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APPLICATIONS OF GOLD NANOPARTICLES IN THE CANCER THERAPY

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Abstract: ***Nowadays, nanotechnology is a rapidly evolving field. Because of their magnificent chemical and physical properties, gold nanoparticles are a prominent contender for cancer therapy in the field of nanomedicine. In this review article, firstly, we have described the current cancer therapies and their side effects on the patient. Then the passive and active targeting of cytotoxic drugs in the chemotherapy employing gold nanoparticles as a carrier. Finally, application of gold nanoparticles in the photothermal and photodynamic therapy based upon its unique localized surface plasmon resonance.***

Keywords – Gold Nanoparticles, chemotherapy, targeted drug delivery, localized surface plasmon resonance, photothermal therapy, photodynamic therapy.

I. INTRODUCTION

Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body. Metastasis is a process in which cancerous tumors spread into nearby tissues and can travel to distant places in the body to form new tumors [1]. Widespread metastases are the primary cause of death from cancer. Cancer is a leading cause of death worldwide, in 2020 around 10 million deaths occur due to cancer. The most common cancers are breast, lung, colon and rectum and prostate cancers. Many cancers can be cured if detected early and treated effectively [2]. Advancement in the Nanotechnology which has been done in the past few years, made the treatment of the cancer more precise and thus effective. According to the American society for testing and materials (ASTM international 2006), nanoparticles are those particles which have two or more than two dimensions in the size range of 1-100 nm [3]. Nanoparticles such as AuNP helps to mitigate the side effects in current cancer treatments by targeting tumor cells specifically.

Table 1: Current Cancer Therapies [1]

	How it works	Side effects and limitations
Chemotherapy	In this treatment drugs are used to kill cancer cells.	kills or slows the growth of healthy cells that grow and divide quickly for example cells in a Bone marrow, Hair, Skin, Gonads.
Hormone Therapy	Slows or stops the growth of cancer that uses hormones to grow. It has been done by two mechanisms = 1) Blocking the body's ability to produce hormones 2) Interfering with hormone's behavior in the body.	hormone therapy blocks your body's ability to produce hormones and may change hormones behavior which may give rise to side effects like loss of interest in sex, mood changes, fatigue, nausea, hot flashes, menopause in females, weakened bones and enlarged breast in males.
Hyperthermia	body tissue is heated to as high as 113 °F to damage and kill cancer cells	can cause burns, blisters, discomfort, or pain.
Immunotherapy	It is a type of cancer treatment that helps your immune system to fight with cancer. Types of this therapy are = 1) Immune checkpoint inhibitors 2) T-cell transfer therapy 3) Monoclonal antibodies 4) Treatment vaccines 5) Immune system modulators	Produce side effects by acting against healthy cells and tissues in your body. It may cause pain, swelling, soreness, fever, chill, weakness, muscle and joint aches
Photodynamic Therapy	Photodynamic therapy uses a drug called photosensitizer which is activated by light, to kill cancer cells. The light can come from a laser or from LEDs.	It may kill or damage healthy cells in the body which are nearer to cancer site. Moreover, it is less effective in treating large tumor because the penetration power of the light in the body is less (up to 1 cm only)
Radiation Therapy	Radiation therapy kills cancer cells or slows their growth by damaging their DNA. Types of radiation therapy are = 1) External beam therapy 2) Internal radiation therapy	There is a limit to the amount of radiation an area of your body can safely receive over the course of your lifetime. Moreover, this therapy can also affect nearby healthy cells
Surgery	Surgeon removes cancer from your body.	Severe pain and high risk of infections after surgery. Also, the blood Cancer and cancers that have spread in the body are unable to treated by surgery.

III. APPLICATION OF GOLD NANOPARTICLES IN CHEMOTHERAPY

Most of the chemotherapeutic drugs are the cytotoxic. They kill or damage rapidly multiplying cells in the body. Many large tumors have lower growth fraction than normal bone marrow, epithelial lining, RE system and gonads. So instead of killing large solid tumors, cytotoxic chemotherapeutic drugs attack and damage the rapidly multiplying healthy cells. Due to this, Cancer patient go through unbearable pain during chemotherapy treatment. [4]

Table 2: General toxicity of cytotoxic drugs [4]

Organs or Tissue	Side effects of cytotoxic drugs on them
Bone Marrow	Granulocytopenia, Agranulocytosis, Thrombocytopenia
Lymphoreticular Tissue	Suppression of cell mediated and humoral immunity it gives rise to opportunistic infections
Oral cavity	Oral infections, Bleeding gums, Xerostomia, Rapid progression of dental carries
GIT	Diarrhea, Shedding of mucosa, Hemorrhages
Skin	Alopecia, Dermatitis
Gonads	Oligozoospermia and impotence in males, Inhibition of ovulation and amenorrhea in females

Because the selectivity of majority chemotherapeutic drugs is limited, gold nanoparticles can be excellent vehicle to deliver these drugs locally on the tumor site. Thus, AuNPs will help to minimize the side effects of cytotoxic drugs by increasing specificity of chemotherapeutic drugs.

Gold nanoparticles have strong binding attraction for thiols, proteins, carboxylic acid, aptamers and disulfides. Thus, we can attach wide range of chemotherapeutic drugs to them [3] the anchoring groups utilized for attachment of functional molecular linkers to the gold surface generally include: thiolate, dithiolate, dithiocarbamate, amine, carboxylate, selenide, isothiocyanate or phosphine moieties. [5]

Gold is multivalent; it can bind a variety of ligands. By utilizing this property, we can attach variety of ligands to nanogold carrier (loaded with cytotoxic drugs) which will bind specifically to the receptors on the surface of tumor. This mechanism is known as active targeting. Because of the active targeting, the gold nanoparticles unload the drug specifically on a tumor cell without harming healthy cells.

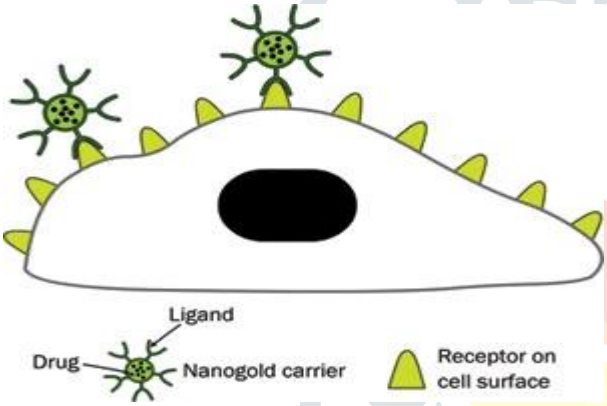

Fig 1. Active targeting. [6]

Small size of gold nanoparticle is also very advantageous, because normally the space between the cells of blood capillaries is 15-30 nm, but a space between the cells of blood capillary near the tumor is more than that. Due to this, tiny gold nanoparticle attached with drugs do not pass through the wall of a healthy blood artery but easily leaked through space between blood capillary surrounding cancer tissue. This mechanism is known as enhanced permeability and retention (EPR) effect. The EPR effect enhance the selectivity of AuNP for malignancies. It is also known as passive targeting [7]

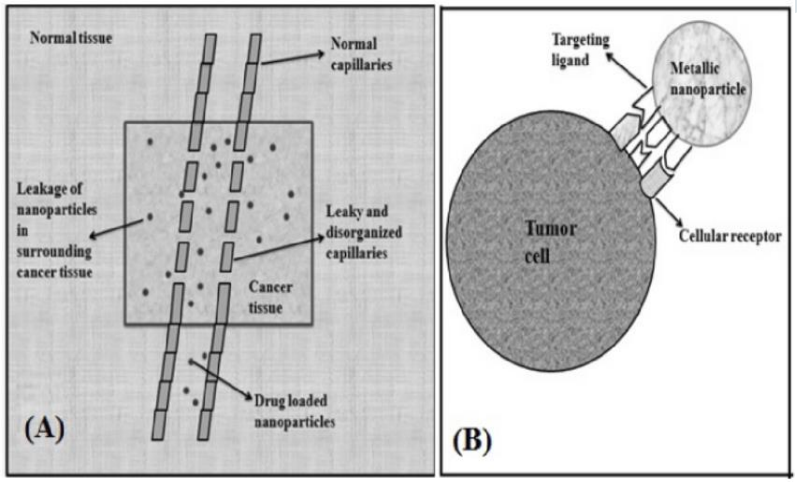

Fig.2 A) Passive targeting B) Active targeting [8]

Apart from its target specificity and capability to form complex with wide range of chemotherapeutic drugs, AuNP shows many unique properties like [9] =

1) easy preparation

2) bioinert
3) non-toxic
4) tenability
5) capability to raise the accumulation of intracellular drugs due to target specific delivery
6) high Biocompatibility

All these unique properties of gold nanoparticles make them ideal candidate for targeted drug delivery in cancerous cells.

III. Application of Gold Nanoparticles in Photothermal and photodynamic therapy.

"Plasmon" is the collective oscillation of conduction electrons on noble metals caused by light stimulation. When the incoming photon frequency is resonant with the collective oscillation of the conduction electron, the "Plasmon resonance" is formed. Because the resonance of an electromagnetic wave on a metal diminishes fast with depth, resonance frequently occurs on the metal surface, which is referred to as "surface Plasmon resonance." The "Localized surface plasmon resonance" (LSPR) occurs when the Surface plasmon resonance (SPR) is limited to a smaller space, such as nanoparticles, which are similar in size to the wavelength of the incoming light.

When the LSPR occurs, the optical extinction of the AuNPs can be maximized more than 1000 times stronger than ordinary organic molecules. The Photothermal therapy (PTT) and photodynamic therapy (PDT) are based on the localized surface plasmon resonance (LSPR) of gold nanoparticles [10].

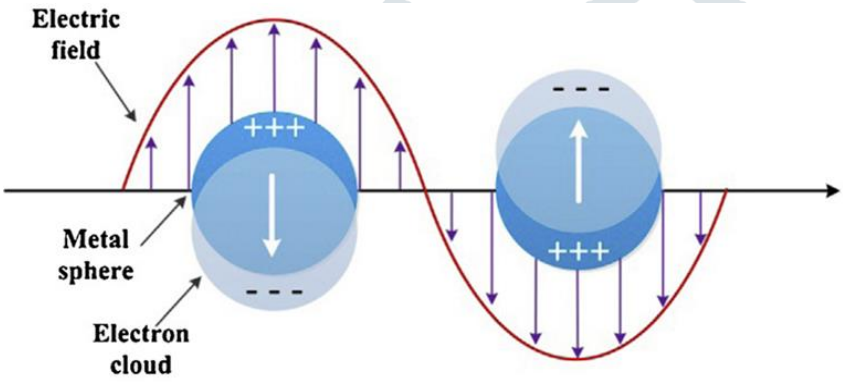

Fig 3. localized surface Plasmon resonance of gold nanoparticle [11]

On the one hand, AuNPs in a photothermal therapy absorb the light and convert it into the heat which is used to destroy tumor cells. Due to photothermal therapy, AuNPs can be use as therapeutic agents without attaching drug entity to it [5]

On the other hand, photodynamic therapy uses a drug that is activated by light, called photosensitizer to kill cancer cells [1]. In Photodynamic therapy, the treatment is delivered through a series of photochemical reactions triggered by photoactivated molecules or materials known as photosensitizer drugs [12]

AuNPs have been widely used to deliver photosensitizer agents for photodynamic therapy (PDT) of cancer [13].

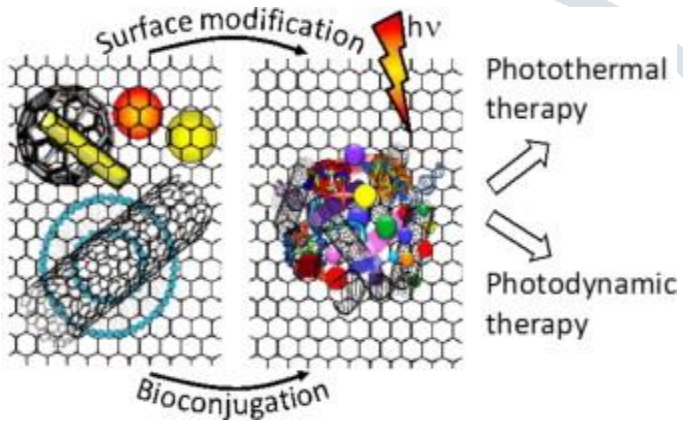

Fig 4. Photothermal and Photodynamic therapy [12]

Ⅳ. CONCLUSION

Unique chemical, physical and optical Properties of the gold nanoparticles make them favorable candidate for Chemotherapy, Photothermal therapy and photodynamic therapy of the cancer**.** The use of gold nanoparticles in cancer therapies is a promising approach to deliver drug at targeted site and save the normal cells surrounding the tumor. Thus, by using AuNPs we can lower the suffering of the cancer patients by mitigating unnecessary side effects happens during therapies. However, gold nanoparticle's

research is still at its infancy. Compared with the large amount of exciting data obtained in laboratory studies, there are very few tumor therapy strategies based on AuNPs that are actually currently used in clinical trials or entering clinical trials.

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