Plant Archives Volume 20 No. 2, 2020 pp. 3615-3626 **e-ISSN:2581-6063 (online), ISSN:0972-5210**

RECENT ADVANCES IN THE IMPLEMENTATION OF GREEN SYNTHESIZED BIOACTIVE METAL NANOPARTICLES AGAINST HUMAN CANCER

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Abstract

Nanoparticles (NPs) have gained profound interest not only in the field of crop improvement but also in the area of developing new alternative and more efficacious treatment strategies for cancer theranostic facilities *i.e.* in cure of cancer and inflammations as combinational therapy. These materials are the chemically and biologically active nano-compounds of a size ranging from 1-100 nm. In this chain, three strategies have been discovered yet to synthesize NPs, *i.e.* physical, chemical and biological (green NPs) methods. Synthesis and implementation of nanoparticles as an anticancer agent is a rapidly growing area in medical science. Its applications in the field of biomedicine are increasing at a tremendous rate. Unfortunately, chemical methods of NPs synthesis involve toxic reducing agents. Thus, there is an urgent requirement for the development of an eco-friendly and reliable technique that utilizes phytochemicals as bioreductants for the synthesis and fabrication of metallic NPs. The green synthesis of bioactive NPs from various parts of the plants, fungal and microbial sources has now a day's an emerging area of research due to their eco-friendly, energy-efficient, simple, low-cost, quick, safer and non- toxic behavior. Interestingly, NPs also play a key role as a tool in the diagnosis of the malignant nature of cells at the initial stage of its development. The active bioreductants found in some plant extracts are known to exhibit potential anti-cancerous activity. The main perspective of this review is to reflect the current availed study on green synthesis of metallic nanomaterials and its therapeutic role in the cure of life-threatening disease cancer, which is one of the deadly diseases. Mostly, cancer is treated by conventional chemotherapeutic agents, which have numerous side effects. In contrast to this, green synthesized metal nanoparticles from different origins have proved to work against various cancer cell lines effectively with little or no toxicity issues in the normal cell line. Targeted drug delivery seems to be easy by the application of these particles. This review provides totally new perspective on the emerging application of anti-malignant green synthesized active bionanomaterials with special attention on their present and future scenario in the diagnosis and treatment of cancer.

***Key words**:* Green nanoparticles, Cancer, Apoptosis, Caspase

Introduction

Cancer, a non-infectious life-threatening ailment leads to a large number of deaths around the whole world, and its burden still continues to grow globally thereby exerting tremendous pressure on communities and health systems. According to the report of WHO, 2020, the annual cancer patients are continuously rising as about 18.1 million people around the world had cancer in 2018, which will nearly double in 2040. WHO also reported that in 2020, one in five people globally will face a cancer diagnosis during their lifetime. Thus, the development of potent and effective diagnostic tools along with antineoplastic drugs will be one of the most persuasive goals in the near future.

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The initiation of cancer refers to out-of-control cell division that invades other tissues because of aggregation of defects, or mutations, in their genetic material. Cancer occurs when these mutated cells flourish continuously, divide, and spread abnormally. In these conditions, cells normally lose their apoptotic property and now these cells are known as malignant cells and this behavior is referred as malignancy. Malignancy is a gathering of illnesses, producing different neurotic and metabolic changes in cell systematics. Malignant behavior of the cells ultimately leads to cancer; a life threatening ailment which may result in life cessation if not cured timely (Gao *et al.*, 2013). It occurs through wide signaling cascades which mainly includes angiogenesis, cell expansion, and metastasis (Mann *et al.*, 2004 and Seigneuric *et al.*, 2010). Malignant cells harbor strange metabolic behaviors in aerobic conversion of glucose to pyruvate, which ultimately results in changes in whole respiratory pathway and this in gene expression also.

Due to the enhanced rate of exposure to harmful radiations and carcinogenic substances, the cases of cancer seem to increase at an-alarming level, every year. According to the report of WHO, more than 14 million patients were diagnosed by cancer (McGuire, 2015). These alarming reports are awaking us about the pace of grimness and mortality because of cancer. Thus, deep concern is needed towards the improvement of medication against irresistible illness of human beings, especially for tumors (Rai *et al.*, 2012), which is only possible by the discovery of potent antineoplastic drugs.

From ancient time till now, we are focused on discovering medicines and drugs against diseases caused by microbes, radiations, toxic chemicals and other environmental ablations in nature. Cancer is one of the hot topics of discussion in the area of research and medical sciences and thus, there has been a huge increment in information on oncogenesis and the advancement of new therapeutics. In this manner, there is a requirement of facilities for the advancement of modest, financially savvy, environmentally benign, and less toxic strategies to control such fatal conditions by simple, quick, and eco-accommodating processes (Wang *et al.,* 2014). Synthetic medicines for malignancy are constrained at various stages and accessible treatments have an unfavorable impact and influence typical cell capacities while giving overabundance medication and radiation exposures (Rothwell *et al.*, 2010 and Wu *et al.*, 2011). In this manner, the advancement of powerful and viable antineoplastic medications is one of the most convinced objectives. The present treatments which display properties to potentially dwindle the development of malignant cell growth or tumors additionally can instigate a serious reaction in the patient diminishing life quality (Rajeswaran *et al.*, 2008. Although, different therapies to reduce malignant growth like chemotherapy, radiotherapy and other medical procedures are available which harms the disease cells, at the same time may have some adverse effects on normal cells in the body also. These medications are extreme and costly and have many side effects like bone marrow issues, male pattern baldness, sickness and emesis. Their improvement of novel and productive anticancer medications which likewise ought to defeat restriction has become a vital issue (Sreekanth *et al.*, 2015). Exploitation of non-anthropogenic; natural entities has been proved to be utmost successful by many scientific approaches to identify novel hits and leads (Newmann *et al.*, 2012).

Nanotechnology: A boon to the man kind

Recent advances in the field of nanosciences and nanotechnology prompt the improvement of various non-organic and natural nanomaterials in conjugation with NPs, which are gaining different utilizations in numerous areas like hardware, medication, material ventures, pharmaceuticals, therapeutics and in nourishment bundling (Surendiran *et al.,* 2009; Duncan 2011; Bhattacharya *et al.*, 2012; Cohen-Karni *et al.*, 2012; Tauran *et al.*, 2013 and Teli and Sheik 2013). Nanomaterials, especially metal nanoparticles, extending from 1-100 nm have distinctive special properties like physicochemical, electrical, optical, and most significant natural as that of their mass metal. Different types of nanoparticles are center shell NPs, inorganic NPs, photochromic polymer NPs and polymer-covered magnetite NPs. Among metallic NPs, the principal ones are AgNPs, AuNPs, CuNPs, NiNPs, PtNPs, PdNPs and SiNPs while others are metal oxide and metal dioxide NPs, for example, CeO_2NPs, CuONPs, FeONPs, MgONPs, TiO_2NPs, ZnONPs, and ZrO_2NPs. Every one of these has a selective arrangement of qualities and applications, and can be blended by either regular or capricious techniques.

Nobel bioactive metal nanoparticles have recently gained utmost interest in medical community due to their engrossing uses in the area of biology and medicine. These bioactive tiny materials specifically have attracted a large attention because of their unique properties such as unusual physiochemical nature and numerous biological properties like antiangiogenesis, antibacterial, anti-inflammatory, antifungal, antiviral and anticancer activities. Broad investigations on the metallic nanoparticles have demonstrated their antimicrobial, antioxidant, and anticancerous potentials. Among all synthesized NPs, AgNPs and AuNPs are more tested against cancer because of their self-potential as an anti-cancerous agent. Besides, the genotoxicity of metal nanoparticles like silver nanoparticles (AgNPs), it is upheld by the formation of double stranded DNA breaks along with fluctuations in chromosomal properties that drives the commencement and execution of apoptotis (Jiang *et al.*, 2013 and Souza *et al.*, 2016). This acting system suggests that AgNPs can be commonly connected with a huge quantity of DNA-targeting antimalignant medications.

People of 16th century are known to utilize mind blowing gold capped materials for some reasons including the medicinal field (Panyala *et al*., 2009). It was affirmed that they utilized materials covered with gold particles for oral drugs, pharmaceuticals, and tissue and organs implantation. Gold nanoparticles (AuNPs) are increasingly huge in explore field inferable from their safe impacts, self-gathered nature, and improved medication conveyance. These particles are accounted for to adjust the P- glycoprotein (Pgp) action and in this manner improve the chemotherapeutic adequacy against multi-sedate resistant malignant cells (Kovács *et al*., 2016).

Strategies for the fabrication of metallic nanoparticles

Distinctive "bottom- up" and "top- down" strategies, involving physical, chemical, and biological approaches are utilized for the production and extraction of nanoparticles. A very common technique, applied for amalgamation and fabrication of NPs is the chemical reduction of metal salts by utilizing chemical entities, for example, 2-mercaptobenzimidazole, N, N-dimethyl formamide, sodium borohydride, sodium citrate, sodium dodecyl sulfate, sodium hydroxide and trisodium citrates (Zhang *et al*., 2010 and Venugopal *et al*., 2017). The physical strategies utilized are laser removal, microwave-assisted, photochemical reduction, sono-compound deposition, UV photograph reduction, gamma beam and sun oriented illumination, thermal disintegration inorganic solvents, molecular beam epitaxy, and so on (Venugopal *et al*., 2014). However, nonstop and unarranged utilization of the above strategies produces undesirable impacts on human wellbeing and the earth attributable to their risky nature and generation of poisonous side-effects. In this way, straightforward, fast, non- poisonous and eco-agreeable strategies by utilizing natural entities like bacteria, yeast, herbal growth, and plants are the options for amalgamation of NPs. The whole process starts with a simple blending of an aqueous plant extract with metal salt solution where the plant metabolites and bioactive materials act as a reducing as well as stabilizing agent Fig. 1. A few natural moieties, for example, microorganisms, green growth, and parasites have also been investigated for amalgamation of NPs (Chaloupka *et al*., 2010).

Plant extracts and herbal removes have demonstrated to be actively participating agents in the reduction of metal ions and their compounds to metallic nanoparticles. They have an indispensable job in nanotechnology as biomedicine in light of their low volume to surface ratio and their bioconjugation with biomolecules.

Ascendancy of using plants for the fabrication of NPs

Plants are usually referred to as "production lines of bionanoparticles". The restorative plants and the plant-based reductants are acknowledged among the worldwide population and furthermore, plant-based compounds have had a beneficial outcome on the wellbeing of the human being. It is assessed that more than 60% of anticancer medications all over the world, which is at present utilized for malignant growth treatment are detached from therapeutic plants. Many research works have been done and still going on, applying the "bottom- up" approaches like pyrolysis, vapor deposition, condensation of atoms and many other processes for the synthesis of NPs Fig. 2. Besides these approaches, green synthesis of NPs by extracts of fungi, algae, microbes and plants are fast-growing areas of the research.

Production of NPs by utilizing plant extracts have many benefits over other bio-organisms because- (i) there are many reports which confirm that plants not only reduce but also stabilize the metallic NPs (Singh *et al*., 2018), (ii) bioactive molecules of many medicinal plants which are involved directly or indirectly during the synthesis of NPs, may act as potent drug for human diseases, (iii) the utilization of plants for the union of the NPs wipes out the long procedure of keeping up cell culture and (iv) this technique is simple for huge scale, quick and relatively cheap combination with the improved solidness of the NPs (Bankar, 2010; Chaloupka *et al.,*

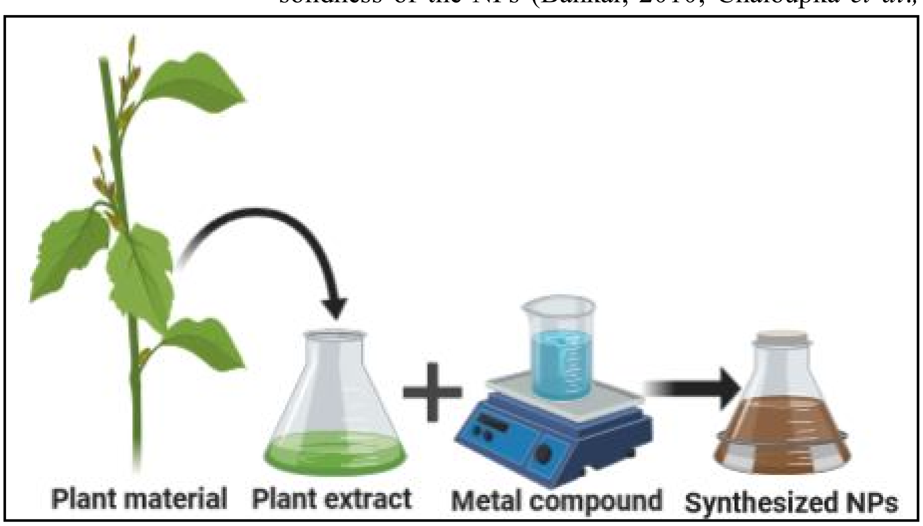

Fig. 1: Common mechanism of green nanoparticle (green NPs) synthesis by plants.

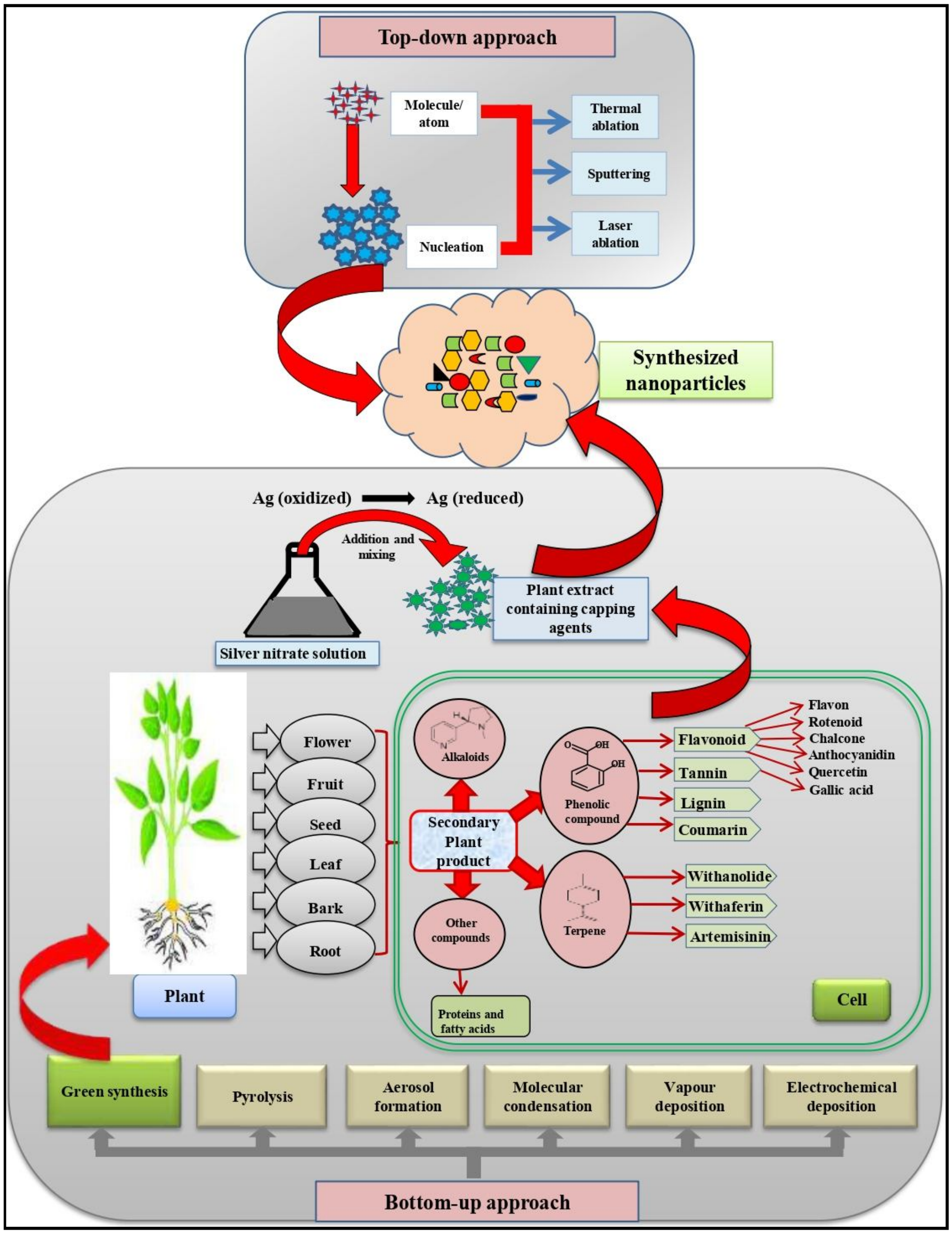

Fig. 2: Holistic approach of synthesis of green nanoparticle (green NPs); involvement of plant secondary metabolites in amalgamation of green NPs.

2010 and Zhang *et al.,* 2010). The procedure includes the basic blending of a watery plant extract with a fluid oxidizing agent (generally oxides and nitrates of metals) where the plant extract works as a reducing specialist in the synthesized nanoparticles (Gardea-Torresdey *et al*., 2003; Kumar *et al*., 2010 and Venugopal *et al*., 2017). Besides, the NP synthesis doesn't include harmful synthetics, solvents, and perilous side-effects, prescribing it reasonable to implement in pharmaceutical and biomedical applications (Kim *et al*., 2014).

Plant based NPs have been contemplated with many herbal extracts and indicated as cancer prevention agents (Patra *et al*., 2016; Zhang *et al*., 2016 and Patil *et al*., 2017). These nanomaterials additionally have several advances in various areas, for example, channels, hyperthermia of tumors, nano- composites, restorative imaging, and sedate conveyance (Tan *et al*., 2008). There are a very vast range of significant uses for metallic NPs in medication and drug stores. AuNPs and AgNPs are the well tested nanomaterials which are utilized in theronostics and in other interdisciplinary field of biotechnology. These can be utilized as artifacts for the organic screening evaliations. After cell take-up, they can go about as exact locations to slaughter malignant growth (Salata, 2004 and Sayeed *et al*., 2006). Moreover, AuNPs are fit for initiating apoptosis in B cell-interminable lymphocytic leukemia (constant lymphoid leukemia) (Mukherjee *et al*., 2007).

Green synthesis of nanoparticles

Biosynthesis of nanomaterials utilizing plant extracts has unsealed another era in quick and nontoxic approaches for the synthesis of NPs. Because plant contains plethora of bioactive entities, these herbals are the "goldmines" in the field of therapeutics. Numerous scientists have detailed the biosynthesis of metallic nanoparticles by extract of plant parts and revealed their potential utilizations (Shankar *et al*., 2003 and 2004; Ankamwar *et al*., 2005 and Chandran *et al*., 2006). They have considered the bioreduction of Ag and Au particles by aerial extracts of *Azadirachta indica* and *Pelargonium graveolens*. Further, they have also investigated the development system of triangular gold nanoprisms by *Cymbopogon flexuosus* (lemongrass) separates. Likewise fast amalgamation of stable gold nanotriangles utilizing *Tamarindus indica* (tamarind) leaf remove as reducing specialists could also be accomplished (Ankamwar *et al*., 2005). According to Kelly *et al*., 2003 the state of metallic nanoparticles impressively altered their physical properties. They have shown amalgamation of AgNPs and AuNPs with an assortment of shapes (round and triangular) and sizes utilizing *Aloe vera* plant separates. It was clarified that plant biomolecules having less molecular weight were responsible for reduction in oxidation sate of gold atom in chloroaurate particles, and synthesis of triangle shaped gold nanoparticles.

Shankar *et al*., 2004 have announced the biofabrication of unadulterated metallic NPs (AgNPs and AuNPs) by the reduction of Ag^+ and $AuCl^{4-}$ ions with the extracts of neem leaves *(A. indica)* and Geranium leaf (*P. graveolens*) stock. It was when presented to the aqueous solution of $AgNO_3$, brought about the extracellular enzymatic union of stable crystalline silver nanoparticles. Metal particles were reduced readily in solution and NPs of 16-40 nm were produced. The created particles were found to be arranged into open, quasilinear (quasiconvex and quasiconcave) superstructures and were predominantly spherical shaped. It was accepted that protein, terpenoids, and other bio-natural mixes in the geranium leaf extract are the causes of the bioreduction of silver particles and in the stabilization of the nanoparticles produced by surface capping. Further, they announced the presence of terpenoids in the geranium leaf may have a possible role in the AgNPs synthesis. Polyols, for example, flavones, polysaccharides, and terpenoids, in the *Cinnamomum camphora* leaf were accepted to be the primary driver of the reduction of silver and chloroaurate particles (Huang *et al*., 2007). Li *et al*., 2007 have demonstrated quick condensation of Se/protein utilizing *Capsicum annum* L. proteins extracts. They likewise exhibited that production of α-Se nanoparticles from *C. annum* L. extracts was possible due to presence of active agents in the form of vitamin C and proteins. The proteins additionally stabilized nanoparticles by means of precipitation on their surfaces and development of Se/protein composites. The capabilities of plant-based bioactive compounds like terpenes, phenols, flavonoids, alkaloids, proteins and carbohydrates to reduce the metal salts and metal compounds to nascent NPs is due to the involvement of bioactive functional groups like -amino, -aldehyde, -keto, and others. These results have been proved by many researchers on the basis of outcomes of FTIR analysis.

Anticancerous potential of plant-based metal nanoparticles

There are many research works accessible which prove that nanoparticles can be utilized as a phenomenal hotspot for sedate conveyance and can be employed as a restorative agent for the disease table 1. As per the data of WHO, discussed previously, the yearly malignant growth cases are to rise from 14 million of the year 2012 to 22 million in the following two decades. Along these lines, there is a critical requirement of improved and successful antineoplastic medications on at urgent basis.

Briefly, size dependent activity of the NPs has also been investigated; small sized NPs are more toxic and more efficient in ROS production (Carlson *et al*., 2008 and Ahmed *et al*., 2017). Apart from these cellular mechanisms NPs have also shown anti- angiogenic (Gurunathan *et al*., 2009) and anti-proliferative (Asharani *et al*., 2009) properties. In normal tissue cells, activation of PI3K/Akt signaling cascade is responsible for the induction and initiation of angiogenesis. This mechanism starts when vascular endothelial growth factor (VEGF) binds to its receptor on endothelial cells. NPs are anti-angiogenic as in presence of these particles; phasphorylation of Akt by PI3K cannot take place which results in termination of signaling pathway. These events ultimately lead to termination of angiogenesis, starving the cell, depriving oxygen and killing the tumor cell (Carlson *et al*., 2008). The anti-proliferative property in cancer cells mediated by NPs is due to their ability to damage DNA, break chromosome–producing genomic instability, disruption of calcium (Ca2þ) homeostasis which induced apoptosis, cell injury and cytoskeletal instability; cytoskeletal injury blocks cell cycle and division, promoting anti-proliferative activity of cancer cells (Gurunathan *et al*., 2009).

Table 1: Green synthesized metal nanoparticles (NPs) against various cancer cell lines.

S. No.	Name of Plant	Plant part used	Synthesized metal nanoparticles	Cancer cell under study	References
1	*Acalypha indica Linn.*	Leaf	Silver	MDA-MB-231	Krishnaraj et al. (2014)
2	Ajwa and Barni	Date extracts	Platinum	Hep G 2, HCT 116 and MCF-7	Radadi et al. (2018)
3	*Albizia lebbeck*	Stem bark	Zinc oxide	MDA-MB-231 , and MCF-7	Umar et al. (2019)
4	*Artemisia oliveriana*	Aerial parts	Silver	A 549	Fard et al. (2018)
5	*Artemisia turcomanica*	Leaf	Silver	Human gastric adenocarcinoma cells	Mousavi et al. (2018)
6	*Couroupita guianesis*	Flower	Gold	HL60	Geetha et al. (2004)
7	*Cynara scolymus*	Leaf	Silver	MCF-7	Erdogan et al. (2019)
8	*Datura inoxia*	Leaf	Silver	MCF-7	Gajendran et al. (2014)
9	*Dendrophthoe falcate*	Leaf	Silver	MCF-7	Sathishkumar et al. (2014)
10	*Eucalyptus*	Leaf	Silver	Gastric malignant growth (MRC-5)	Rashmezad et al. (2015)
11	*Eucalyptus chapmaniana*	Leaf	Silver	HL-60	Sulaiman et al. (2013)
12	Fenugreek seeds	Seeds	Selenium	MCF-7	Ramamurthy et al. (2013)
13	*Iresine herbstii*	Leaf	Silver	HeLa	Dipankar et al. (2012)
14	*Jurinea dolomiaea*	Leaf	Silver	HeLa	Ahmed et al. (2019)
15	*Nepeta deflersiana*	Leaf	Silver	HeLa	Sheddi et al. (2018)
16	*Origanum vulgare*	Leaf	Silver	A 549, and Human prostate cancer cell line	Sankar et al. (2013)
17	*Panax ginseng*	Leaf	Silver	MCF-7, MDA-MB-231, SKOV 3, U-87, and NCI/ADR	Castro aceituno et al. (2016)
18	*Pandanus odorifer*	Laef	Zinc oxide	MCF-7, Hep G-2, and A-549	Hussain et al. (2019)
19	*Piper nigrum*	Seeds	Silver	Hep-2, and MCF-2	Krishna et al. (2016)
20	*Pueraria tuberose*	Tuber	Silver	MCF-7, MDA-MB-231, SKOV 3, and U-87	Sathpathy et al. (2018)
21	*Punica granatum*	Leaf	Silver	HeLa	Sarkar and Kotteswaran (2018)
22	*Quisqualis indica Linn.*	Flower	Copper	B 16 F 10	Mukhopadhyay et al. (2018)
23	*Rhynchosia suaveolens*	Leaf	Silver	DU 145, PC-3A 549, SKOV 3, MCF-7, and B 16 F 10	Bethu et al. (2018)
24	*Rosamarinus officinalis*	Leaf	Silver	HL-60	Sulaiman et al. (2013)
25	*S. grandiflora*	Leaf	Silver	MCF-7	Murugaraj et al. (2013)
26	*Saccharina japonica*	Whole plant	Silver	HeLa	Sreekanth et al. (2015)
27	*Salacia chinesis*	Bark	Selenium	Hep G2, L-132, MIA-Pa-Ca-2, MDA-MB-231,KB, PC-3, and HeLa	Jhadav et al. (2018)
28	*Saraca acosa*	Leaf	Gold, Silver	Du 145 cell line	Patra et al. (2018)
29	*Scutellaria barbata*	Whole plant	Gold	PANC 1	Wang et al. (2019)
30	*Taraxacum officinale*	Leaf	Silver	Hep G2	Saratale et al. (2017)
31	*Withania coagulans*	Leaf	Silver	SiHa	Tripathi et al. (2018)
32	*Withania somnifera*	Leaf	Titanium dioxide	KB cells	Maheswari et al. (2018)

The AuNPs obstruct the phosphorylation of the downstream molecules like Akt, ERK ½ in the PI3K/Akt signaling pathway (Pan *et al*., 2014 and Kang *et al*., 2016). It was demonstrated that AuNPs target malignant growth cells. Up-taken AuNPs target tumor silencer genes and oncogenes to induce the expression of caspase-9, an initiator caspase and responsible for apoptosis (Tiloke *et al.,* 2016). In another investigation, AuNPs focused on the nucleus, promotes cell-cycle arrest, cytokinesis hindrance - which at that point drives the cell over to apoptosis (Kang *et al*., 2013). On numerous occasions, AuNPs are utilized as a conveyance framework (Brown

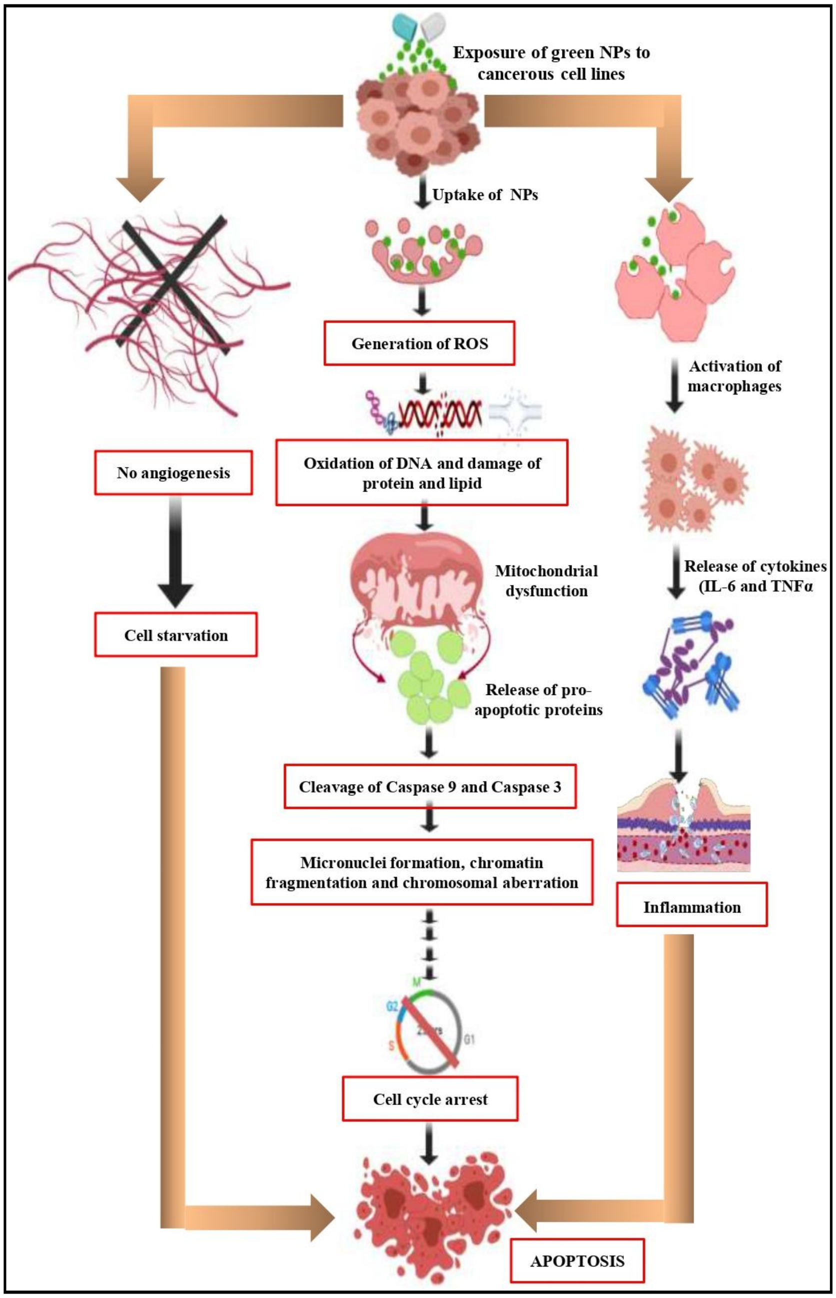

Fig. 3: Mechanism of action of green nanoparticle (green NPs).

biological synthesis of nanoparticles is developing better methodologies and approaches in therapeutic fields. There is the utmost requirement for the replacement of synthetic protocols that involves harmful ingredients and to develop an environmental friendly process. Rapid and green synthetic methods using extracts of plants have shown great potential in metal nanoparticle synthesis. Phytonanotechnology has provided new opportunities for the development of an economical, efficient, eco-friendly and simple process. The presence of proteins, amino acids, organic acids, vitamins as well as secondary metabolites such as flavanoids, alkaloids, polyphenols, terpenoids, heterocyclic compounds and polysaccharides acts efficiently as metal reductants, capping, and stabilizing agents for the synthesized NPs.

Cancer is one of the fatal and diverse groups of disorders with varied biological properties. As per GLOBOCA, 2012, 14.1 million new malignant growth cases were enrolled and 8.2 million cancer deaths happened in 2012 around the world. The systems for the treatment of malignant growth have huge symptoms which make the patient practically and phycologically impaired. Nanomedicine to diminish malignant growth is a developing part of nano-biotechnology with the prime job in disease the board with cutting edge ideas and treatment techniques. Metallic nanoparticles possess a strong capacity to reduce the cellular and metabolic capabilities of cancerous cell lines and

et al., 2010) or in conjugation with the restorative molecule (Abel *et al.*, 2016) or possibly with gene to give fundamentally better toxicity to malignancy cells.

Conclusion

The role of nanoparticles as an anti-cancer agent has opened new opportunities in the field of medicine. This will eliminate the use of costly drugs for malignant growth treatment. Metal nanoparticles are the best for treating diseases that involve cell proliferation and cell death. Nanobiotechnology is an emerging field that has made its commitments to all circles of human life. The when it is synthesized through the botanical extracts, its efficacy is enhanced. It induces apoptosis through several cell mechanisms which include, generation of ROS, mitochondrial dysfunction, G2/M phase cell cycle arrest, increased production of apoptotic proteins (BAX, CASP 3, CASP 9 and miR-192), and decreasing the levels of non-apoptotic proteins (Bcl-2). AgNPs execute well as malignant growth therapeutics since they can disturb the mitochondrial respiratory chain which initiates the generation of ROS which in turn damages DNA. NPs instigate apoptosis by oxidative stress, in which Bcl-2 assuming a significant job in mitochondrial external film permeabilization and loss of mitochondrial membrane potential.

Futuristic scenario of green NPs as anticancer agent

Many research works have been executed by keeping in mind, the antiproliferative properties of NPs against cancer cells. Still, a vast team work of scientists from all over the world is engaged to strengthen the proof towards the use of NPs as combinational therapy against cancer. Many *in-vitro* as well as *in- vivo* cytotoxic activities of NPs on cancerous cell lines like MCF-7, HeLa and others have been attested successfully which shows the eminent candidature of these, plant based green NPs in cancer therapy. Oral administration of nano- metal particles fabricated by plant extracts has been also practiced which provides a safer use of it. Besides all these successful achievements, there is a strong need of more and more optimization, and characterization of these biogenic materials before its broadcasting in medical field.

This may be mainly due to toxicity of metals (like silver, gold, arsenic) used during the amalgamation of NPs. A slight narrow knowledge about the exact nature of capping agents and other active functional groups and their roles, derived from the plant parts may also be a restriction for use of NPs at wide level. In future, there should be broad inspection on safety measurements, dose optimization as well as impact of nanoparticles on non-cancerous cells.

Acknowledgement

LS has collected and written the manuscript. AR has done the formatting works and drawn the pictures.

Formatting of funding sources

The authors are thankful to CAS- Botany (BHU), ISLS, BHU and DST- PURSE and FIST for providing funds and internet facility. Lakee Sharma is thankful to CSIR- Delhi, India for providing financial support in the form of fellowship.

Conflict of interest

There is no any conflict of interest between authors.

Figure ligands

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