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

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Abstract

Green synthesis methods are gaining significance as promising routes for the sustainable preparation of nanoparticles, offering reduced toxicity towards living organisms and therefore the environment. Among nanoparticles, gold nanoparticles (AuNPs) attract much attention thanks to their usability and high performance in imaging techniques. The wide availability of biological precursors employed in plant based synthesized AuNPs allows for the event of large-scale production during a greener manner. Gold nanoparticles (AuNPs) are widely explored and are well-known for his or her medical applications due to their large volume specific surface areas with high diverse surface activities than bulk gold. These properties have made Au-NPs of great importance within the event of fantastic promising prospect for biomedical and environmental applications. In impression of this, biosynthesized NPs are gaining more attention due to bioactive plant secondary metabolites help in green synthesis and also due to their unique biological applications. This review, therefore, focuses on a simplistic, eco-friendly, reliable, and cost-effective green synthesized Au-NPs as a promising agent for cancer therapy. By consideration of preparation methods, green synthesis is one in every of the foremost promising approaches for compensation of the constraints of those physical and chemical methods. Au-NPs have many applications in biomedical field. Improving delivery of anticancer agents to tumors using NPs is one altogether the foremost promising research areas within the sector of nanotechnology. As observed during this recent review generally, to provide novel drug, the green synthesis approach of gold NPs indicates as an honest promising prospect on cancer therapy.

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Introduction

Nanotechnology is a modern exploration field that involves design, synthesis, and development of particles ranging in size from 1 to 100 nanometers. Nanoparticles may be metal or non-metal in an elementary state. It can be broadly classified into inorganic and organic nanoparticles. Organic nanoparticles are carbon nanoparticles whereas inorganic nanoparticles are magnetic nanoparticles, noble (gold and silver) nanoparticles, and semiconductor (titanium oxide and zinc oxide) nanoparticles. The field of nanotechnology is one of the essential areas for recent material science researchers. To date, interest of nanotechnology is the development of environmentally benign technology for the synthesis of metal nanoparticles with miraculous and boundless applications in the fields of food, health, pharmaceutical, agriculture, cosmetics, defense and environmental safety [1].

Nano-particles provide various applications that are increasing rapidly. It can be synthesized physical and chemical methods considering their enormous application in biomedical field [2,3]. These methods are costly and use harmful chemicals, which have negative effects; as a result this using a green synthesis of inorganic nano-particles is safer [4]. Green synthesis of noble metals is important because they are environment-friendly and are safe to human health [5]. The green synthesis of nano-particles is of great interest due to the rising need to decrease toxicity, increase renewable resources, biocompatible, safer and provide environment-friendly solvents. These have captured the attention of major corporations in the last few decades [6]. This approach also produces pure nanoparticles unlike the chemical methods wherein the produced nanoparticles formulation is contaminated with the chemicals used within the process [7].

As a medical point of view, the green synthesis of nanoparticles has been shown to greatly increase their clinical application. Gold nanoparticles can be synthesized by chemical, physical and biological methods. The biological methods are very useful because it provides natural capping agents without need of high pressure, temperature, toxic chemicals, and excessive energy. Using plant extracts to synthesize nano-particles is relatively cheaper than nano-particles synthesis by microorganisms [8].

Au-NPs have been widely studied and applied in the field of tumor diagnosis and treatment because of their special fundamental properties. The plant extract-mediated synthesis of the Au-NPs has been reported for human wellness; applications of Au-NPs include as anticancer [9,10,11], and antioxidant [12,13]. For therapeutic cancer, there is a need to develop a new planned drug. It has been reported that medicinal plant mediated Au-NPs are good aspirant for controlling the growth of different cancerous cells without affecting normal cells [9,10,11]. Several studies have investigated the synthesis of Au-NPs by green methods using plant extracts, yeast, bacteria, fungi and honey [14].

Metallic nanoparticles such as (silver, gold and platinum) NPs have been widely tested in humans. For medical uses, green synthesized nanoparticles should be biocompatible and non-toxic proprieties must be used. The most common method which has been used to produce Ag-NPs is chemical synthesis, enlisting reagents whose function is to reduce the silver ions and stabilize the NPs. However, these reagents are toxic and may have potential health hazards [12].

These production methods are usually labor-intensive and expensive. During the earlier period, it has been publicized that numerous biological systems, including plants, bacteria, yeast, algae and fungi can transform inorganic metal ions into metal nanoparticles via the reductive capacities of the proteins and secondary metabolites present in these organisms. Bearing this aspect, we plan to review the green synthesis approaches of silver and gold nanoparticles as promising prospect for cancer therapy come to the forward-facing due to the fact that they do not harm the environment and give economic and rapid results [15].

Recently, Au-NPs received much attention for the critical disease diagnosis and the treatment of several diseases e.g., cancerous cells, HIV, and rheumatoid arthritis, whereas substantial exploration is currently promising for possible applications as anticancer, antibacterial and bio-diagnostic material [22]. Furthermore, the non-immunogenic and non-toxic nature of Au-NPs with high permeability and the high retention effect suggest further support of the informal accumulation and penetration for the treatment of tumor sites. Several advanced methods of Au-NPs are still under development due to its distinctive values in the therapeutic field [23, 24]. As Yaqoob et al reports, Au-NPs formerly played a significant role in human welfare in the clinical diagnostic field as well as numerous medical applications. Further advanced research demonstrates that Au-NPs are becoming attractive and the most promising method in cancer, anti-bacterial and AIDS treatment [25].

Cancer is an abnormal growth of tissue or cells exhibiting uncontrolled division autonomously resulting in a progressive increase in the number of cell divisions [26]. It is a disease of the genes in the cells of our body. Cancer could be a major ill health with in the world because it causes significant sickness and death in worldwide [27] and there are increasing demands for anticancer therapy [28].In keeping with WHO report in 2018, there have been 18.1 million new cases and 9.5 million cancer-related deaths worldwide [29].

In 2040, quantity of latest cancer cases annually is going to be expected to rise to 29.5 million and therefore the number of cancer-related deaths to 16.4 million at 2040. In January 2019, there have been an estimated 16.9 million cancer survivors with in the United States. The quantity of cancer survivors is anticipated to extend 22.2 million by 2030[30]. The combat against cancer is problematic particularly with in the development of therapies for cruelly reproducing tumors. Chemotherapy is accessible for treatment of cancer but still it shows low specificity and is controlled by dose limiting toxicity. It is an effort to seek out the therapy and medicines for the treatments of various sorts of cancer. Therefore, conventional methods require the mix of controlled released technology and targeted drug delivery is more practical and fewer harmful. Nanomaterials are expected hopefully to revolutionize cancer diagnosis and therapy [31].

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Green chemistry is an emerging technology that promotes the implementation of a set of principles to reduce the utilization and generation of chemical hazardous wastes [32]. As a result of this, a green method reduces the industrial labor impact on the ecosystem. Through their development, scientists are providing possible solutions to costly process and hazardous materials encountered when using traditional physicochemical synthesis methods [33-36]. The employment of environment-friendly reagents and solvents, reducing high energy consumption methods, using non-toxic biomolecules, such as DNA, proteins, enzymes, carbohydrates as well as plant extracts, allow synthesizing biocompatible metallic NPs by reducing metal ions aqueous solutions [37, 38].

Application of Plant-Based Materials in Cancer Therapy

Among natural resources, plants, thanks to their huge variety with influential phytochemicals and therapeutic properties, have an important role in treating many ailments worldwide, including cancer [39]. In line with scientific records, over 80% of the world's population relies on plant-derived pharmaceuticals for health, and additionally, medicinal plants have played a critical role in extending lifetime [40,41].

In some plants, the therapeutic properties can relate to low-molecular-mass compounds called secondary metabolites. Terpenoids, alkaloids, and phenolics are the most groups of secondary metabolites [42,43]. Certain plant species can play an important role in blocking or activating transduction pathways in live cells by creating associated secondary metabolites with antimutagenic and cancer capabilities [44]. Certain plant-derived anticancer drugs contain vincristine [45], emodin [46], paclitaxel [47], kaempferol [48], linalool [49], colchicine [50], rutin [51], and quercetin [52]. Although the quantity of plant-derived anticancer compounds is vast, only some have reached clinical use after successfully navigating the lengthy, expensive, and bureaucratic path from identification to cancer therapy effectiveness [44]. In their publication, Iqbal et al. [53] extensively documented some important medicinal plants and their anti-carcinogenic phytochemicals against a selected form of cancer. Additionally, Ijaz et al. [54] explicitly listed the plant-derived anticancer compounds against numerous skin carcinoma cell lines. Figure 1 illustrates a schematic process for anticarcinogenic phytochemical synthesis, characterization, and potential applications as cancer treatment agents.

Even thoughsignificant therapeutic advantages, the effectiveness of natural products is compromised by their poor stability, low aqueous solubility, limited bioavailability, and short retention period; all of those factors restrict their therapeutic applicability [55,56].

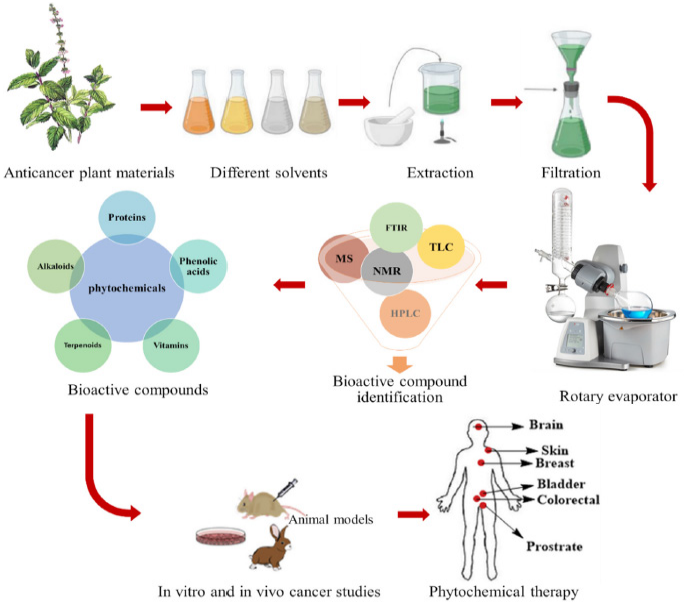

Figure 1: Schematic process of identification, characterization, and future application of herbal plants in cancer therapy [57].

Green Synthesis of AuNPs

Phytochemical compounds in plants, like proteins, organic acids (including fatty acids and phenolic acids), vitamins, carbohydrates, alkaloids, and secondary metabolites, function reducing, stabilizing, and capping agents for nitrate and chloride precursors during the green synthesis of MNPs [58,59]. Figure 2 schematically depicts the method of plant-mediated biosynthesis of MNPs.

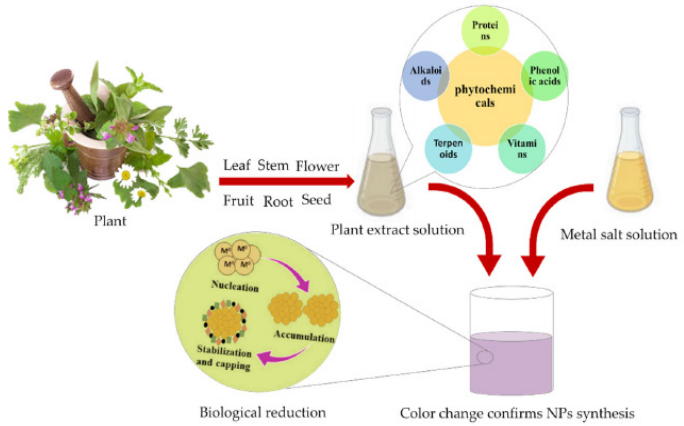

Figure 2: Schematic illustration of biosynthesis of metallic NPs from a plant [57].

Anticancer activity of green synthesized Gold Nanoparticles

Au-NPs possess excellent stability and biocompatibility, flexible shapes and sizes, easy-to-function surfaces, high drug loading capacity as well as low toxicity, providing benefits to develop a more effective, on-target cancer therapy [60].Au-NPs has been used to target the delivery of chemotherapy agents, to supplement the radiation and thermal therapy, and to increase the contrast in various types of cancer and diseased organs. Nanotechnology has focused on the synthesis of nanoparticles with improved antioxidant activities against various diseases, including cancer and Alzheimer's [61].

Significantly, Au-NPs have become versatile candidates used for cancer detection and therapy due to their futuristic physicochemical properties. But still, the use of toxic chemicals in developing Au-NPs is of great concern since it may create en-

vironmental issues. To combat with this, biological methods of fabricating Au-NPs are the much preferred choice. Hence, synthesis of Au-NPs using plants, seaweeds, and microbes are advantageous over physical and chemical methods. On this context, the phytocomponents present in the natural source contribute to added bio-compatibility and cytotoxicity by stabilizing the Au-NPs. There have been numerous studies stating on the anticancer properties of Au-NPs synthesized through biological approach. More studies about the comparative evaluation of Au-NPs against cancer and normal cells are needed for further extended research [62].

Au-NPs have been widely studied and applied in tumor treatment and diagnosis because of their special fundamental properties. In a series of biomedical applications of Au-NPs, its role in tumor diagnosis and treatment is particularly prominent. In order to make Au-NPs more suitable for tumor diagnosis and treatment, their natural properties should be systematically and intensely understood [63]. Anticancer activity of plant extract-mediated Au-NPs are the center of attraction and are considered as a novel therapeutic drug [64, 65].

*In this review we focused on eco-friendly green synthesized Au-NPs from the aerial parts of plant extract were characterized by UV-**V**is spectroscopy, X-ray diffraction (XRD), FTIR, GC-MS* Atomic force microscopy (AFM), *Transmission electron microscopy (TEM), Electron microscopy assay, Zeta potential analysis and particle size analysis, Energy dispersive X-ray spectroscopy (EDAX)and SEM microscopy methods.* Cytotoxicity test to examine the *anticancer activities of green synthesized Au-NPs were analyzed by MTT (microculturetetrazolium technique).*

The summary of anticancer activities of green synthesized Au-NPs against human cancer cell line were also critically reported in Table 1. As shown in Table 1 below, anticancer activities of green synthesized Au-NPs from aerial part extract of medicinal plants on different cancer cells indicates as a good promising candidate in synthesis for anticancer drugs for cancer therapy.

Table 1: Anticancer activities of green synthesized Au-NPs on cancer cells.

No	Plant used for Green synthesized AuNPs	Plant extract	Cancer cells	Anticancer activity	References
1	Cassava (*Manihotglazovii*)	Leaf extract	T47D	Very Good	[66]
2	*Lavanduladentata* L.	Aqueous extract	K-562	Excellent	[67]
3	*Marsdeniatenacissima*	Leaf extract	A549	Very good	[68]
4	ginger	Ginger extract	FTC-133	Excellent	[69]
5	green tea extract	Green tea extract	HepG2	Excellent	[70]
6	*Annonamuricata (Ramaphal fruit)*	Fruit extract	Hep2	Excellent	[71]
7	*Scutellariabarbata*	Leaf extract	PANC-1		[72]
8	*Agrimoniapilosa*	Aerial part	HaCaT, and AGS,	Good	[73]
9	*Oleaeuropaea(OE)* and *Acacia nilotica(AN)*	Mixture of OE fruit and AN husk extract.	MCF-7, TCT-116 and HCepG-2	Very good	[74]
10	*Azadirachtaindica*	Leaf extract	CHANG and HuH-7	Good	[75]
11	*Lotus leguminosae*	Aerial parts	MCF-7	Excellent	[76]
12	*Fragrans*	Isolated Fusariumsolani	MCF-7, HeLa and Human Embryonic Kidney cell	Very good	[77]
13	*Curcuma wenyujin*	Aerial parts	A498	Very good	[78]
14	*Abiesspectabilis*	Aerial parts	T24 cells	Good	[79]
15	*Solidago Canadensis*	Leaf extract	H4IIE-*luc* and HuTu-80 cells	Very good	[80]
16	*Breyniaretusa*	Leaf extract	HeLa	Excellent	[81]
17	*Shoreatumbuggaia*	Bark extract	SW579 cell lines.	Excellent	[82]
18	*Orchid plant*	Aerial part Extract	AMJ-13	strong anti-cancer	[83]
19	*Benincasahispida*	fresh peel (aqueous) extracts	HeLa cells	Excellent	[84]
20	***Brazilian Red Propolis (BRP)***	***BRP*** extracts	**T24 and PC-3 cells**	Very good	[85]

NB:T47D = breast cancer cells; SW579 =Thyroid cancer cell lines; K-562 = a myelogenous leukemia cell line; PANC-1 = Pancreatic cancer cell; HaCaT(Keratinocyte) = Normal cell, AGS, = cancer cell (adenocarcinoma); MCF-7= breast cell; TCT-116 = colon cell; HCepG-2 = hepatocellular carcinomacells; HuH-7= liver cancer cells; A498 = renal cancer cell; T24= bladder cancer cells.

As summarized in Table 1 above, anticancer activities of different aerial part of medicinal plant extract via green synthesized Au-NPs on cancer cells indicates as a good promising candidate in order to synthesize anticancer drugs for cancer therapy. The strong anticancer activity and selectivity towards cancer cells marks the product very potential candidate for development of cancer defensive and treating Nano drug.

Conclusions

Living organisms are one-cell or multicellular structures with typically 10 µm across for one cell, therefore the much smaller NPs (1–100 nm) can interact with cell surfaces. NPs or their active nano-complexes can penetrate and have the organism's external envelopes. The plasma membrane's permeability for small-sized Au-NPs allows for accumulation of them in internal compartments of cells.

Gold nanoparticles (Au-NPs) are well-known thanks to their wide spectrum of properties, activities and applications in diverse fields of researches are nowadays studied extensively. Green synthesized Au-NPs are more suitable for tumor diagnosis and treatment, their natural properties and therefore the interrelationships between green synthesized activities should be systematically and profoundly understood. In general, the green synthesized gold nanoparticles are promising candidate on cancer therapy.

Finally, overall, there's an important must explore the toxicological properties. The medicines derived from chemical compound show the drug resistance whereas metallic NPs don't have any such issues. There is no disinclination that these green synthesized NPs are the foremost promising and emerging within the field of applied therapeutics. In short, green synthesized Au-NPs showed anticancer potential. Further studies are needed to work out the precise mechanism behind the antimicrobial and anticancer activity at the molecular level.

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