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Herbonanotechnolgy: Drug Delivery through Gold Nanoparticle

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ABSTRACT

This article has been made to review how herbonanotechnology important to cure cancer with the help of gold nanoparticles. Herbal drugs are very active moiety for cancer treatment than the conventional drug therapy. Limitation due to hydrophobic that leads to lower the bioavailability that can be overcome by the use of nanocarriers such as nanoparticles conjugated with anticancer herbal bioactive. Such nano chemotherapeutic agents exhibit improve bioavailability. Cancer nanotechnology has become a prime field of investigations for scientists nowadays there are several nanocarrier systems used for effective cancer treatment and gold nanoparticles (GNPs/AuNPs) have become important vehicles for the delivery of anticancer drugs into their targets. These nanoparticles can be used for selective transportation mechanism through receptor-ligand binding. This review aims to facilitate to know the different strategies used for AuNPs synthesis and showing the need and future perspectives of AuNPs in bionanotechnology.

INTRODUCTION

Nanotechnology has gained great attention over time. The main component of nanotechnology is the nanoparticles. Nanoparticles are particles between 1-100 nm in size and are made up of carbon, metal, metal oxides, or organic matter. The nanoparticles have unique physical, chemical, and biological properties at nanoscale compared to their respective particles at higher scales. This is due to a relatively large surface area to the volume, increased reactivity, and stability in a chemical process, enhanced biological activity, etc. These properties of nanoparticles give various applications in targeting specific disease. "Nanotechnology" gives attractive therapies to the pharmaceutical that will enhance the health of people. The main aim of nanoparticles to enhance the drug bioavailability of the herbal drug. (1)

Nanoparticles are the sub-nanosized colloidal structures containing synthetic or natural polymers varying in size from 1-1000nm. The drug is dissolved, entrapped, encapsulated, or attached to a nanoparticle matrix. Depending upon the method of preparation, nanoparticles can be nanotubes, nanospheres, or nanocapsules. (1)

NANOCARRIERS:

A nanocarrier is a nanomaterial used for a transport system for another substance, such as a drug. Commonly used nanocarriers are micelles, polymers, carbon-based materials, liposomes, and other substances. Nanocarriers are used in drug delivery due to their unique characteristics made them useful in chemotherapy. Nanocarriers include polymer conjugates such as polymeric nanoparticles, lipid-based carriers, dendrimers, carbon nanotubes, and gold nanoparticles. Lipid-based carriers contain both liposomes and micelles & Examples of gold nanoparticles are gold nanoshells and nanocages, nanotubes. Different types of nanomaterials used as nanocarriers allow for hydrophobic and hydrophilic drugs to be delivered throughout the body (Gupta et al, 2010). Since the human body contains mainly water, the ability to deliver hydrophobic drugs effectively in humans is a major benefit of nanocarriers. 2 (1)

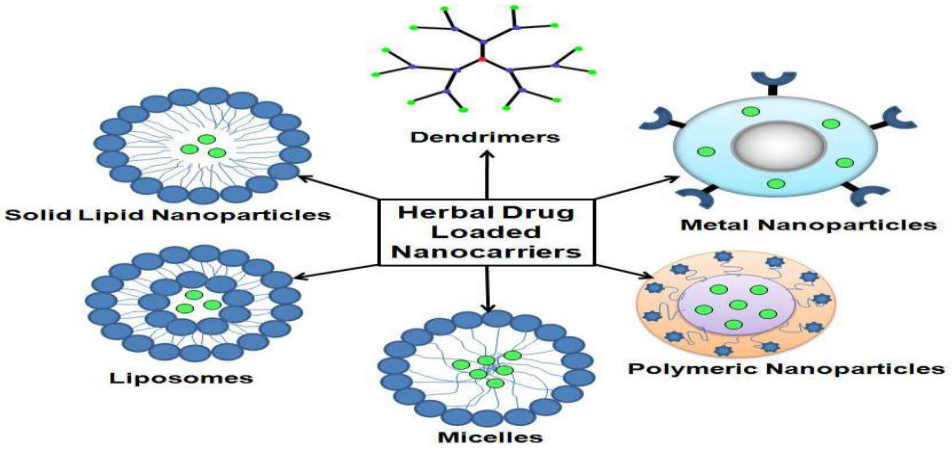

Figure No. 1: Different types of nanocarriers

NEED OF NANOPARTICLE DELIVERY SYSTEM FOR HERBAL DRUGS:

Herbal nanoparticles were selected to overcome the drawbacks of traditional herbal drugs and conventional drug therapy because of the following reasons (Ansari et al., 2012):

- Nanoparticles can be used to target the herbal medicine to an individual organ which enhances selectivity, drug delivery, effectiveness, and safety.

- Nanoparticles can be utilized to improve the herbal drug solubility and help to localize the drug in a specific site thus resulting in better efficacy (Sharma, 2014).

- Nanoparticles can deliver high concentrations of drugs to disease sites because of their unique size, shape, and high loading capacities.

- Delivering the drug in small particle size increase the entire surface area of the drugs therefore it founds quicker dissolution in the blood.

- Shows increased permeation and retention time, i.e., enhanced permeation through the barriers because of the small size and retention due to poor lymphatic drainage (Chidambaram et al., 2012).

- Exhibits passive targeting to the disease site of action without the addition of any particular ligand moiety.

- Decreases the side effects. (2)(1)

- Enhanced surface area results in a faster dissolution of the active moiety in an aqueous environment, such as the human body. Faster dissolution shows greater absorption and bioavailability.

- Advantages of nanostructure-mediated drug delivery include the ability to deliver drug molecules directly into cells (26) and the capacity to target tumors within healthy tissue. (2) (13)

For a few decades, Nanoparticles are used for drug delivery systems for various chemotherapeutic drugs to increase drug safety and efficacy. They play an important role in enhancing the concentration of drugs in cancer cells by increasing drug accumulation by passive and active targeting mechanisms as well as by reducing drug efflux from cancer cells. In passive targeting of nanoparticles the mechanism by which the drugs leak from blood vessels supplying cancer cells and accumulate in the cells by enhanced permeability and retention (EPR) effect. The active targeting of nanoparticles, on the other hand, target ligands conjugated on the surface of nanoparticles, resulting in greater cellular uptake by receptor-mediated endocytosis and therefore enhance drug accumulation in cancer cells. The mechanism based on the interaction between tumor ligands conjugated on the surface of nanoparticles and cell-surface receptors or antigens on cancer cell. (3)

Most of the drugs are not very soluble, which makes it difficult to administer appropriate doses (6) (7). These drugs can be “solubilized” by formulating them into crystalline Nano suspensions and they are stabilized by using surfactants (7) or formulating them with organic or lipid nanoparticles that keep them in circulation for a longer period (8) (9) (10). If an effective compound has a short half-life in the circulation then its stability can be enhanced tremendously by encapsulation it within nanosized liposomes as a drug carrier (9). Nanoparticles important for many drugs have difficulty in crossing the blood-brain barrier to attack the brain tumor. Drug-loaded nanoparticles can penetrate this BBB and have been shown to greatly improve therapeutic concentrations of anticancer drugs in brain tumors (11) (12). In the treatment of cancer best way to treat it by enhancing the concentration of drugs at the site for sufficient time for therapeutic action to take effect.

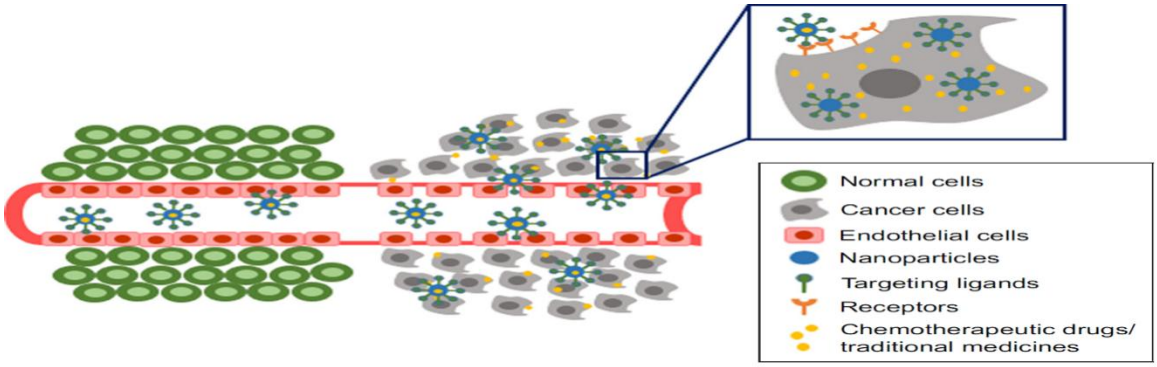

Figure No. 2: Action of nanoparticles on cancerous cell

Nowadays importance of herbal medicines has been enhanced because of their ability to treat different diseases with fewer side effects. However, the efficacious drug delivery of herbal medicines is not still been achieved. This can be achieved by using different scientific approaches to deliver herbal medicines with the help of novel formulations such as polymeric nanoparticles, liposomes, proliposomes, solid lipid nanoparticles, and microemulsion suppressant potential to deliver herbal medicines effectively. 22

Since ancient times, herbal medicines have been widely used worldwide because of there better pharmacological effect and fewer side effects as compared to conventional medicines (Goyal et al., 2011; Thakur et al., 2011). Due to the lack of scientific justification and processing difficulties, herbal medicines were not considered for the development of novel formulations for a long period. But now, the modern phytopharmaceutical research can solve the scientific needs of herbal medicines in developing novel drug delivery systems (nanoparticles, liposomes, solid lipid nanoparticles, etc.).in conventional medicines, the only a limited amount of dose reaches to the targeted site, and the majority of drug get distributed throughout the body, depending on physicochemical properties resulting in lower therapeutic effect. The main importance of a novel drug delivery system (NDDS) is targeted drug delivery, which decreases the dose frequency, enhances solubility and absorption, and lower the elimination, that's why among all the NDDS, Nanoparticles is considered to be an important drug delivery system. (2)(4)

Advantages of biosynthesis of nanoparticles from herbal extracts:

Nanoparticles synthesized using plant extracts have advantages over conventional methods.

Low cost of production

- Economically& effective
- Fewer accidents& lower side effects (13)
- Safe products

Table No. 1: Examples of herbal nanoparticles

HERBAL DRUG	PHARMACOLOGICAL APPLICATIONS	CLINICAL USE LIMITED DUE TO	OVERCOME OF LIMITATION BY NANOPARTICLES.	METHOD OF PREPARATION NANOPARTICLES
Centella Asiatica (Family-Apiaceae)	Anxiolytic, leprosy, wounds, cancer, fever, allergy, and syphilis	physical instability, high hygroscopicity.	Improve physical stability and avoid moisture entrapment	ionic gelation method.
Curcumin Family-Zingiberaceae	anticancer, anti-inflammatory, antioxidant, antiviral, antimicrobial, etc	short half-life, poor water solubility, poor bioavailability.	Enhance bioavailability	wet milling technique.
Danshen: (Family-Lamiaceae),	coronary heart disease, cerebrovascular diseases, and hyperlipidemia	Slow pharmacological action	enhanced oral bioavailability.	
Dodder Family-Convolvulaceae	include anti-cancer, anti-aging, immune-stimulatory effects.	poor aqueous solubility.	Enhance solubility.	nano-precipitation method
Murva Family- Asclepiadaceae	anemia, fever, diabetes, stomach disorders, typhoid.	low aqueous solubility and poor bioavailability	improve its solubility and bioavailability.	
Paclitaxel Family-Taxaceae	anti-tumoral activity	limited aqueous solubility (0.7-30 ug/ml-1) limited its efficacy	enhance drug stability, improve bioavailability.	the sequential simplex optimization method
Quercetin (Family-Fabaceae	antioxidant activity, anticancer & antiviral activities	low aqueous solubility and instability, poor bioavailability	improves therapeutic efficacy and bioavailability.	solvent evaporation method
Genistein	osteoporosis, cardiovascular diseases, breast, and uterine cancer.	low aqueous solubility and poor bioavailability	improve its solubility and bioavailability	nano-precipitation method

Cancer is one of the major causes of death worldwide. Despite efforts to mitigate risk factors in recent decades, the prevalence of cancer is continuing to increase [14]. The current strategy to cure cancer by the use of chemotherapy, radiotherapy, and/or surgical resection. But in radiotherapy and chemotherapy are known for side effects. Furthermore, poor pharmacokinetics and pharmacodynamics characteristics of anticancer drugs arising from poor solubility, stability, and metabolism pose different challenges of toxicity, inefficacy, and limited bio-distribution. Thus, it is important to develop effective formulations that can overcome the above-mentioned challenges and provide selective targeting of tumor sites without significant damage to the viability of healthy tissues. So a need to study how different herbal moiety important as an anticancer.

What Is Cancer?

Cancer is the growth of abnormal cells in the body in an uncontrolled manner. In that old cell do not die, instead, grow out of control and forming new abnormal cells and form a mass known as a tumor. (15)

Cancer develops by series of molecular events that fundamentally changes the properties of cell. As these cells grow they form new characteristics, such as changes in cell structure, decreased cell adhesion, and production of new enzymes.[22]. In the case of metastasis cancer cells travel from a primary site to anywhere in the body and start to grow they are and form a new tumor. Pancreatic cancer and uveal cancers. Another important factor to develop cancer is a genomic mutation in a cancer cell.[21]A tumor can be benign or malignant. A benign tumor means cells are confined to one area and are not able to spread to other parts of the body. This not cancer. and malignant tumors can spread by traveling through the bloodstream or lymphatic system (lymph fluid).[23] . By definition, the term "cancer" applies only to malignant tumors.[26]

Cancer that first developed in a tissue or organ is known as primary cancer. [22]. Tumors containing cells whose growth and morphological characteristics are markedly different from those of normal cells. Criteria for malignancy is increased cell proliferation, loss of differentiation, infiltrative growth, and metastasis to other organs. (30)

Properties of cancer cell-

Cancer cells have several characteristics that are different from normal cells.

- Multiple changes are involved in the conversion of a normal cell to a cancer cell:-

1. Autocrine stimulation; grow in the absence of growth factors

2. Resistance to cell death; persistent telomerase activity

3. Rapid growth; overtake population, invade other tissues.

4. Angiogenesis-– secrete substances that cause blood vessels to grow toward tumor(26)

5. Clonal nature of cancer

- A germline mutation causes hereditary cancer.
- A somatic mutation causes sporadic cancer.
- Ability to metastasize
- Cancer cells and stem cells are surprisingly similar.
- The same characteristics of cancer cells are the use of anaerobic glycolysis.[25]

The mechanisms of drug resistance in the cancer cells.

Chemotherapy failure in 90% of patients because of resistance produced by a cancer cell. This is maybe acquired resistance or cell adaptation i.e cells adapt to damage, stress.[25]Cancer cells produce resistance to drugs in a different way such as the inactivation of the drug, multi-drug resistance, cell death inhibition (apoptosis suppression), altering in the drug metabolism, epigenetic changing, changes in the drug targets, enhances DNA-repair and target gene amplification. (31)

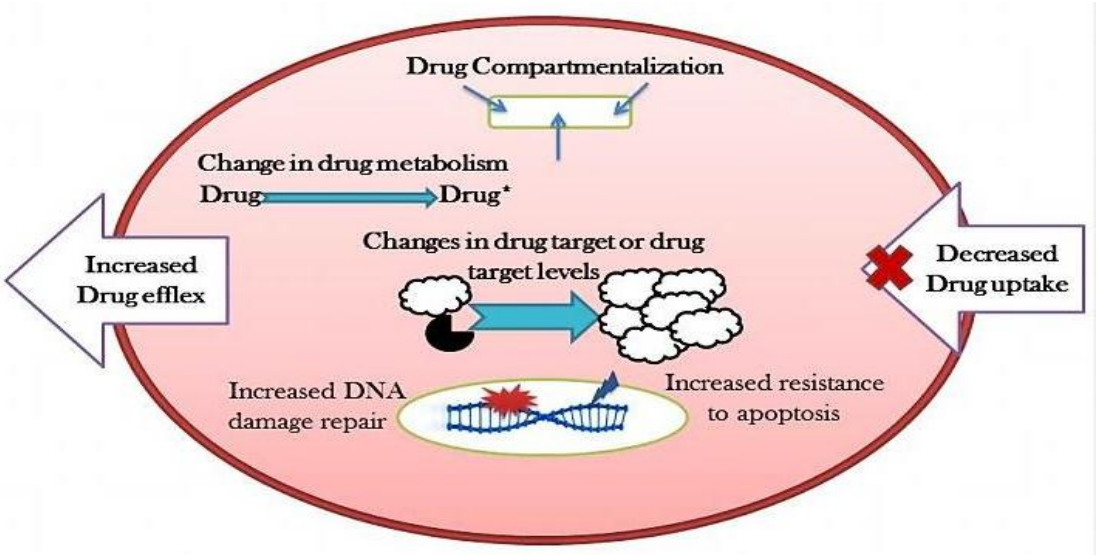

Figure No. 3: Mechanism of drug resistance

Due to this drug resistance and side effects of conventional therapy need to develop newer techniques to treat cancer and this can be done with the help of nanotechnology (nanoparticles). For active targeting, nanoparticles are conjugated to targeting ligand on its surface that plays important role in increasing drug selectivity to the cancer cells. A large number of herbal drugs were reported for their selective delivery to cancer cells by active targeting nanoparticles. [23]. So nanoparticles plays an important role in increasing the concentration of drug at the target site as well as decrease drug efflux from the cancer cell. (27)(29).

The role of nanotechnology in cancer therapy is in drug delivery. The therapeutic index of nearly all drugs recently used can be improved if they are more effectively delivered to their biological target by the appropriate application of nanotechnologies.

A nanoparticle is loaded with a drug able to penetrate this barrier and shows an enhanced concentration of anticancer drugs in brain tumors. For better therapeutic action it is important to maintain the concentration of drugs at the target site. Nanomedicines also have to face challenges in cancer therapy like specific targeting, localized drug delivery. Hence the newly developed nanomedicine and nanodevices such as quantum dots, nanowires, nanotubes, nanocantilevers, and nanopores, nanoshells and nanoparticles are the most important applications for various cancer treatments. The gold nanoshell-antibody complex can be used to treat breast cancer cells. Nanoparticles are attached to chemotherapeutic drugs and allow them to cross the blood-brain barrier for targeting brain tumors. (16)

According to fundamental and technological viewpoint nanoparticles with controlled size, the shape is important. From a long time, there had been much interest in the preparation of different nanoparticles of different sizes and shapes. Another important class of nanoparticles is metallic nanoparticles with important properties like optical, electronic, and magnetic properties. In the metallic nanoparticles, the gold nanoparticles are interested due to easy synthesis, and ability to adjust shape, size, and solubility in different variety of solvents and pH conditions. (17)

Gold Nanoparticles as Nanomedicines for Effective Cancer Treatment

One of the most important challenges in an anticancer targeted delivery system is to develop a proper carrier tool. This day's nanotechnology gives a great platform to develop such carriers to treat with greater efficiency. For this purpose, metallic nanoparticles gate great importance regarding this research field because of their novel size dependant properties and behavior, that make them stable, suitable for targeted, controlled, and sustain drug release. The successfully developed and examined metallic nano-sized particles, gold nanoparticles (AuNPs) are explored for various nanotechnology-related biomedical applications, considering thus their nontoxicity and unique optical, physicochemical, and biological properties.

Gold nanoparticles are important in cancer therapy due to their several properties. The optical characteristics of the gold nanoparticles (GNPs) are unique and they show high absorption efficiency in the absence of photobleaching. They also show very high light absorption and scattering power due to enhanced surface area at the nanoscale. These properties make them an effective system for cancer imaging and analysis [32]. Localized surface plasmon resonance characteristics may be present in gold nanomaterials of particular shapes like nanocages, nanorods, and nanostars. This surface plasmon resonance (SPR) effect makes them more valuable in the targeted elimination of carcinoma. (17)

The surface charge of AuNPs, is in terms of zeta potential, enhance their physicochemical stability and further implementation in the cellular process and bioaccumulation. In previous research studies have mentioned, the toxicity level assigned to AuNPs is strongly dependent on the particle surface charge, thus the positively charged gold nanoparticles cause cell death at a lower concentration, while the neutrally charged particles determine cellular death at

significantly higher concentration. Hence we can conclude that surface charge on gold nanoparticles has great application in targeted drug therapy. (18)

Gold nanoparticles are widely used in the biomedical field and biotechnology because of their large surface area, high electron conductivity.

This is used in targeting brain tumors where the conventional treatments are not effective, this can be done because of their size in nanometer increase the interaction of nanoparticles with biological cells, increase permeability and retention and this is the important properties of nanoparticles to accumulate and interact with tumor cells. Thus the gold nanoparticles provide safest and less toxic drug delivery. They are available in the form of gold nanorod, nanotubes, nanofluids. (18)

Mechanism of Action/Targeting Strategies For Cancer Using Gold Nanoparticles (Gaps)

Gold nanoparticles target cancer cells through active targeting and passive targeting techniques (17). Gold particles serve as an anticancer in various ways like photothermal, photodynamic, and anti-angiogenic and drug delivery .the mechanism of action of herbal gold nanoparticles is anti-angiogenic and inhibits the normal cell signaling and processes due to VEGF binding to VEGFR. In a recent study, it was shown that AuNPs target cancer cells specifically. Once inside the cells, AuNPs target tumor suppressor genes and oncogenes to induce effective expression of caspase-9 which is an initiator caspase involved in apoptosis cycle arrest, cytokinesis inhibition – which then pushes the cell over to apoptosis. In another research AuNPs targeted to the nucleus.so gold nanoparticles are used as a delivery system by conjugation of active moiety, maybe even gene to give better toxicity against cancer cells. Due to their photo-optical characteristics applied in both photothermal and photodynamic therapy.

AuNPs are used as a probe because of their strong SPR absorption in near-infrared regions leading to heating effects followed by irradiating with a non-ionizing source of energy like lasers. The application of laser to the AuNPs, the SPR band is converted to heat which causes hyperthermia eventually leading to cell necrosis. Photodynamic therapy is based on the use of a photosensitizer like 5-aminolevulinic acid (5-ALA) which when irradiated, is excited and reacts with molecular oxygen present in the cell to produce ROS which damages lipid,

proteins, DNA, etc. and drives it to apoptosis or necrosis (cell death). AuNPs have been used to deliver these photosensitizers specifically to the tumor cells. (19)

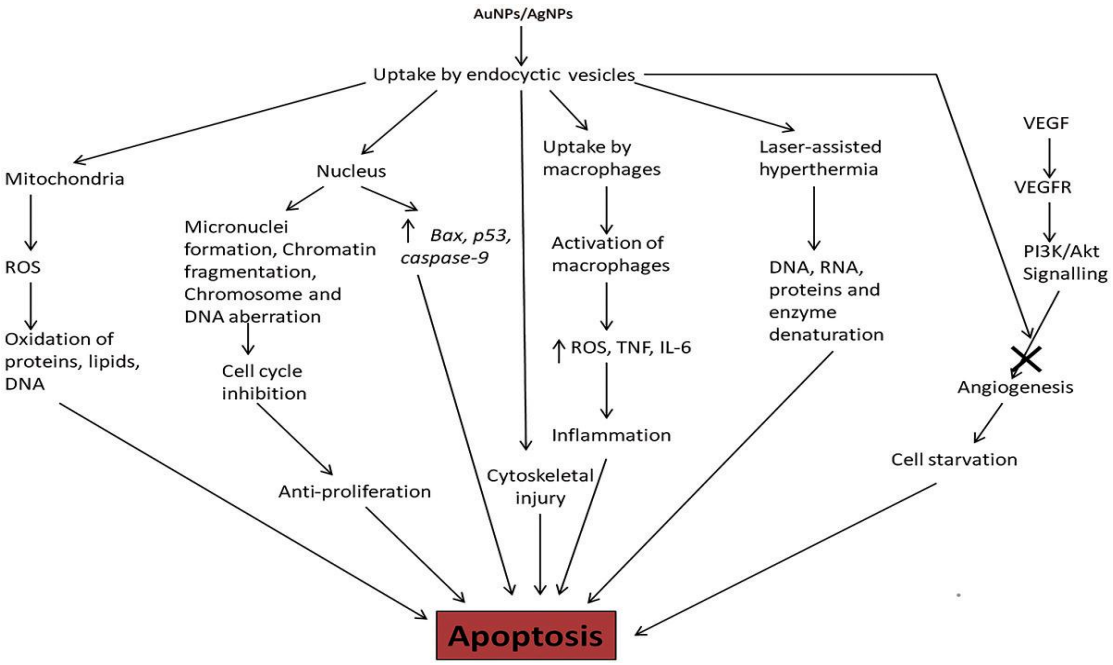

Figure No. 4:

Major mechanisms of AuNPs and AgNPs to exert their anti-cancer properties: AuNPs and AgNPs are taken up by the cell by endocytosis, the vesicles are distributed in the cytoplasm and nucleus producing toxic effects leading to apoptosis or programmed cell death (ROS – reactive oxygen species, TNF –Tumour necrosis factor, VEGF – Vascular endothelial growth factor, VEGFR – Vascular endothelial growth factor receptor and IL-6 – interleukin-6).

Chemical Phenomena's and their role in nanoparticle formation(20)

The synthesis of AuNPs by chemical reduction contains two major steps:

1) The use of reducing agents such as sodium borohydrides, citric and oxalic acids, polyols, hydrogen peroxide, sulfites, and many others. That gives electrons to reduce the gold ions, Au3+ and Au+ to Au0 which is the electric state for nanoparticles;

2) The use of stabilization agents such as trisodium citrate dihydrate, sulfur ligands (mostly thiolates), phosphorus ligands, polymers, surfactants, and others. They stabilize nanoparticles against aggregation by imputing a repulsive force that controls the growth of the

nanoparticles in terms of rate, final size, or geometric shape. The stabilizing agent may be the same molecule that acts as the reduction agent.

SYNTHESIS

The synthesis of gold nanoparticles was first given by Michal Faraday for a multi-colored solution through the reaction of gold chloride with sodium citrate [8].170 Non-oxidized state of gold is Au^0. The Au^0 is the final desirable state for nanoparticles. So, the major step involving the synthesis of AuNPs is reducing Au^1 or Au^3 to Au^0 by adding an electron donor (reduction agent) in the reaction. The precursor of choice for the majority of researchers is chloroauric acid, HAuCl4 with gold in its Auþ3 oxidation states.

CHEMICAL METHODS

Synthesis of gold nanoparticles by using different chemical agents.

Synthesis with citrate e the Turkevich Method

The well described, the synthesis method was presented by Turkevich in 1951 by the use of trisodium citrate as a reducing agent. The publication resulted in several others with some differences in the basic method presented. The size and stabilization of gold nanoparticles are dependent upon the HAuCl4/sodium citrate ratio, pH control, and temperature influence.

Synthesis with NaBH4 with/without citrate

The addition of sodium borohydride (NaBH4) to the Turkevich method was established in an attempt to simplify the synthesis, by eliminating the heating process.

Synthesis by Brust-Schiffrin method

This is a very sophisticated method to synthesize spherical GNPs that are soluble in organic solvents, this is the Brust-Schiffrin method. In this formation of small nanoparticles (<10 nm in diameter) is due to the high affinity of the thiol ligands to the gold surface, preventing NPs growth.

BIOLOGICAL METHODS

Green synthesis method

In this synthesis of gold nanoparticles from plant extract, described the synthesis of gold nanoparticles (AuNPs) using seed aqueous extract of *Abelmoschus esculentu* produced AuNP by using *Avena sativa* biomass, used leaf extracts of two plants, Magnolia Kobus and Diospyros kaki, obtaining particles from 5 to 300 nm (avg 40 nm). Used *Elaeis guineensis* (palm oil) leaves extract.

PHYSICAL METHODS

Development of gold nanoparticles by using bacteria, fungi, and plant extract.

Table No. 1: Some advantages and disadvantages of gold nanoparticles

Advantages of gold Nanoparticles	Disadvantages of Nanoparticles
1 Possibility of high scale production. 2 Long stability [39]. 3 Controlled of active drug can be achieved. 4 Lyophilized [40], Freeze-dried to form a powder formulation. 5 These are inert and non-toxic carrier systems due to the presence of a non-reactive gold core. 6 They are detectable up to a low concentration of 10-6 M. 7 Gold nanoparticles can be formed in monodisperse form having a size of 1 - 150 nm. (17)	1 Less drug loading capacity. 2 Dispersion included the amount of water. 3 The less capacity to load hydrophilic drugs.

Gold Nanoparticles In Medical Applications Are:

The nanoparticles flow in endocytosis and are diffused through the lipid bilayer of the cell membrane. Nanoparticles conjugated with antibodies against exclusive cancer cell surface receptors are used to specifically bind with cancerous cells. The functionalized nanoparticles

are used for targeted entry into cells. Phthalocyanine-stabilized gold nanoparticles are a potential delivery vehicle for photodynamic therapy [28].

_ Therapeutic Agent Transport: The large ratio of surface area volume of gold nanoparticles enables their surface to be coated with hundreds of molecules (including ligands, antibodies, and therapeutic, diagnostic, and targeting agents).

_ Photodynamic Therapy: Heat can be generated by gold nanoparticles when excited by light with 700e800 nm wavelengths. When positioned inside a tumor, the particles rapidly heat up, killing tumor cells.

_ Sensors: Gold nanoparticles can be used in Raman spectroscopy as substrates to enable/improve measurements of vibrational energies of chemical bonds. This strategy can be used for protein detection.

_ Probes: In dark-field microscopy, gold nanoparticles can produce an array of colors that can be used for biological imaging applications.

_ Diagnostics: Gold nanoparticles are also used to detect biomarkers in the diagnosis of heart diseases, cancers, and infectious agents.

_ Treatment: gold nanoparticle can be used to improve the radiation therapy dose delivery or can be used for treatment when activated to gold-198. (18) (21)

SUMMARY

It has made a great impact on selective recognizing of the cancerous cells, targeted drug delivery and overcoming limitations of the conventional chemotherapies. Some nanotechnology-based formulations have already been launched in the market and many are undergoing research and clinical trials. As cancer is one of the most serious lethal diseases, the contribution of nanotechnology in precise treatment avoiding the life-threatening side effects can potentially contribute to a positive movement for a life-saving approach. Gold nanoparticles are suited well for cancer therapeutics due to their higher biocompatibility and lesser toxicity. They can be utilized actively or passively both for the targeting of tumor cells. Goldnanoparticulate systems satisfy all the criteria that a nanocarrier must-have for effective cancer elimination. (17)

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