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Green Synthesis of Gold Nanoparticles Using Plant Sources for Cancer Therapy: A Review.

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ABSTRACT

Nanotechnology is a rapid growing field and making a high impact in human life with increased application in biomedical field. In nanotechnology, the biosynthesis of nanoparticles using a plant extracts has an important application in medicinal field. Green synthesis of nanoparticles using biological method is very eco-friendly and economical method, when compared to the other chemical synthesis processes. Presently available literature reveals that nanoparticles are synthesized using various sources such as medicinal plants, marine plants and microorganisms. Different types of nanoparticles such as Iron oxide, Indium oxide, Palladium, Copper, Cadmium oxide, Calcium, Zinc oxide, Silver and gold nanoparticles are produced using various sources. Recently researchers are looking forward for the development of protocols for the synthesis of stable, reproducible and biocompatible Gold nanoparticles using cost-effective procedures for diagnostic and therapeutic applications. Cancer is a very common and world's second leading deathly disease which requires advance therapeutic strategies. The biosynthesized Gold nanoparticles will play a vital role in cancer therapy, which will reduce the side effects to the patients due to radiation and chemo therapy. The present study is an extensive review on the synthesis of Gold nanoparticles from various natural sources for cancer therapy.

Keywords: gold nanoparticles, plant extract, green synthesis, cancer therapy

Abbreviation: AuNPs- Gold nanoparticles

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INTRODUCTION

Nanotechnology is the application of science to control matter at the molecular level [1]. It is a rapidly growing field of science and technology with increased progress in biomedical applications which includes diagnostics, imaging, therapeutics and drug delivery [2]. The word "Nano" is a Greek term meaning small with a size of one billionth of a meter or 10^{-9}nm [3]. Nanomedicine has was arisen naturally from Ayurveda, which is a 5000 year-old system of Indian medicine. These ayurvedic medicinal systems use noble metals such as silver, gold, etc in nanoforms for various medical applications [4]. Nanoparticles are clusters of atoms in the range of 1-100 nm [5]. NPs are broadly divided into two such as organic and inorganic nanoparticles, among which organic nanoparticles include carbon nanoparticles whereas inorganic nanoparticles includes noble metal nanoparticles such as Silver and Gold nanoparticles, magnetic nanoparticles and semi-conductor nanoparticles such as zinc oxide and titanium oxide. Now a days, there is a growing interest in inorganic nanoparticles due to their superior material properties [6].

Nanoparticles are more biocompatible than other conventional therapeutics in biomedical, that are commonly exploited for drug encapsulation and delivery. Reduced size of these nanoparticles play an important role in improving the bioavailability and compatibility of these for therapeutical applications in diseases like cancer [7]. Cancer is the most common cause of mortality and it is the major public health problem in many parts of the world. Cancer is one of the unbeaten health challenges. It has caused several million deaths and according to the reported statistics, it is estimated that cancer will cause 13 million deaths in 2030 [8]. Worldwide, breast cancer is the second most cause of death among women [9]. Various types of cancers initially show response to chemotherapy but it will develop resistance in due course of time [10,11]. Cancer is one of the most intractable diseases because of its innate characteristics such as the ability to avoid apoptosis, metastasize and invade [12]. Various cancer treatments are chemotherapy, radiation therapy, surgery and immuno therapy. Chemotherapy is the process of using anti-tumour drugs to treat cancer. Different chemotherapeutic drugs are used to treat different types of cancers. Radiation therapy is the widely accepted way to treat cancer, but one demerit is, it could be sensitive to both cancer and normal cells [13]. Chemotherapeutic agents and chemo preventives used for cancer therapy will cause side effects such as anemia to the patients and is very expensive. In chemotherapy there are no sufficient clinically useful cytotoxic agents which is selective to a particular cancer cell. Most of the chemotherapeutic agents have anticancer activity with a capacity to elicit apoptosis [14]. The physiologically determined apoptosis, cell death and is necessary to maintain homeostasis, in this homeostasis which refers to the balance between cellular loss and cell proliferation. Various natural as well as synthetic agents which have demonstrated to elicit apoptosis in cancer cells, in these synthetic derivatives are found to have more active than parent compounds [15]. Surgery is also used to treat and diagnose the localized cancer. Immunotherapy is another treatment method which uses the hosts own immune system to fight against cancer. In order to overcome these drawbacks, it is important to find alternative drugs or therapies for cancer treatment [16].

Various metallic nanoparticles have a wide range of applications in various fields, among which Gold (Au) plays a very important role. Au nanoparticles are excellent nanomaterials which provide a powerful platform in biomedical applications of drug delivery, biosensing, biomolecular recognition and molecular imaging [17]. It is also used in analytical methods such as colorimetric techniques such as detector, as catalysts and sensors [18]. Different Gold nanoparticles have various advantages over other metal nanoparticles due to its non-cytotoxicity and biocompatibility. Gold nanoparticles are commonly capable of delivering large biomolecules without restricting themselves as carriers of only small molecular drugs [19]. AuNPs are also used in diagnosis of cancer cells and chemotherapy [20,21]. In the last few years, researchers realized the possible toxic levels of Gold nanoparticles due to the use of toxic chemicals in several processes for the production of nanoparticles in the form of stabilizing agents or reducing agents. This has initiated the new way of synthesis of metallic nanoparticles using natural sources. Now researchers are being targeted towards, "Green chemistry" for the synthesis of Nanoparticles [22]. The term green nanotechnology denotes the synthesis of various nanomaterials using biological sources [23].

Biosynthesis is more advantageous over other classical methods of synthesis due to its eco-friendly procedure and biological entities [24]. Recently biosynthesis of nanoparticles from plant source is reported successfully and this has potential applications in different areas such as diagnosis, treatment, commercial product manufacturing and development of surgical nanodevices [25]. The various biological sources used include bacteria, fungi or parts of plants such as fruits, leaves and flowers [26]. Nanoparticles synthesized using

microorganism makes the process difficult due to the issues related to handling and disposal. But these problems can be avoided by the use of plant extracts. It will also make the synthesis process more simple and facile. Green synthesis of nanoparticles by using plant extracts is very efficient, easy and eco-friendly when compared to microbial assisted synthesis methods [27]. Different parts of the plants such as fruit peels, fruit, root, callus and bark are studied for the synthesis of gold nanoparticles in different size and shapes [28]. The use of plants is gaining importance because of their versatile and unique constituents and its applicability in the field of medicine [29]. Gold is the most widely used nanoparticle for localization and treatment of cancer [30]. In recent works, the use of plants such as *Mangifera indica* [31], *Piper betle* [32], *Anacardium occidentale* [33] and *Citrus limon* [34] showed high efficiency in the synthesis of gold nanoparticles. Synthesis of various nanoparticles and its applications are gaining more importance in biomedicine [35]. These nanoparticles could be derived from various sources of solid, liquid and gas phases. They can be synthesised by using different methods like chemical, physical and biological. Several nanoparticles are synthesized using plant extracts, these plant sources contains secondary metabolites such as Phenolic acid, flavonoids, alkaloids and terpenoids. These compounds are helpful in the reduction of metal ions into metallic Nanoparticles [36]. The primary and secondary metabolites which are involved in the redox reaction are non-harmful and produce eco-friendly nanoparticles. Various reports states that biosynthesized nanoparticles control genotoxicity, apoptosis related changes and oxidative stress. These plant mediated biosynthesized nanoparticles will convert food waste and agriculture waste into useful by-products and energy [37].

Gold Nanoparticles for Cancer Therapy

Gold metal is termed as a symbol of power and wealth. AuNPs are considered to be a real jewel based on their significant growth of applications for sensing, delivery, heating and labelling properties, these shows their significance in life science and/or biology. Plant mediated biosynthesis of AuNPs is gaining importance due to the simplicity in synthesis procedures [38]. Gold nanoparticles were effective against viral and bacterial mediated diseases and used for treating various diseases like cancer, retinal neovascularisation and diabetics, etc [39]. Study on AuNPs are considered as an important field of research due to their major applications in biomedical science including tumour imaging, drug delivery, photo thermal therapy and immuno-chromatographic identifications of pathogens in clinical specimens [40].

Gold nanoparticles are synthesized by the reduction of $HAuCl_4$ by reducing agents in the presence of a stabilizer. AuNPs appear in ruby red colour due to a Surface Plasmon Resonance phenomenon which was first proposed by Mie by using Maxwell equation. This is due to the resonance of incoming light with the surface electrons of nanoparticles which reflects light at the visible spectrum of wavelength of around 520 nm. AuNPs of different shapes such as rod-like, spherical, oblong etc, can be synthesized [41]. Concentrations of reagents, temperature, pH, pressure, time of reaction are some of the important parameters which need to be controlled for the synthesis of gold nanoparticles. Elemental gold has many unique properties which have attracted and fascinated mankind since its discovery [42]. Being very unreactive, gold does not tarnish in the atmosphere and so keeps its attractive colour forever. The new field of nanotechnology made it possible to discover the unique properties of mater when subdivided to the nanoscale [43]. Gold at 25 nm manifests a number of interesting physico-chemical properties that have fascinated many disciplines of science including: material scientists, catalysts, biologists, surface and synthetic chemists and theoreticians in great number. Today, in the 21st century, gold chemistry is based on solid ground regarding the preparation and characterisation of a wide variety of fundamental compounds with gold atoms and gold clusters as core units [44].

Gold nanoparticles as drug carriers

Developing anticancer agent is to avoid side effects caused by conventional drugs and to improve the efficiency of drugs. Because in targeted drug delivery, drugs target the affected areas and deliver the drug which reduces the side effects caused by conventional drugs [45]. Recently this targeted drug delivery is the main area of interest for the scientists, and various works have been done to synthesize systems for targeted drug delivery such as nanoparticles, polymer gels, quantum dots, Fe_3O_4 and ZnO [46]. In this, gold nanoparticles have the ability of bio-imaging of affected cancerous cells for therapeutic use [47]. Gold nanoparticles have unique physical and chemical properties and have strong binding attraction for proteins, carboxylic acid, thiols and disulfides so they are used in the field of bioscience in drug delivery for cancer [48]. Two factors are used in drug delivery systems such as transport and drug release. In these drugs are loaded on

nanoparticles with the help of pro-drug, treated by cells and they have functional flexibility due to their monolayer so that they can provide an efficient system [49]. There is an increasing interest in modifying existing drugs to reduce non-specific side effects and allows higher dose delivery to target cells/tissues [50]. AuNPs may not simply acts as passive drug carriers but enhance therapeutic effects and influence drug-cell interaction [51].

Gold nanoparticles in thermal therapy

Thermal therapy is a very strong candidate in cancer treatment and therapy as it induces targeted heat destruction of tumour regions. In clinical therapy gold nanoparticles are selected because of their higher penetration in tissues and results in minimal damage [52]. This hyperthermia is known to induce apoptosis in many tissues and increase local control and survival in combination with chemotherapy and radiotherapy. In clinical trials, it is normally used in combination with other treatments which includes radiotherapy and can be delivering externally with heat generation by radiofrequency waves, ultrasound or microwaves [53]. Bio-nanoprobes are used with multiple functionalities in absorbing optical energy and convertion to heat with coupling optical lasers [54].

Gold nanoparticles as radiosensitisers

Gold nanoparticles which deliver drugs to tumor tissues can selectively enhance radiation therapy leading to increase tumor cell killing. Radiosensitisation is generally useful to increase photon absorption of high-Z elements and resulting large portion of primary ionizing photon energy to tumor cells/tissues [55]. Radiosensitization has phenomenological mechanisms by which sensitisation remains unclear. Gold nanoparticles radiosensitize to increase photoelectric photon absorption by high-Z materials at kilovoltage photon energies [56]. If sensitisation occurs by physical method, for clinical translation and optimisation of effect it would be beneficial to know the importance of gold nanoparticles concentration, size, surface coating and distance from target material such as DNA on gold nanoparticles mediated radiosensitisation [57].

Gold nanoparticles as contrast agents

The properties of gold nanoparticles which includes biocompatibility, size, ability to bind target agents and high atomic number (high-Z) means to have potential as contrast agents. Gold nanoparticles have the potential to improve contrast with structural imaging modalities which includes MRI and CT. It is possible that functionalised gold nanoparticles are used in the field of molecular imaging of cancer and expression of molecular markers [58]. Nanoparticles could be clearly imaged by structural imaging because they accumulate in kidney and bladder during renal excretion [59]. In vivo imaging using gold nanoparticles as contrast agents for biomedical imaging and electrochemical applications [60]. To improve the definitions of heavy vascularised tumours by increasing accuracy of tumour diagnosis, increasing photon absorption and definition in the radiotherapy planning, contrast material such as iodine is used [61].

Gold nanoparticles in clinical trials

Nanomedical research remains immature and their complete clinical impact is not fully known. AuNPs are able to traverse through the vasculature, be localized in targeted areas, and can be attached to single strands of DNA nandestructively [62] Various new nanomaterials are being developed for cancer therapy and there arises a need to translate these materials to clinical trials in a safe manner [63]. Nanotechnology Characterisation Laboratory was found to collaboration between three US federal organisations such as the US Food and Drug Administration, the National Cancer Institute and the National Institute of standards and Technology. It performs and standardizes the pre-clinical characterisation of nanocarriers intended for cancer therapy. This NCL could perform physiochemical in vivo and in vitro characterisation and tested over 180 nanocarriers to date [64].

Green Synthesis of Gold Nanoparticles

Gold nanoparticles have been investigated in diverse areas such as *in vitro* assays, *in vitro* and *in vivo* imaging, cancer therapy, and drug delivery. In order to be useful for cancer treatment, the AuNPs must be non-cytotoxic for normal cells. This biocompatibility of gold nanoparticles helps utilization in biomedical field.

Plant mediated synthesis of nanoparticles which are biologically synthesized have a wide range of applications because of their remarkable chemical and physical properties and have potential applications as optical receptors, catalysts and antimicrobials [65, 66].

Recent increasing awareness of green chemistry must be considered as the nontoxic and eco-friendly method. Integration of nanotechnology with green chemistry's principle is one of the key issues in nanoscience research [67]. The toxicity of gold nanoparticles depend on the shape, size, surface charge, synthesis method and functionalized molecules but its cytotoxicity is at an acceptable level and is considered to be non-toxic [68]. Many research articles reported that synthesis of AuNPs by plants such as *Gymnemasyl vestre* [69], *Cassia auriculata* [70], *Eletturia cardamomum* [71], *Allium sativum* [72]. Gold nanoparticles play a wide range of applications in nano-scale devices and technologies due to its resistance to surface oxidation and chemical inertness [73]

Green synthesis of nanoparticles using plant extract is an easy, eco-friendly and efficient method in comparison to chemical mediated synthesis method. Plant extracts acts as stabilizing agents and low-cost reducing agents [74]. Recently different types of nanoparticles are synthesized using various plant sources. Biosynthesis of monodispersed nanoparticles with specific shapes and sizes has challenge in bioscience and it has major advantages in pharmacological industry to cure different viral and bacterial diseases [75]. This eco-friendly synthesis of nanoparticles is considered as building blocks of these generations to control various diseases. Many reports related to this field states that biosynthesized nanoparticles will control oxidative stress, apoptosis related changes and genotoxicity [76].

For biosynthesis, the fundamental principle is reduction of metal ions to nanoparticles, various plants are reported for synthesis of silver, gold and other various metal nanoparticles. In this gold has received more attention when compared to other metal nanoparticles. Gold nanoparticles are biocompatible and have low toxicity, this makes them excellent carrier metal for sensors, drug delivery system, and diagnostic tools [77]. The principle is metal salts comprising of metal ions is first reduced to atoms by reducing agents. These obtained atoms nucleate in small clusters that grow into particles. In this process of green method, biomass or extracts of various plants act as reducing agents [78]. The involvements of protein like cofactors and enzymes which have redox potential play a key role in metal reduction [79].

Green synthesis is a non-toxic and environmental friendly method. Gold nanoparticles were synthesized using immersed aqueous solution of $HAuCl_4$ without using any reductant in one approach [80]. Another green synthesis approach was developed to synthesize gold nanoparticles by using high-power ultrasounds and sodium dehydrate [81]. A new approach for the synthesis of gold nanoparticles by using aqueous NaCl solution from the bulk gold substrate by natural chitosan without using reductant and external stabilizer [82].

Gold nanoparticles of size 15-80nm was synthesis by green synthetic route, in this method $HAuCl_4$ was reduced by using citrus fruit extracts [83]. *Terminalia arjuna* fruit was cleaned in running tap water and with distilled water. 10g of plant source was added with 100ml of double-distilled water and boiled at 50-60º C for 5min. It was then filtered using Whatman No.1filter paper. The filtrate was collected in 250ml flask and was stored at room temperature for further use. From this 1ml of *T. arjuna* extract was added to 100ml of 1mM $HAuCl_4$ solution at room temperature and reduction of AuNPs was clearly observed within 15mins [84]. For synthesis of AuNPs, a certain volume of plant extract was added to the $HAuCl_4.3H_2O$ solution and the volume was adjusted to 10 ml with de-ionized water. The final concentration of Au was 1.3×10^{-4} M. The reduction process of Au^{3+} to Au nanoparticles was followed by the change in the color of the solution from yellow to violet to dark pink and green depending on the plant extract concentration. The nanoparticles prepared at different $_P$H of the solutions were adjusted using 0.1N NaOH or 0.1N HCl solution [85]. Biosynthesis of AuNPs involved the mixing of chloroauric acid and *Z.officinale* extract in water. 1ml of this extract is added to 25ml of 1mM $HAuCl_4$aqueous solution and kept at boiling condition for 20mins. This formed nanoparticle was identified by visual colour change from light yellow to reddish wine colour. Bioreduction of $AuCl^{4-}$ ions in solution are monitored by using the UV-Vis spectra of the solution in the range of 400-800 nm [86].

For synthesis of AuNPs, 50 ml of 0.01M of $HAuCl_4$ was added into 25 ml of aqueous extract of grapes. Now this reaction mixture was shaken for thorough mixing and allowed to settle at room temperature. Colour change indicates the formation of AuNPs. Physical, chemical and biological properties of AuNPs strongly

depends on the methods of preparation. Due to high reactivity of gold nanoparticles, the aqueous solutions of AuNPs are not stable and undergo agglomeration rapidly. Therefore lyophilisation process was used to preserve these perishable materials [87].

Previous reports states that gold nanoparticles were successfully synthesized using *Z. officinale* extract as a novel stabilizing and reducing agent of gold salts. *Z. officinale* has many medicinal properties and function against rheumatism, diabetes and digestive disorders and its extract have antioxidant characteristics since it possesses hydroxyl radicals and superoxide anion scavenging property [38]. By using marine cyanobacterial cultures, intercellular synthesis of AuNPs was produced. Biosynthesis of AuNPs is the most eco-friendly and less expensive process. Gold nanoparticles synthesized have antitumor activity on cancer cell lines [88].

The cytotoxicity of various AuNPs synthesized from different sources have been listed in Table 1.

Table 1: Representing plant sources synthesis of nanoparticles and their activity in various cell lines

Plant	Nanoparticle	Size	Activity	Reference
Acalyphaindica Linn	Au	30nm	Cytotoxicity MDA-MB-231 breast cancer cell line	[87]
*Allium cepa*L.	Au	~100nm	Anti cancer activity MCF-7 cancer cell line	[88]
Aloe vera	Au	14- 74nm	Anti cancer activity in Hela cells	[89]
Azadirachtaindica A. Juss	Au	2-100nm	MCF-7 breast adenocarcinoma cell line	[90]
C. guianensis	Au	100nm	Anti cancer HL-60 cells	[91]
Cannabis indica	Au	32 nm	cell viability MDAMB-231 cells	[92]
Syzygiumaromaticum	Au	12 - 20 nm	Cytotoxicity and viability SUDHL-4 cell line	[93]
*Camellia sinensis*L.	Au	25nm	Viability MCF7 cells	[94]
*Justiciagendarussa*L.	Au	27 nm	Cytotoxicity human lung cancer A549 cells	[95]
Mirabilis jalapa L.	Au	100nm	Viability Human cerival cell line	[96]
*Terminalia catappa*L.	Au	10-35nm	Cytotoxicity in HeLa cell line	[97]
*Zingiberofficinale*Rosc.	Au	10nm	Anticancer activity Breast cancer ADR cell	[98]

Green Synthesized Gold Nanoparticles for Cancer Therapy

The general toxicity and interaction of gold nanopaticles synthesized from *Allium cepa* L plant extract with MCF-7 cancer cell line for *in vitro* anticancer studies the experiment is done by Parida. This study showed clearly that abundant gold Nanoparticles in the range of 100 nm in diameter. AuNPs cell viability results show that cytotoxic activity on MCF-7 cancer cell line was dose dependent manner. This indicates that high concentration of AuNPs will reflect low cell viability. Hence AuNPs effectively inhibits the growth of MCF-7 cancer cell line [89].

Camellia sinensis L plant extract was used to synthesis gold nanoparticles with biological entities to overcome such antagonistic effect. In this study the cytotoxicity assay was carried out with different concentrations of AuNPs against MCF-7 cell lines. The synthesized AuNPs was in the size range of 25 nm. It results a decrease in the percentage growth of cancer cells. The *in vitro* anti-cancer experimental study using *Camellia sinensis L* plant extact on MCF-7 cancer cell line was successfully proved by Boruah [94].

The Ankamwar discussed about the anti-cancer activity of *Terminalia catappa* L. Gold Nanoparticles were synthesised from the above plant extract which is in the range of 10–35 nm. The synthesized AuNPs

showed significant anti-cancer activity against HeLa cell line. From this study Ankamwar stated that the biologically synthesized AuNPs exerts more cytotoxicity than the chemistry- based ones [96].

The induction of apoptosis was induced in HL-60 cells by gold nanoparticles from *C. guianensis* plant extract. AuNPs synthesized by biological method and it is in the range of 100 nm. From this study the results shows that biosynthesized AuNPs induced a dose-dependent cell death in HL-60 cancer cell line and it might contribute to the cancer therapy. Chan *et al*., 2006 investigated the anti-cancer effect of AuNPs against *Aloe vera*. The average size of synthesized AuNPs is 14-74 nm in diameter. This study showed that AuNPs of *Aloe vera* exhibited moderate inhibition of HeLa cancer cell line in dose dependent manner. The percentage growth of HeLa cell line gradually decreased as the increased concentration of AuNPs. The cytotoxicity assay was carried out to show the anti-cancer effect of different concentrations of AuNPs against HeLa cell lines and results in the decreased percentage of growth [87].

CONCLUSION

Gold nanoparticles have major applications in the field of cancer diagnostics, catalysis, nanomedicine, therapeutics and biological sensors. Biosynthesis of AuNPs in nanotechnology field has increased its importance to create cost effective, eco-friendly, stable nanoparticles and their major applications in agriculture, medicine and other fields. From various previous studies it is known to be a safer and better process by using natural plants for synthesis nanoparticles. Thus the present review envisions the importance of plant mediated nanoparticles production by conferring the various literatures reported so far. The synthesis of AuNPs using natural plant extracts is an important aspect of nanotechnology and the applications of nanoparticles in various fields. Biosynthesis of AuNPs are not time consuming process when compared to other biological process. As we know that second leading cause of death in the world is cancer. The AuNPs play a key role in cancer treatment and serves as an economical process of drug delivery.

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