].

Table 1: Anticancer activity of recently synthesized AgNPs using different plant extracts.

No	Name of the plant used	Part of the plant used	Cancer cells	Anticancer Activity	Selectivity	References
1	<i>Hypericum Perforatum</i>	Aerial part	Hela, Hep G2, and A549	Very good	Excellent	112
2	Banana	Leaf	A549 and MCF7	Excellent	Excellent	118
3	<i>Mangifera indica</i> seed	Seed	HeLa and MCF-7	Good	Excellent	120
4	<i>Heliotropium bacciferum</i>	-	MCF-7 and HCT-116	Very good	Excellent	123
5	<i>Carica papaya</i>	Fruit peel	MCF-7 and Hep-2	Good	Excellent	125
6	<i>Zingier officinale</i>	Leaf	AsPC-1, PANC-1, and MIA PaCa-2	Very good	Excellent	127
7	<i>Cocos nucifera</i> L.	Fruit	HepG2	Very good	Excellent	129
8	Chinese herbal medicine residues	-	HCT116, HepG2 and HeLa	Very good	Excellent	134
9	<i>Carica papaya</i>	Leaf	HepG2, MCF-7 and A549	Very good	Excellent	135
10	<i>P. frutescens</i>	Leaf	(COLO205) and (LNCaP)	Good	Excellent	140
11	<i>Ziziphus nummularia</i>	Leaf	Hela and breast cells	Very good	Excellent	141
12	<i>Gloriosa superba</i>	Tuber	A549	Excellent	Excellent	150
13	<i>Ocimum americanum</i>	Leaf	A549	Excellent	Excellent	151
14	<i>Solanum incanum</i>	Leaf	HepG2 and MCF-7	Very good	Excellent	154
15	<i>Eriobotrya japonica</i>	Leaf	MCF-7 and HeLa	Very good	Excellent	159
16	<i>Rhizophora apiculata</i>	Leaf	HeLa	Good	Excellent	160
17	<i>Eucalyptus camaldulensis</i>	Leaf	A549, HT29 and MDA-MB-231	Very good	Excellent	161
18	<i>Cyperus conglomeratus</i>	Root	MCF-7	Very good	Excellent	162
19	<i>Caesalpinia pulcherrima</i>	Leaf	HCT116	Good	Excellent	166
20	<i>Ruta graveolens</i>	Leaf	HeLa and HepG2	Very good	Excellent	169
21	<i>Cucumis prophetarum</i>	Leaf	A549, MDA-MB-231, HepG2, and MCF-7	Good	Excellent	173
22	<i>Fumaria parviflora</i>	Leaf	MDA-MB-468	Very good	Excellent	174
23	<i>Teucrium polium</i>	Leaf	Hela	Excellent	Excellent	177

Conclusion

The superb biocompatibility and stability of AgNPs greenly synthesized using plant extract combined with their high biological activities including anticancer makes them one of the leading potential candidates for cancer therapy. Although almost all the very recently synthesized AgNPs explored displayed a concentration dependent anticancer activity, their selectivity was found to be excellent. Fulfilling one of the most required criteria of a cancer drug in being quite selective to the cancer cells, the way for increasing their potential is needed, thereby decreasing the dose of treatment to tackle the problem that may be associated with long term usage. Deep investigations on the mechanism of the nanoparticles action may be one of the promising ways to solve the problem and help the development of AgNPs based genuine cancer drug.

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