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Therapeutic Uses of Green Synthesized Nanoparticles for Cancer

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Abstract-

Nanotechnology has emerged as a considerable tool for the development of nanomedicine to treat different type of life-threatening cancers with higher efficacy. The conventional treatments of cancer have many disadvantages and side effects. As an alternative to these conventional methods nanomaterials can be used. Nanoparticles have demonstrated great potential in diagnosis and therapy of cancer as these nanoparticles are eco-friendly, less toxic, biocompatible, cost-effective and useful in targeted drug delivery, detection of cancer biomarkers and bioimaging, even in early stages tumor can be visualized. However, to avoid the drawbacks related to their chemical and physical methods of synthesis, researchers have initiated the utilization of green or bio-synthesized nanoparticles. This review aims to summarize the uses of green synthesized nanoparticles for the management of cancer.

Keywords-

Cancer, Nanotechnology, Nanoparticles, Green synthesis, Green synthesized nanoparticles, Plant extracts, Cancer nanotherapy, Anticancer activity, Cytotoxicity, Apoptotic activity

Introduction-

Unhealthy diet, cigarette smoking, physical inactivity are major causes of developing tumor risk in the economically developing countries. Due to this reason, tumor load in the future is likely to be larger (Global Cancer Facts & Figures 3rd Edition, 2015). The most common approaches for cancer treatment

and management are surgery, chemotherapy, radiation therapy and hormone therapy (Vickers A, 2004). These conventional treatments of cancer lack specificity and selectivity which results in various side effects on the surrounding healthy tissues (in the case of surgery and radiotherapy) and on the whole organism (in the case of chemotherapy) (Villaverde G *et al*., 2019). The chemotherapeutic treatments have their intrinsic problems such as toxicity, for example a common chemotherapeutic agent, 5fluorouracil is known to cause myelotoxicity (Macdonald JS., 1999), cardiotoxicity (Rexroth G, 1994). Cyclophosphamid has been shown to have bladder toxicity in the form of hemorrhagic cystitis, immunosuppression, alopecia and at high doses cardiotoxicity (Fraiser LH *et al*., 1991). Therefore, to abstain these limitations of conventional cancer treatments such as drug toxicity, unpredictable side effects, drug resistance problems and lack of specificity, a need of a secure and non toxic theranostic approach were felt because it would helpful to the world if doctors could search out and destroy the very first cancer cells that would otherwise have caused a tumor to develop in the body (Ratan Z *et al*., 2020; Krukemeyer MG *et al*., 2015).

The non toxic natural therapies may reduce adverse side effects in contrast to conventional therapies. In several studies, many plant products have shown promising anticancer activities in treating cancers in humans (Avni G. Desai *et al*., 2008). There are four classes of plant-derived anticancer agents in the market, the vinca alkaloids (vinblastine, vincristine and vindesine), the epipodophyllotoxins (etoposide and teniposide), the taxanes (paclitaxel and docetaxel) and the camptothecin derivatives (camptotecin and irinotecan) (Avni G. Desai *et al.*, 2008). To increase the specificity and therapeutic efficacy of the natural therapy, nanotechnological modalities may prove to be better alternative for the management of cancer. In recent years, so much potential in relation to therapeutic and diagnostic application of nanomedicine is seen to improve cancer therapy through the development of engineered nanocarriers which are capable to deliver therapeutic agents particularly to tumoral cells without affecting or damaging the healthy tissue (Vickers A, 2004; Villaverde G *et al*., 2019). Nanomaterials such as nanoparticles have demonstrated great potential in cancer imaging and therapy but to avoid the drawbacks related to their chemical method of synthesis scientists and researchers have initiated the utilization of green or bio-synthesized NPs, because these are biocompatible and eco friendly molecules (Rajasekharreddy P *et al.*, 2014). Nanoparticles have high stability, high specificity, high drug carrying capacity, ability for controlled release, possibility to use in different route of administration and the capability to deliver both hydrophilic and hydrophobic drug molecules as a result enhance therapeutic efficacy of a particular drug. Therefore, nanoparticles have significant advantages over the conventional drug delivery (C.Karuppusamy *et al.*, 2017). Theranostic nanoparticles can be utilized to visualize and quantify the biodistribution and target site accumulation of nanoparticles, to monitor drug release, long-term drug efficacy, for the prediction of a potential treatment response and for the characterization of tumour angiogenesis. The nanoparticles can very precisely find diseased cells and carry the medicine to them, as a result, less dosage is sufficient and

thereby fewer side effects (Parva Nasimi P *et al*., 2013). Currently, one of the most attractive and challenging approaches is theranostics approach (the combination of therapy and diagnosis), which will be the personalized therapy for cancer treatment **(**Ratan Z *et al*., 2020).

Green synthesized nanoparticles-

For the synthesis of nanoparticles physical and chemical methods are not suitable for medical applications because of toxic substances absorbed onto the NPs surfaces and the synthesis methods must be cost-effective, due to this reason, environmentally sound and economically feasible methods are required (Kalishwaralal, K. *et al.,* 2008). Natural sources such as plant extracts, algae and a broad range of microorganism like bacteria, actinomycetes, fungi and yeast are used in green synthesis of nanoparticles (Priester *et al.,* 2014; Barabadi *et al.,* 2017; Honary *et al.,* 2015; Rahimi *et al.,* 2015; Salunke *et al.,* 2016; Ovais *et al.,* 2016; Mukherjee *et al.,* 2015; Patra *et al.,* 2014; Ovais *et al.,* 2017). Nanoparticles synthesized from plants add benefits of plant's medicinal property. In the green synthesis, usage of toxic chemicals can be replaced by biomolecules from plants which contain terpenoids, aldehydes, vitamins, alkoids, polysaccharides which act as reducing, capping and stabilizing agents for the formation of the desired nanoparticles (S. Shiva Samhitha *et al.,* 2021). During green synthesis, a metal salt is synthesized with plant extract and the process is completed in minutes to couple of hours at typical room temperature (Hussain I *et al.,* 2016). The reducing moieties on the nanoparticles assist them in high loading capacity of imaging probes, targeting ligands and therapeutic molecules (Patra, S *et al.,* 2015). There are several types of Nanoparticle tools with differint size, shape, compositions, and functionalities and each type can potentially be fabricated using different techniques (Edina C. Wang *et al.,* 2014). Some examples are Gold nanoparticles (AuNPs), Iron oxide nanoparticles (IONPs), Titanium oxide nanoparticles (TiO2NPs), Silver nanoparticles (Ag NPs), manganese oxide, copper, silica and magnetic iron oxide nanoparticles (MnO2NPs, CuNPs, SiNPs, Fe3O4 MNPs) (Karmous I *et al*., 2019).

Researcher has proved that green methods for nanoparticles synthesis have advantages of less chances of failure, low cost and ease of characterization, therefore these are more effective than traditional approach (Abdelghany TM *et al.,* 2018). Green synthesized nanoparticles are non–toxic, cheap and enviornmentally friendly, still some major hurdles are there to look upon in clinical trials such as biodegradability, dose and route of administration (Ravanshad, R. *et al.,* 2018). Applications of green synthesized nanoparticles are anti-cancer activity, magneticallly responsive drug delivery, photo-thermal therapy and bio-imaging (Hamed *et al.,* 2017). There are various researches and investigations which provides information about the green synthesized nanoparticles having potential and effective alternative for cancer theranostics. Some of the researches related to the green synthesized nanoparticles used against cancer are briefly discussed ahead.

Green synthesized nanoparticles against cancer-

Biosynthesized nanoparticles may act upon cancer cells to the cellular and intracellular levels. The physicochemical properties of nanoparticles permit their easy uptake into the cancerous cell and the interactions with its different components (nucleic acids, proteins, enzymes, lipids, membranes, and organelles) which causes the molecular and cellular modifications which may be either inhibitory (mainly of anticancer properties such as cell viability, tumor invasion, growth, proliferation, and progression) or stimulating (mainly of apoptotic pathway and cell death) (Piao MJ *et al.*, 2011). The nanoparticles based therapy provides efficient cellular uptake and selective cell targeting (Al-Otaibi AM *et al.,* 2022). Where targeting agents or ligands bind to the surface of tumor cells in such a way that triggers the receptor endocytosis that causes the delivery of the therapeutic agents to the interior of the cancer cells (Deura, 2008). For example, Green nanostructures produced using the electron rich phytochemicals including epigallocatechin gallate (EGCG) from tea, mangiferin (MGF) from mango and allied phytochemicals can be utilized as rendering tumor specificity due to their strong tumor cell receptor avidity to produce tumor specific molecular imaging and therapy agents (Thipe V *et al.*, 2022).

If we address the cancer therapy development, the major focus is to stop cancer cell proliferation by inducing apoptotic pathways i.e. intrinsic pathway and extrinsic pathway in cancer cells (Kumari R *et al.*, 2020). In various researches, green synthesized nanoparticles induced apoptotic activities in cancer cells, for example, the AgNPs-CEPA were prepared by reduction method using the aqueous extract of A. cepa, these AgNP CEPA were used to treat human colorectal cancer cell lines (HT-29 and SW620) and found to inhibit cell proliferation and alter Bcl2 family gene expression. Moreover, significant induction of apoptosis compared to A. cepa and AgNO3 which indicates that AgNP-CEPA induces apoptosis by inhibiting Bcl2 family gene expression, suggesting that this formula is a promising anticancer agent for treating colorectal cancer (Abdellatif A *et al*., 2022). In other study, *Cynara scolymus* were employed to synthesize AgNPs and it is found that these nanoparticles modulates mitochondrial apoptosis via generation of ROS, regulates the apoptotic proteins and cause MCF7 breast cancer cells death (Erdogan O *et al.,* 2019). There was another research, where dried and clean longan peel powder was used as the reducing and stabilizing agent for the synthesis of silver nanoparticles, these nanoparticles showed antitumor activity against lung cancer. Cytotoxicity and stimulation of apoptosis was observed on human lung cancer H1299 cells *in-vitro* by MTT and trypan blue assays. AgNPs significantly suppressed the H1299 tumor growth in a xenograft severe combined immunodeficient (SCID) mouse model. These results suggest that these nanoparticles may act as potential beneficial molecules in lung cancer chemoprevention and chemotherapy, especially for early-stage intervention (He Y *et al.*, 2016). Researchers have also reported in a study that selenium nanoparticles green-synthesized by apigenin (SeNPs-apigenin) were used to treat breast cancer. Various assays showed SeNPs-apigenin treatment can successfully limit MCF-7 cell proliferation and viability in a concentration-dependent manner and trigger

apoptosis *in-vitro*. This demonstrates that SeNPs-apigenin treatment could directly target Bcl-2, Bax, caspase-3 and results in the discharge of cytochrome C from mitochondria into the cytosol, accompanied by the initiation of cell death which leads to permanent DNA damage and killing of MCF-7 cells. In addition, treatment with SeNPs-apigenin increased reactive oxygen species production and oxidative stress in MCF-7 cells (Al-Otaibi AM *et al.,* 2022).

Silver nanoparticles (AgNPs) synthesized from biological methods showed significant inhibitory activities against the viability of certain cancerous cell lines, the bio-extracts collected from different plant parts (e.g., leaf, root, flower or fruit) were used as reducing agents. 23 plant extracts which were used for AgNPs preparation, many of these AgNPs were either toxic to the breast cancer cell line MCF-7 or inhibited its growth and inhibit the brain cancer cell line HNGC2 (Baharara J *et al.,* 2015)**.** Greenly synthesized AgNP produced using a bioactive fraction of *Pinus roxburghii* were reported to have cytotoxic activity against lungs and prostate cancer cells (Kumari R *et al.,* 2020). Biosynthesized AgNPs using phycocyanin reported having cytotoxic action against breast cancer cell line and Ehrlich ascites carcinoma bearing mice (IC50 − 27.79 ± 2.3 µg/mL) (El-Naggar NE *et al.,* 2017). Similarly, *Moringa oleifera* (Vasanth K *et al.,* 2014), *Tropaeolum majus* (Valsalam S *et al.,* 2018), *Punica granatum* (Sarkar S *et al.,* 2018), *Gloriosa superba* (Muthukrishnan S *et al.,* 2018), *Teucrium polium* (Hashmi F *et al.,* 2020) plant extracts used to synthesize AgNPs and reported to be cytotoxic against cancer cell lines and it was also reported the cytotoxic effect on HeLa cell lines by silver nanopaticles that were synthesized from *Morinda citrifolia* root extract (Suman TY *et al.,* 2013). Dose-dependent cytotoxicity against MDA-MB-231 cells was also observed by the AgNPs synthesized from microbial culture of *Bacillus funiculus* and it was done by the formation of oxidative stress that activates the caspase-3, showing a potential alternative agent for human breast cancer therapy (Gurunathan S *et al.,* 2013). Anticancer activity against Hepatocellular carcinoma (HCC) was also shown by AgNPs synthesized utilizing *Phyllanthus emblica* leaf extract (Singh D *et al.,* 2019). Anticancer property was observed against human epithelial (HeLa) cancer cell line and human breast cancer cell line MCF-7 by AgNPs that were synthesized from leaves extract of *Artemisia vulgaris* (Rasheed T *et al.,* 2017) and they showed cytotoxic activity against lung cancer A549 cells (Gengan RM *et al.,* 2013), breast cancer MCF-7 cells, cervical cancer HeLa cells (Jeyaraj M *et al.,* 2013), colon cancer HT29 cells (Sanpui P *et al.,* 2011) and Dalton's lymphoma ascites tumor (Sriram MI *et al.,* 2010). In other studies, Banana leaf mediated AgNPs exhibited anticancer potential against A549 and MCF7 cell lines (Raghavendra N *et al.,* 2021), *Mangifera indica* seed mediated AgNPs against Hela and MCF7 (Donga S *et al.,* 2021), AgNPs synthesized by *Heliotropium bacciferum* showed anticancer potential against HCT-116 (Mohd S H K *et al.,* 2021) and AgNPs produced using *Zingiber officinale* displayed anticancer potential against AsPC-1, PANC-1 and MIA PaCa-2 cell line (Wang Y *et al.,* 2021). AgNPs synthesized using *Cissus quadrangularis* exhibited anticancer effect against the human liver cancer cell line HepG2 (Sankar, R *et al.,* 2013). The biosynthesized crystalline

AgNPs of 30-70 nm in size synthesized using plant extracts of *Cucurbita maxima*, *Moringa oleifera* and *Acorus calamus* showed pronounced anticancer effect against A431 skin cancer cell line (Nayak *et al.*, 2015) and the AgNPs synthesized from leaf extract of *Coriandrum sativum* showed significant *in vitro* anti breast cancer efficacy against human breast adenocarcinoma (MCF-7) cell line with an IC50 value of 30.5 µg/mL (Sathishkumar P *et al*., 2016). In another study, it was reported that the AgNPs synthesized using fruits, leaves, seeds and root extract of *Citrullus colosynthis* exhibited anti-cancer activity against four different human cancer cell lines such as HepG2, MCF-7 (breast carcinomas), Caco-2 and HCT-116 (colon carcinomas) (Leela A *et al.,* 2008). Spherical AgNPs synthesized using aqueous leaf extract of *Abutilon indicum* were found to exhibit a dose dependent antiproliferative effect against COLO 205 (human colon cancer) cells with a half maximal inhibitory concentration (IC50) value of 3 and 4µg/mL and 48 h of exposure (Mata R *et al.,* 2015).

In other study aqueous peel extract of *Musa paradisiacal* were used to synthesized crystalline AuNPs with particle size ranging within 50 nm demonstrated significant cytotoxicity effect towards human A549 lung cancer cells at a concentrations of 100µg/mL (Vijayakumar S *et al.,* 2017). Aqueous and ethanolic extract of *Taxus baccata* synthesized nanostructure AuNPs showed anticancer activity on cell lines, such as Caov-4, MCF-7 and HeLa which was observed in MTT assay. In addition, an *in vitro* experiment on cell exposure to *T. baccata*-mediated AuNPs confirms the caspase-independent death program as an anti-cancer mechanism with increased efficacy for cancer therapy (Kajani AA *et al.,* 2016). Priya and Iyer reported that green synthesized AuNPs synthesized from plants (*Camellia sinensis, Coriandrum sativum, Mentha arvensis, Phyllanthus amarus, Artabotrys hexapetalus, Mimusops elengi, Syzygium aromaticum*) showed anticancer activity against the human breast cancer cell line, i.e., MCF7 (MR Kamala Priya *et al.*, 2015). Moreover, biosynthesized gold nanoparticles produced using an aqueous extract of the *Dysosma pleiantha* rhizome has antimetastatic potential by interfering with the microtubule polymerization in the human fibrosarcoma cell line HT-1080 (Karuppaiya P *et al.,* 2013). Similarly, leaf extracts of *Mentha piperita* generated AuNPs were tested against MDA-MB-231, A549 and normal 3T3-L1 cell lines *in vitro*, these AuNPs showed significant anticancer activities in vitro (Ahmad N *et al*., 2017). Also, in the extracts of blackberry, blueberry, turmeric and pomegranate different antioxidant constituents were found, the pomegranate have the ability to produce more uniform size and shape NPs of Au and Ag in the range of 20–500 nm. These NPs could be used for the management of cancer and the antioxidant therapy (Nadagouda MN *et al*., 2008). Gold nanoparticles synthesized using *C. wenyujin* and assessed its potency against *in vitro* renal cancer cells. CWAuNPs exhibited cytotoxicity against renal cancer cell lines A498 and SW-156 which was assessed with MTT assay. Apoptosis by CWAuNPs in A498 cell was measured using apoptotic staining DAPI, Rhodamine 123, and H2DCFDA and further confirmed with flow cytometric analysis and the molecular mechanism was analyzed with qPCR and immunoblotting analysis of caspases, proapoptotic and antiapoptotic proteins (Liu R *et al.,* 2019).

Likewise, green synthesized titanium nanoparticles (TiO_2-NP's), synthesized using various plant extracts, fungi and bacteria shown to have anticancer activities (S. Shiva Samhitha *et al.,* 2021) and the green synthesized Cr_2O_3 nanoparticles were produced using a leaf extract of *Abutilon indicum* (L.) Sweet as a reducing and capping agent which exhibited significant anticancer and antioxidant activities against MCF-7 cancerous cells compared to chemically synthesized Cr_2O_3 nanoparticles (Khan SA *et al.,* 2021). In other research, highly stable and spherical copper oxide nanoparticles (26-30 nm) were synthesized using extracts of *Acalypha indica* which showed powerful anticancer activity in the MCF-7 breast cancer cell line (Sivaraj R *et al.,* 2014) and CuNPs synthesized using *Ficus religiosa* leaf extract exhibited anticancer effects via ROS-mediated apoptotic mechanism involving the disruption of mitochondrial membrane potential in A549 cells (Sankar *et al.,* 2014). Green synthesis of platinum NPs was done utilizing tea polyphenols, these platinum NPs were capable of inducing cell death in human cervical cancer cells by arresting the G2/Mphase of cell cycle (Alshatwi AA *et al.,* 2015).

Till now, we have discussed anticancer activity of different green synthesized nanoparticles but killing of tumor is not difficult, it is important to save the normal cells during the radiotherapy. For this reason, radio protective agents are combined with radiotherapy that differentially protect the normal cells and kill the tumor cell. Some chemicals have been reported that can modify the radiation response when given before exposure (Kumar sd *et al.,* 2003), for example, **t**hiol synthetic compounds e.g., Amifostine, approved as a radioprotector by the Food and Drug Administration (FDA, USA) but for limited clinical indications and not for nonclinical uses (Obrador E *et al.,* 2020). Since, the nanoparticles are known to possess excellent radio-protective potential and are capable to modulate the radiation induced effects on the body so these can be used as a radioprotector too. It was reported in a study that AgNPs synthesized from root extract of *Chlorophytum borivillianum* (CB-AgNPs) have the potential to mitigate the oxidative stress in testis of Swiss albino mice produced due to 6 Gy dose of gamma radiation (Vyas R *et al.,* 2020). Thus, the green synthesized nanoparticles can be used as theranostic agent, have potential to be beneficial in cancer diagnosis, therapy and ultimately improve the anticancer therapy in a less or non-toxic way (Rajasekharreddy P *et al.,* 2017).

Limitations of using nanoparticles in biomedical applications-

The biggest challenge in nanotechnology based cancer diagnosis is reliability, nonspecific binding of nanoparticles probes, aggregation and unfit detection conditions can affect nanoparticles-based detection signals (Yang–Wei Lin *et al.,* 2011). Other challenge is to develop nanoparticles based devices having high sensitivity with easy handling and cost-efficiency (Ye Zhang *et al.,* 2019). In the use of nanoparticles, for example, silver nanoparticles as therapeutic agents there are some basic hindrances in terms of toxicity. To overcome these drawbacks and for use in preclinical trials on humans or any other living being these nanoparticles should be biocompatible , non-toxic and free from side effects (Ratan Z

et al., 2020). There are many challenges to overcome in routine clinical practice too (Hamed Barabadi *et al.,* 2017). One more limitation is the protein corona effect, i.e. adsorption of proteins on the colloidal NPs' surfaces when the nanoparticle enters the biological system (Del Pino P *et al.,* 2014).

Conclusion and future perspectives-

In conclusion, the green synthesized nanoparticles can overcome the downside of conventional methods used in diagnosis and treatment of different type of cancers due to their biocompatibility, pronounced anticancer therapeutic and diagnostic efficacy. Use of nanoparticles particularly green synthesized nanoparticles are going to help in the treatment of several types of cancers that do not have cures today and this will increase the survival rate and health standards of cancer patients. It is anticipated that green synthesized nanoparticles will be used as therapeutic and diagnostic agents for cancer as well as other diseases in the near future predominantly. However, more research on this is needed to confirm the effective and safe utilization in clinical translation. In addition, the mass-scale production of cost-effective biosynthesized nanoparticles is required to achieve this.

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