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RECENT TREND OF PLANT MEDIATED NANOPARTICLES IN CANCER TREATMENT: A REVIEW

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ABSTRACT

Cancer is one of the leading causes of deaths due to its great complex in nature. Conventional cancer treatments like surgery, radiotherapy or chemotherapy will damage the cancer cells and some healthy cells in the body. The development of an eco-friendly process is an important and emerging area in the field of nanotechnology. Green synthesis of nanoparticles is an easy, efficient and cost effective. This study has been promoted for further exploration of plant mediated nanoparticles for cancer therapy. The new approaches improve screening, diagnosis, and treatment of cancer and also contribute to the rising costs of healthcare. Further clinical trials are needed for proving the chemopreventive and therapeutic potential of nanoparticles and to check the adverse effects.

Key words: Cancer, Eco-friendly, Green synthesis, Nanoparticle, Nanotechnology, Therapy

INTRODUCTION

Cancer is one of the most serious fatal diseases in today's world that kills millions of people every year. It is one of the major health concerns of the 21st century which does not have any boundary and can affect any organ of people from any place [1]. More than 60 % of world's total new annual cases occur in Africa, Asia, and Central and South America. These regions account for 70 % of the world's cancer deaths. It is expected that annual cancer cases will rise from 14 million in 2012 to 22 million within the next two decades [2]. A variety of approaches are being practiced for the treatment of cancer each of which has some significant limitations and side effects [3]. When exploring new strategies for the treatment of cancer, one possibility is the use of nanomaterials. For more than 30 years, nanomaterials have been used as pharmaceutical carriers to enhance the *in vivo* antitumor efficacy of drugs. The first studies in the 1970s used nanoscale drug carriers, such as liposomes entrapping anti tumor pharmaceuticals [4]. Nanotechnology is a promising field of interdisciplinary research, since it opens up a wide array of opportunities in different fields including pharmacology, electronics, parasitology, and pest management [5]. Nanoparticles have received considerable attention in recent years due to their wide range of applications in the fields of diagnostics, biomarkers, cell labelling, antimicrobial agents, drug delivery, cancer therapy, and mosquito control [5, 6]. It involves different therapies based on alkylating agents, anti metabolites, biological agents, *etc.*; but one of the principal problems is the side effects due to difficulties in differentiating between cancerous and normal cells, which produces systemic toxicity [7]. Biological approaches using microorganisms and plants or plant extracts for metal nanoparticle synthesis have been suggested as valuable alternatives to chemical methods [8]. Green synthesis of nanoparticles is an easy, efficient and eco-friendly approach, where most researchers are looking at the eco-friendly and green synthesis of nanoparticles paves the way for the researchers around the world to explore the ability of various herbs in synthesizing nanoparticles. The use of plants for the preparation of nanoparticles could be more advantageous [9, 10] because it does not require elaborate processes such as intracellular synthesis and multiple purification steps or the maintenance of microbial cell cultures. Several plants and their parts have been successfully used for the extracellular synthesis of metal nanoparticles [11].

History of Cancer

Cancer is the second leading cause of death in the world after cardiovascular diseases. Half of men and one third of women in the United States will develop cancer during their lifetimes. Today, millions of cancer people extend their life due to early identification and treatment. Cancer is not a new disease and has afflicted people throughout the world. The word cancer came from a Greek words karkinos to describe carcinoma tumors by a physician Hippocrates (460–370 B.C), but he was not the first to discover this disease. Some of the earliest evidence of human bone cancer was found in mummies in ancient Egypt and in ancient manuscripts dates about 1600 B.C. The world's oldest recorded case of breast cancer hails from ancient Egypt in 1500 BC and it was recorded that there was no treatment for the cancer, only palliative treatment [12].

Cancer

Cancer is not a single disease. It is a group of more than 200 different diseases. Cancer can be generally described as an uncontrolled growth and spread of abnormal cells in the body. Cells are basic units of life. All organisms are classified as unicellular or multicellular cells. Multicellular cells divide to produce more cells only when the body needs them. Sometimes cells keep dividing and thus creating more cells even when they are not needed a mass of extra tissue forms. This mass of extra tissue is called a tumor. Tumors are found in all kinds of tissues, and can be benign or malignant. Cancer prevalence is on rise. According to the International Agency of Research for cancer (IARC), a 50% increase in cancer rate within the next 20 years is expected [13].

Treatment of Cancer

A variety of approaches are being practiced for the treatment of cancer each of which has some significant limitations and side effects [3]. Treatment includes surgical removal, chemotherapy, radiation, and hormone therapy. Chemotherapy, a very common treatment, delivers anticancer drugs systemically to patients for quenching the uncontrolled proliferation of cancerous cells [14]. Unfortunately, due to nonspecific targeting by anticancer agents, many side effects occur and poor drug delivery of those agents cannot bring out the desired outcome in most of the cases. Cancer drug development involves a very complex procedure which is associated with advanced polymer chemistry and electronic engineering. The main challenge of cancer therapeutics is to differentiate the cancerous cells and the normal body cells. That is why the main objective becomes engineering the drug in such a way as it can identify the cancer cells to diminish their growth and proliferation. Conventional chemotherapy fails to target the cancerous cells selectively without interacting with the normal body cells. Thus they cause serious side effects including organ damage resulting in impaired treatment with lower dose and ultimately low survival rates [15].

Nanotechnology in Cancer treatment

Nanotechnology is the science that usually deals with the size range from a few nanometers (nm) to several hundred nm, depending on their intended use [16]. It has been the area of interest over the last decade for developing precise drug delivery systems as it offers numerous benefits to overcome the limitations of conventional formulations [17, 18]. It is very promising both in cancer diagnosis and treatment since it can enter the tissues at molecular level. Cancer nanotechnology is being enthusiastically evaluated and implemented in cancer treatment indicating a major advance in detection, diagnosis, and treatment of the disease. Various researches are being carried out in order to discover more accurate nanotechnology based cancer treatment minimizing the side effects of the conventional ones [16]. Nanoparticles are now being designed to assist therapeutic agents to pass through biologic barriers, to mediate molecular interactions, and to identify molecular changes. They have larger surface area with modifiable optical, electronic, magnetic, and biologic properties compared to macroparticles. Current nanotechnology based drug delivery systems for cancer treatment, which are already marketed and under research and evaluation, include liposomes, polymeric micelles, dendrimers, nanospheres, nanocapsules, and nanotubes [19, 20]. Nanotechnology based formulations that have already been marketed are DOXIL (liposomal doxorubicin) and Abraxane (albumin bound paclitaxel) [21].

Metal oxide NPs in the treatment of cancer

Metals like Silver, Gold, Iron, Zinc and Copper have been routinely used for the synthesis of nanoparticles. Nanoparticles have received much attention recently due to their use in cancer therapy. Studies have shown that different metal oxide nanoparticles induce cytotoxicity in cancer cells, but not in normal cells. In some cases, such anticancer activity has been demonstrated to hold for the nanoparticle alone or in combination with different therapies, such as photocatalytic therapy or some anticancer drugs. Zinc oxide nanoparticles have been shown to have this activity alone or when loaded with an anticancer drug, such as doxorubicin. Other nanoparticles that show cytotoxic effects on cancer cells include cobalt oxide, iron oxide and copper oxide. The antitumor mechanism could work through the generation of reactive oxygen species or apoptosis and necrosis, among other possibilities [22].

Limitations

Metal nanoparticles are usually synthesized using various chemical methods such as chemical reduction, solvo-thermal reduction, electrochemical techniques [23, 24] and photochemical reaction in reverse micelles [25]. Among them, chemical reduction is the most frequently applied method. Previous studies showed that the use of a chemical reducing agent resulted in generation of larger particles and consume more energy. It was also reported that more side products were formed by chemical approaches which are not eco-friendly. Moreover, the chemically synthesized nanoparticles were reported to show less stability and more agglomeration [26]. Hence there is a need to develop an eco-friendly protocol that could produce stable and dispersible nanoparticles of controllable size by consuming less energy.

Green synthesis of nanoparticles

Indian greeneries are the chief and cheap source of medicinal plants and plant products. From centuries till date, these medicinal plants have been extensively utilized in Ayurveda. Recently, many such plants have been gaining importance due to their unique constituents and their versatile applicability in various developing fields of research and development [27]. Environmentally friendly synthesis methods are becoming more and more popular in chemistry and chemical technologies. This trend has several origins, including the need for greener methods counteracting the higher costs and higher energy requirements of physical and chemical processes. For this reason, scientists search for cheaper methods of synthesis. The other reason is that conventional methods for nanoparticle synthesis usually require harmful reductants such as sodium borohydride or hydrazine and many steps in the synthesis procedure including heat treatments, often producing hazardous by-products. In order to reduce the environmental impact of nanoparticle synthesis, greener routes have been investigated for over a decade. The principles of green chemistry were presented by Anastas and Warner who developed 12 principles that eloquently describe green chemistry [28]. Green chemistry should aim at thwarting waste, minimizing energy use, employing renewable materials, and applying methods that minimize risk. The three main concepts for the preparation of nanoparticles in a green synthesis approach are the choice of the solvent medium (preferably water), an environmentally friendly reducing agent, and a nontoxic material for the stabilization of the nanoparticles [29]. Many approaches were investigated, and microorganisms such as bacteria, yeasts, fungi, and algae were used in the biosynthesis of metal nanoparticles. More recently, the utilization of plants for the production of metal nanoparticles has spurred numerous investigations in the field of green synthesis. Nanobiotechnology is presently one of the most dynamic disciplines of research in contemporary material science whereby plants and different plant products are finding an imperative use in the synthesis of nanoparticles (NPs). One of the first approaches of using plants as a source for the synthesis of metallic nanoparticles was with alfalfa sprouts [30], which was the first report on the formation of silver nanoparticles (AgNPs) using a living plant system. Most of the NPs synthesized via green synthesis are investigated for investigated for biomedicine and more particularly as antibacterial agent.

Plant mediated Nanoparticles used in cancer treatment

The role of nanoparticles as an anti-cancer agent should open new doors in the field of medicine. The silver nanoparticles (AgNPs) synthesized from root extract of *Asparagus Racemosus* showed cytotoxicity on ovarian cancer cell line PA-1. The study confirms that the AgNPs have great promise as anticancer agent [31]. The study revealed that the activity of *Cassia tora* at three different doses (25, 50, and 75µg/mL) was dose-dependent; the 75µg/mL dose showed the highest activity against the colon cancer cell lines [32]. Gold nanoparticles (AgNPs) from *Abutilon indicum* leaf extract and their cytotoxic mechanism in colon cancer cells [33]. The in vitro anticancer effect of (*Sargassum glaucescens*) SG-stabilized AuNPs was determined on cervical (HeLa), liver (HepG2), breast (MDA-MB-231) and leukemia (CEM-ss) cell lines [34]. Aqueous dispersed gold nanoparticles (AuNPs) were successfully synthesized by green chemical and biological synthesis processes using citrus pectin, sodium alginate, chitosan and aqueous extract of fermented fenugreek powder by gamma radiation showed anticancerous activity [35]. AuNPs synthesized from *Antigonon leptopus* exhibit good anticancer activity against MCF-7 breast cancer cells at 257.8µg/mL [36]. *Areca catechu* nut have been used for the synthesis of gold nanoparticles showed cytotoxic effect on HeLa cell lines [37]. Anticancer activity of the *Tylophora indica* nanoparticles was also done in vitro and its IC50 dose was found out. The cell line used in this assay was a breast cancer cell line, MCF-7 [38]. Biofunctionalized silver nanoparticles (AgNPs) using the aqueous extract of *Cassia fistula* flower showed effective cytotoxic potential against MCF-7 and the inhibitory concentration (IC_{50}) was recorded at 7.19µg/mL [39]. The cytotoxic activity of biologically synthesized AgNPs from *Erythrina indica* on MCF-7 (breast cancer) cells and HepG2 (hepatocellular carcinoma) cells [40]. *Bambusa arundinacea* (Ba) and *Bambusa nutans* (Bn) determine the cytotoxicity effect of AgNPs on the PC3 cancer cell line and the Vero normal cell line [41]. AgNPs biosynthesized from *Premna serratifolia* leaves displayed significant anticancer activity in carbon tetrachloride-

(CCl_4-) induced liver cancer in Swiss albino (BALB/c) mice [42]. Silver nanoparticles were synthesised from different origin using plant extracts *Cucurbita maxima* (petals), *Moringa oleifera* (leaves) and *Acorus calamus* (rhizome) showed anticancer activity against epidermoid A431 carcinoma [43]. Satin leaf *(Chrysophyllum oliviforme)* extract mediated syntheses of silver nanoparticles have been screened for anticancer activities [44]. *Andrographis echioides* AgNPs inhibited proliferation of human breast adenocarcinoma cancer cell line MCF-7 [6]. *Potentilla fulgens* Wall. ex Hook showed cytotoxic activity against various cancer cell lines and 0.2 to 12µg/mL nanoparticles showed good toxicity. The IC_{50} value of nanoparticles was found to be 4.91 and 8.23µg/mL against MCF-7 and U-87 cell lines [45]. Biosynthesized silver nanoparticle from *Momordica charantia* leaves aqueous extract shows anticancer activity against Breast cancer cell line MCF-7 [46]. Silver nanoparticles synthesized using *Acalypha indica* L show only 40% cell inhibition against human breast cancer cells (MDA-MB-231) [47]. The MCF-7 cells lose their 50% viability at 5*µ*g/mL for the AgNPs produced by *Dendrophthoe falcata* [48]. Silver-(protein-lipid) nanoparticles prepared using seed extract of *Sterculia foetida* shows cellular DNA fragmentation against HeLa cancer cell lines [49]. *Datura inoxia*-AgNPs inhibited 50% proliferation of human breast cancer cell line MCF-7 at 20*µ*g/mL after 24 h incubation by suppressing its growth, arresting the cell cycle phases, and reducing DNA synthesis to induce apoptosis [50]. A silver nanoparticle of *Moringa oleifera* shows anticancer activity on human cervical carcinoma cells [51]. The biological synthesis of silver nanoparticles using *Melia dubia* nanoparticles showed remarkable cytotoxicity activity against KB cell line with evidence of high therapeutic index value [52]. The cytotoxic assays of *Chrysanthemum indicum*-AgNPs showed no toxicity toward 3T3 mouse embryo fibroblast cells at a concentration of 25*µ*g/mL [53]. Biosynthesis of gold nanoparticles using seed coat of *Cajanus Cajan* has been studied using liver cancer cells (HepG2) cells [54]. The characterized bio-functionalized *Gymnema Sylvestre* was tested for its in-vitro anticancer activity against human colon adenocarcinoma cell [55]. Green synthesised *Argemone mexicana* mediated gold nanoparticles showed dose-dependent cytotoxic and apoptotic effect in MCF-7 breast cancer cells [56]. The biosynthesis of copper oxide NPs (CONPs) from different plant extracts, such as that of *Ficus religiosa* or *Acalypha* *indica* [57, 58]. These NPs showed cytotoxic effects on A549 human lung cancer cells and MCF-7 breast cancer cells, respectively. The mechanism of cytotoxicity was demonstrated to be through the induction of apoptosis with enhanced ROS generation. The aqueous leaf extracts of *Morinda pubescens* showed the cytotoxic activity against HEpG2 cell lines and can be used as anticancer agents [59]. *Origanum vulgare* mediated biosynthesis of silver nanoparticles showed dose dependent response against human lung cancer A549 cell line [60]. *Ficus religiosa* derived AgNPs was effective at a dose 50μg/ml against the DAL induced mice model (30–35 g) [61], complete apoptosis (95%) was observed at 25μl/mL of *Alternanthera sessilis*-assisted AgNPs for prostate cancer cell (PC3), whereas 99% growth inhibition was obtained for breast cancer cells (MCF-7) [62]. *Albizia adianthifolia* leaf extract synthesized AgNPs showed 21% and 73% cell viability for A549 cells and 117 and 109% normal peripheral lymphocytes after 6 h exposure at 10μg/mL and 50μg/mL extract, respectively. This indicates that the AgNPs are nontoxic to the normal PLs cells [63]. The cytotoxic effects of AgNPs from the *Citrus reticulate* juice on B16/ F10 melanoma cell line [64]. The 50% cell inhibition of A549 cells was obtained at 43μg/mL of AA-AgNPs and induces cell death by the generation of ROS resulting in apoptosis [65]. The nuclear condensation, cell shrinkage, and fragmentation are noticed for MCF-7 cells treated with *Sesbania grandiflora* mediated AgNPs (20μg/mL) after 48 h in Hoechst staining. These changes indicate the activation of DNA repair due to the cleavage of the substrates [66]. The cell death (100%) of the HeLa cell line was observed with 100μg of AgNPs synthesized using the root of *Morinda citrifolia* [67]. Longer exposures to *Eucalyptus chapmaniana*-AgNPs (0.02mmol/mL) resulted in 85% cell death after 24 h incubation [68]. The viability (50%) of A375 cells was found at different concentrations of AgNPs synthesized using *Phytolacca decandra, Gelsemium sempervirens, Hydrastis canadensis*, and *Thuja occidentalis* [69]. AgNPs produced using extracts of *Aloe*, *Magnolia* leaves, and *Eucalyptus* leaves at concentrations 2–4 ppm were found to be no cytotoxic to Human Embryonic Kidney 293 cells [70]. Green synthesized AgNPs from methanolic extracts of *Vitex negundo* L. showed 50% inhibition of the cell viability of human colon cancer cell lines (HCT-15) when administered at 20μg/mL. The increased cytotoxic efficacy of AgNPs at increasing concentrations has also been reported in HeLa cell lines [71].

The viability of HL-60 cells decreased to 44% after 6 h treatment with the *Rosmarinus officinalis*-AgNPs at 2mM and cell death increased to 80% after 24 h incubation [72]. Cytotoxic activity was extremely sensitive to the size of the nanoparticles produced using *Iresine herbstii* leaf and the viability measurements decreased with increasing dosage (25-300μg/mL) against the HeLa cell line [73]. The piperidine, piperlongumine, and piperlonguminine present in *Piper longum* may be responsible for the synthesis of silver nanoparticles and exhibited a significant cytotoxic effect (94.02%) at 500μg/mL on HEp-2 cell lines [74]. AgNPs synthesized from *Annona squamosa* leaf extracts were also reported to possess potential cytotoxicity against breast cancer (MCF-7) cells [75]. *Cissus quadrangularis* and *Baliospermum montanum* nanoparticle were studied against Hep2 and Vero cell line [76, 77]. The stem latex of *Euphorbia nivulia* capped AgNPs solubilizes the AgNPs in water and acts as a biocompatible vehicle for the transport of nanosilver to human lung carcinoma (A549) cell lines [78]. *Aloe Vera*-conjugated AgNPs treated with Human Dermal Fibroblasts (HDF) cells [79].

Fungus

Chryseobacterium artocarpi CECT 8497 and *Pleurotus ostreatus* AgNPs were evaluated against cells (MCF-7) [80, 81]. *Schizophyllum commune*s, a mushroom fungus, were tested against Human Epidermoid Larynx Carcinoma (HEp-2) cell lines [82]. *Saccharomyces boulardii* silver nanoparticles shows anticancer activity on MCF-7 cells [83]. Photo-bio-synthesis of gold nanoparticles using edible mushroom *Pleurotus Florida* shows anticancer activity [84].

Sea weeds

A silver nanoparticle (AgNPs) was synthesized using *Saccharina japonica* extract and their cytotoxicity to cervical carcinoma cells was examined [85]. The bio functionalized polyshaped AuNPs synthesized with an aqueous macroalgae extract showed a satisfactory anticancer effect on the cell lines [86]. The aqueous extract of *Gelidiella Sp*. showed cytotoxic activity against Hep-2 (Human laryngeal) cell lines [87]. *Sargassum polycystum* was evaluated against (MCF-7) cell lines [88].

CONCLUSION

This review encompasses the various treatments of cancer and the effectiveness of nanoparticles acting as an excellent anticancerous tool. Cancer is a leading cause of death and it claims the lives of approximately seven million people worldwide. The research on plant assisted synthesis of nanoparticles is an emerging area in the field of cancer nanotechnology.

They can be easily synthesized by biological methods without much need of sophistication. This method is completely safe, economic viable, easy to scale up, less time consuming and environmental friendly. Thus it deserves urgent attention so that biogenically green synthesized nanoparticles will result in a significant payoff for the field of bionanomedicine. However, further investigations using animal studies and clinical trials are needed for proving the chemopreventive and therapeutic potential of nanoparticles and to check the adverse effects. There is still in need of further optimization and characterization and to elucidate the molecular mechanism involved in cell growth inhibition for full understanding of their whole potential, thereby permitting the employment of synthesized nanoparticles as cancer therapeutic agents.

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