Original Article

GOLD NANOPARTICLE USED IN CANCER THERAPY

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Abstract

Recent fast developments in nanotechnology have stoked a developing interest in the study of nanoparticles, particularly when it comes to medical applications. Understanding the properties of gold nanoparticles (AuNPs) and doing extensive study has resulted to a growing body of information that is pushing the limits of nanotechnology in interesting directions all the time. The use of AuNPs to manage cancer, including its diagnosis, monitoring, and therapy, appears to be of increased attention at the moment. The goal of these initiatives is to fundamentally alter the way that cancer is currently treated. In this article, we will primarily focus on how AuNPs are currently being used to treat cancer.

Keywords: Cancer management, Gold nanoparticles (AuNPs), Research progress.

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1. INTRODUCTION

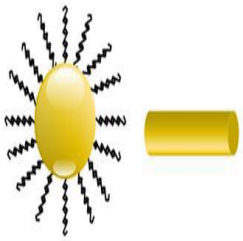
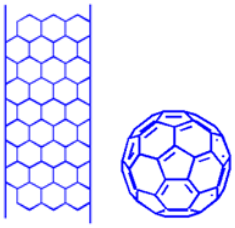
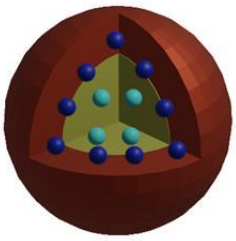
The World Health Organization (WHO) reports that in 2017, cancer was the biggest cause of death globally. By 2030, it is expected that 12 million people will have lost their lives to cancer around the world. (S. Lee et al., 2009). As a result, finding effective techniques for cancer therapy, monitoring, and diagnosis are a never-ending task. Radiation treatment, chemotherapy, and surgery are just a handful of the methods utilized today to treat cancer(Kneipp et al., 2010). Despite being used and approved for many years, these procedures nevertheless have drawbacks and negative outcomes. For instance, surgery can only be used to remove large, visible, and resectable tumours. Chemotherapeutic drugs destroy both malignant and healthy cells, including bone marrow cells, because they only impact rapidly dividing cells. Radiation therapy always has undesirable side effects on healthy tissues that are exposed to it, like gamma rays. Considering the limitations of existing treatment options, it is crucial to improve cancer therapy by preferentially delivering therapeutic chemicals to cancerous cells while protecting normal tissue from tumour.(Cai, 2008).

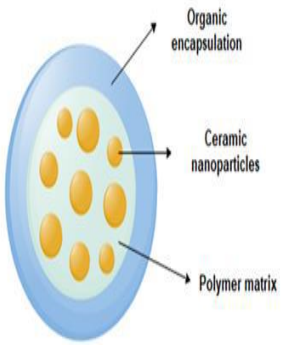
Nanotechnology and nanoparticles have rapidly reached the stage of therapeutic use in recent years(Duncan et al., 2010). AuNPs have a variety of applications because of their unique physical and chemical properties, some of which are described below. Small size, surface effects, quantum size effects, electrical effects, optical effects, and other characteristics make AuNPs unique.(Xie et al., 2018; Xie et al., 2007; de Jong, 2008) .They are also reasonably safe, stable, and simple to make. Compared to conventional medications, AuNPs are more capable of penetrating the body and pose less of a threat when used for therapy and diagnostics(López-Marzo et al., 2018; J. Wang et al., 2018). AuNPs can therefore be broadly applied in biomedicine, particularly in the treatment of cancer.

A major field of study is the creation of multifunctional nanoparticles for cancer treatment and detection(Smilowitz et al., 2018). For MRI detection, for instance, gold nanoparticles (AuNPs) might be utilized; when combined with polyethylene glycol (PEG) molecules, the resulting nanoparticles would have a longer half-life in live organisms (Dong et al., 2018). Tumor-specific In a mouse model of adenocarcinoma, F3 peptides work well as Adriamycin's targeted delivery system.(Mei et al., 2018).

A detailed understanding of nanoparticles, especially AuNPs, might aid significantly in cancer therapy. In this paper, we review the literature on AuNPs published over the last decade, trace their development in studies of cancer treatment, and speculate on potential molecular pathways driving the disease.

1.1. Classification of Nanoparticles

Inorganic NPs	Properties	Structure	References
Gold NPs	Advantages include near-infrared absorbance, localised surface plasmon resonance (LSPR), high surface-to-volume ratio, and the capacity for passive and active targeting.		(García Calavia et al., 2018)
Carbon Based NPs	excellent mechanical properties, heat conductivity, and electrical conductivity. Since they are made entirely of carbon, they have great stability, excellent conductivity, minimal toxicity, and are environmentally friendly.		(Khan et al., 2019)
Quantum dots	Quantum dots have been effective for imaging cells, organs, and tumours because to their stability, photobleaching resistance, multiple colour excitation fluorescence, and overall fluorescent brightness as well as advancements in their synthesis, surface chemistry, and conjugation.		(Valizadeh et al., 2012)
Silica NPs	Condensation of silanes results in the creation of silica nanoparticles, which include an amorphous silicon and oxygen network. The degree of condensation very minimally affects the density of the nanoparticles, which is around 2 g/cm-3, and the refractive index is found to be 1.43. Water and ethanol, which are polar solvents, allow the nanoparticles to spread easily.		(Colombeau et al., 2016)
Upconversion NPs	High photostability, substantial anti-Stokes shifts, crisp emission bandwidths, minimal toxicity, and low autofluorescence background are all features of upconversion nanoparticles.		(16, 17)

Ceramic NPs	Calcium, titanium, silicon, etc., are just a few examples of the metals and metalloids that make up the oxides, carbides, phosphates, and carbonates that make up ceramic nanoparticles. Because of their many useful properties, including as high resistance to heat and chemical inertness, their applications are rather varied.		(Thomas et al., 2015)

1.2. Classification of Cancer Therapy

Chemotherapy	Alkylator
	Antibiotics
	Antimetabolites
	Topoisomerases inhibitors
	Mitosis inhibitors
	Others
Hormonal therapy	Steroids
	Anti-estrogens
	Anti-androgens
	LH-RH analogs
	Anti-aeromatase agents
Immunotherapy	Interferon
	Vaccines
	Interleukin 2
Targeted therapy	Anti-angiogenic agents
	Monoclonal antibody
	mTOR inhibitors
Radiation therapy	Hypoxia Aleviation
	Radio sensitization

2. Characteristics of AuNPs

Due to their size and shape variability, AuNPs exhibit distinct chemical and physical characteristics (Ma et al., 2018). The gold core of the AuNPs is initially largely non-reactive and harmless. The manufacturing of AuNPs is a pleasure because of the well regulated diameter range, which is generally between 1 and 150 nm. Third, different AuNPs properties and sizes can control how drugs are released in different locations, making them efficient drug carriers(X. Wang et al., 2018).

AuNPs have been designed in a variety of forms to meet various therapeutic purposes. Reducing chloroauric acid yields gold nanoparticles (AuNPs) with diameters of 1 to more than 100 nm, which are used in imaging and radiation sensitization.A silica core is contained within a spherical gold nanoshell with a gold shell ranging in thickness from 50 to 150 nm (AuNS). The core diameter and shell wall thickness of AuNSs may be changed to alter their optical characteristics. Typically, gold nanorods are made by reacting cetyltrimethylammonium bromide with chloroauric acid on gold seeds (CTAB)(Mohammadi et al., 2018; Navaee & Salimi, 2018). Depending on whether or not light is being reflected, the absorption wavelength of AuNRs will have one of two peaks due to the light's Plasmon resonance in either the longitudinal or lateral directions. The ratio of these particles' lengths to their diameters may change the size range of AuNRs, which spans from 25 to 200 nm. AuNPs also come in other forms, such as hollow gold nanospheres and nanocages(Menon et al., 2018).

3. AuNPs and cytotoxicity

Prior to their use in the treatment of cancer, research on the toxicological profile is discussed because the efficiency of AuNPs mainly depends on how harmful they are by nature. It has been discovered that the cytotoxicity of AuNPs increases with decreasing nanoparticle size, rising surface charge, and reducing functional groups.AuNPs are biocompatible materials with promise in biological applications because there is no indication of acute and severe toxicity in the literature (Yuan et al., 2018). A recent study found that the size of the AuNPs had a substantial impact on how hazardous the reaction was, suggesting that the toxicity of AuNPs may be more complex than previously thought. Menon et al. (2015); H. Zhang et al. (2018); According to studies, modifying the surface of an AuNPs particle can change its cytotoxicity, interactions with biological components, and absorption. (Choi et al., 2013).

3.1. Nanoparticle size and cytotoxicity

The cytotoxicity of gold nanoparticles (AuNPs) is mostly determined by their size (Dcore). High cytotoxicity has been observed for AuNPs (Dcore<2.0nm) due to their ability to infiltrate nuclei. The cytotoxicity of AuNPs is modest and only marginally rises with increasing Dcore when their size is more than 10 nm (Baek & Patra, 2016). Pan et al. showed in 2007 that different sized AuNPs (Dcore =0.8, 1.2, 1.4, 1.8, and 15nm) had different cytotoxicities. It was found that the cytotoxicity of gold nanoclusters (AuNCs) was much higher than that of gold nanoparticles (AuNPs) when the Dcore was more than 10 nm. Indicating that cytotoxicity is also impacted by cell type, various cell lines displayed varying IC50 values for four different sized AuNCs made using the MTF approach (Dcore=0.8, 1.2, 1.4, and 1.8nm) (Shao et al., 2015). When tested on Chinese hamster ovary cells, Vetten et al. discovered that 20 nm AuNPs were marginally more hazardous than 14 nm AuNPs.

Physical characteristics of AuNPs, such as their shape and level of dispersion, can also influence their cytotoxicity. Physiological activities of cell membranes and organelles, as well as phagocytosis of AuNPs by cells in various morphologies and dispersion states, might be affected by the amorphous and colloidal nature of AuNPs in biological media (Y. Zhang et al., 2018). In their study of the cytotoxicity of AuNPs with various morphologies, Wang et al. discovered that AuNRs had the highest level of cytotoxicity whereas nano hexapods showed zero even at very high concentrations (200 mg/L).(Montasser et al., 2017). According to the research conducted by Wang et al., cellular aggregation/assembly of AuNPs increases the number of reactive oxygen species produced by the cells, which in turn alters cell function by increasing the residence period of the reactive oxygen species. (Jia et al., 2015).

3.2. Surface charge and cytotoxicity

The rate of phagocytosis and the distribution of AuNPs within cells are both affected by their surface charge. According to studies by Hauck et al., electrolyte coatings on AuNPs may be used to regulate their uptake by mammalian cells and so exert some level of control over this process (Facchi et al., 2017). Although several studies have shown that negatively and electrically neutral AuNPs are less harmful than positively charged AuNPs, it is still unknown how surface charge affects biocompatibility (Tang et al., 2018). According to study by Pillai et al., positively charged AuNPs exhibit significant cytotoxicity and are easily taken up by cells. This result shows that the net charge of AuNPs influences how easily cells can take them up (Qnet). Positively charged AuNCs were shown to be substantially more hazardous to cells than neutral or negatively charged AuNCs in a study by Goodman et al (X. Qin et al., 2018). Electrically neutral AuNCs (Dcore=1.5nm) were discovered by Schaeublin et al. to be less harmful to HaCaT cells than charged AuNCs. Additionally, they found that both negatively and positively charged AuNCs are dangerous. This data indicates that cell type is an important consideration when assessing the cytotoxicity of similarly charged and sized AuNPs (Ali et al., 2018). The findings of studies comparing the cellular interactions of AuNPs with Dcore=16 and 58nm particles lend credence to this hypothesis (Higashi et al., 2018).

We also consider the influence of particle size and surface charge on engulfment-induced cytotoxicity. According to

Jiang et al., HeLa cells need not kill bacteria electrically neutral or negatively charged AuNPs, but they do phagocytose positively charged AuNPs more frequently as particle size increases.(H. Liu et al., 2013).

3.3. Surface modification and cytotoxicity

Targeting is possible to some extent when AuNPs' surfaces are modified with ligands or stabilizers, and the cytotoxicity of AuNPs may also be influenced by the type of ligands used(Chen et al., 2013). Compared to CTAB-modified AuNRs, which have been shown to significantly restrict PC-3 cell proliferation, polypeptide YSA-modified AuNRs may have a less significant effect on cell proliferation. Despite the fact that biocompatible ligands often lessen the cytotoxicity of AuNPs, Deol et al. discovered that increasing the density of dendrimers on the surface of glutathione-modified AuNPs increased their cell toxicity.(S. Chuang et al., 2017).

4. AuNPs in Cancer management

4.1. AuNPs as drug delivery agents targeting cancer cells

AuNPs have the order to enhance the pharmacokinetics of drugs when utilized as drug delivery vehicles, leading to fewer adverse effects and the possibility of higher, more precisely calibrated dosages. A common application of AuNPs is as a vehicle for delivering substances into cells. It's possible that the payload is a small molecule drug, but it could just as easily be a large biomolecule like protein, DNA, or RNA. (Abnous et al., 2018). On the other hand, there are several factors to consider while designing a medicine delivery system. The study found that the absorption and intracellular placement of AuNPs were correlated with their size, charge, and surface chemistry.

Pancreatic cancer cells have high levels of EGFR expression, making them ideal candidates for therapy with gold nanoconjugated cetuximab and gemcitabine. Using a citric acid reduction process, Jiang et al. produced AuNPs with diameters ranging from 2 to 100 nm and linked trastuzumab to them.According to research, they are effective against SK-BR-3 and other HER-2 positive breast cancer cells. Smaller AuNPs show a propensity to separate from the cell membrane, while those between 40 and 50 nm in diameter are more successfully targeted and have a definite endocytosis effect. Chen et al. investigated methotrexate (MTX) side effects in vitro and in vivo anticancer effects using AuNPs with a size of around 14 nm as the carrier linkage. The findings demonstrated that, when coupled with AuNPs, MTX may be effectively and quickly condensed in tumour cells, considerably reducing the dose-dependent effect of effectiveness(François et al., 2011). Similar research was done by Goel et al., who discovered that AuNPs may deliver medications as well as precisely infrared photothermal damage to tumour cells when paired with near-infrared light.

4.2. AuNPs application in tumor imagine

To improve the prognosis of malignancies, early diagnosis is the most effective strategy. The determination of tumor target areas for intensity modulated radiation therapy methods like 3-dimensional conformal radiation therapy and image-guided radiation therapy rely on accurate and clear images (Kumar et al., 2018). Numerous studies conducted over the past several years have looked at the use of functional imaging to develop strategies for radiation therapy for cancer. In order to make up for their lack of spatial resolution, positron emission tomography (PET) and single photon emission computed tomography (SPECT) are more sensitive and selective in distinguishing cancerous from non-cancerous tissue. (Jafarizad et al., 2017; K. D. Lee et al., 2015). High spatial resolution increases the success rate of tumor treatment. The most widely used contrast agents are iodine-based, but they are not very tumor-specific and only have a 10-minute half-life in the blood. (Butterworth et al., 2010). AuNPs have drawn the most interest among these nanoparticles because of their sophisticated production, stability, and particularly strong X-ray absorption capability.

Due to their high atomic number, small size, and high biocompatibility, tiny ag nps (AuNPs) may prove to be effective contrast agents. Tumor cells may be actively or passively targeted by AuNPs at this time. Osmotic tension effect (EPR)-based passive targeting allows for enhanced tumor tissue imaging (Saleh et al., 2018). Combining AuNPs with tumor-specific targeting agents, such as EGFR monoclonal antibodies, enables GNP to actively target tumour cells. If you look at energies higher than 80 keV, gold's mass decay is larger than iodine's, suggesting that gold-nano is more efficient. Imaging studies using X-rays revealed that the gold-nanomixed group's malignant liver cell clusters were much more aggressive than the control group's basic liver cancer cells. For early diagnosis, it is essential to be able to recognize tumours in vivo with a few millimeter in diameter using this new technique(Shrivas et al., 2018).

4.3. AuNPs application in tumor radio sensitization

Due to their distinct qualities, such as size and tumour cell inactivation potential, AuNPs are dispersed differently in different tissues.Radiation treatment is often used to treat practically all tumour forms, including breast cancer(Hébert et al., 2010). High-energy particles, X-rays, and gamma rays are some of the rays. Radiation treatment, however, does not differentiate between healthy and malignant tissues. Therefore, one of the

radiation therapy's limitations continues to be decreasing normal tissue damage(Bikram et al., 2007). After giving 1.9nm AuNPs to breast cancer model mice for two minutes, Herold et al. found that with 30 Gy, both tumor volume and the risk of dying within a year dropped significantly (Agasti et al., 2009). Stern et al. demonstrated that injecting AuNPs into a tumor location prior to radiation greatly decreased tumor volume and inhibited further tumor growth.(Hong et al., 2006).

Currently, research is focusing heavily on targeting AuNPs. By altering the volume, mass, and charge of AuNPs, it is possible to reduce toxicity and boost efficiency by chemically combining chemical medicines or certain biomacromolecules with AuNPs(Paciotti et al., 2004). PEG-GNP conjugates were created by Zhang et al. utilizing various AuNP diameters(H. Zhang et al., 2013). Zhang et al. discovered that coculturing with HeLa cells significantly increased the number of conjugates that entered cells compared to pure AuNPs(Chang et al., 2015). FA-GNP conjugates were developed by Khoshgard et al. by the synthesis of folate and AuNPs. The uptake of FA-GNPs by the cells increased significantly when these conjugates were given to HeLa cells, which express a lot of folate receptors. This was found to be the case (Smilowitz et al., 2018). Khoshgard et al. found that when cells were co-cultured with FA-GNPs, the DEF (dose enhancement factor) was 1.230.09 times higher than it had been for cells that had received only standard irradiation. The cytoplasm was the primary absorption location, according to the findings, and C225-GNPs were taken up significantly more readily.

The mechanism of AuNPs' radio-sensitization remains unclear at this time. Breast cancer cells co-cultured with AuNPs and then subjected to radiation were tested by Jain et al. in hypoxic, normoxic, and aerobic conditions. In comparison to aerobic settings, hypoxic conditions resulted in a greater absorption of AuNPs by cells. The proliferation of breast cancer cells is greatly inhibited in hypoxic environments(Sun et al., 2014). Under normoxia and mild hypoxia, AuNPs had more sensitizing effects. However, there is no appreciable sensitivity when there is a shortage of oxygen. In accordance with the study of Yasui et al., AuNPs are mostly found in the cytoplasm, upregulate DNA repair by reducing the production of proteins associated to DNA repair, and enhance the expression of proteins related to endoplasmic reticulum stress.(H.-S. Chuang et al., 2018; Lin et al., 2017).

4.4. AuNPs application in tumor hyperthermia

Thermo-therapeutic methods include exposing cells to temperatures between 42 and 47 degrees Celsius in order to stimulate them and/or initiate intracellular and extracellular breakdown pathways. Apoptosis is induced, perfusion is reduced, and tumour oxygenation is decreased, among other intracellular and extracellular processes that are affected by hyperthermia(S. Chuang et al., 2017). Near-infrared light absorption and scattering benefits of AuNRs or AuNSs are substantial (wavelengths from 650 to 900nm). AuNPs are capable of producing heat when subjected to electromagnetic radiation, particularly near-infrared light, according to surface Plasmon resonance effects. Normal tissues absorb very little near-infrared light because AuNPs have an absorption peak in the visible spectrum (450–600 nm). Hyperthermia is generated when AuNPs are activated by near-infrared laser irradiation, with little collateral damage to healthy tissues. Therefore, the benefits of selectivity and reduced trauma offered by gold nano mediated thermo-therapeutics make it an attractive alternative to conventional treatments. PEG-conjugated AuNPs were given to animals with a colon cancer mouse model before being placed to the tumour site and subjected to an 800 nm near-infrared light beam. This medication markedly boosted the mice's survival rate(Ruan et al., 2015). Furthermore, the skin reaction was limited to the tumour location and did not differ from the control groups in the body's normal region. According to Stuchinskaya et al., laser-irradiated AuNPs in combination with anti-HER-2 antibodies may effectively target and kill breast cancer cells that overexpress the HER-2 protein, proving that these AuNPs are a type of photothermal therapy and a valuable medium. Anti-EGFR antibody AuNRs, according to Huang et al. studies, may destroy tumour cells at lower laser intensities without heating up healthy cells (L. Qin et al., 2018). According to the research of Hainfeld et al., photothermal treatment was used to completely eradicate tumors in rats injected with modified cetuximab AuNPs while causing the least amount of harm to surrounding healthy tissues (Ngwa et al., 2011). Near-infrared light was used by Wang et al. to kill prostate cancer DU-145 cells and cancer stem cells by covalently attaching the nucleic acid aptamer CSC13 to the surface of AuNRs. (Chanda et al., 2014).

Near-infrared radiation is absorbed by AuNPs, which increases the rise in tumour temperature. AuNPs can also be employed to increase the tumor's ability to absorb X-ray dosages. Radiation treatment and heat work together effectively. Two hours of X-ray irradiation at 43.5 degrees Celsius causes an 8:1 enhancement ratio due to heat in a tumour. Therefore, hyperthermia is among the most potent radio sensitizers obtainable. (Berbeco et al., 2011). However, tumour hyperthermia has certain drawbacks, including low selectivity, difficulties accessing deep tumours, and early heat tolerance.

4.5. AuNPs application in tumor gene therapy

Cancer patients can benefit greatly from gene therapy, which was pioneered at the millennium's close (Woiski et

al., 2017). Gene therapy is built on the precise delivery of nucleic acids to cancer cells.Effective transfection reagents are required to preserve nucleic acids from nuclease destruction when they have been released from cells and before they can perform their functions in the nucleus. DNA's surface is shielded from DNase I deterioration by AuNPs(Joseph et al., 2018). The DNA on the particles' surface is protected from the enzyme because of steric hindrance and hence remains intact. On the other hand, the activity of the enzyme is inhibited by a region of intensely concentrated ions around the DNA. Liposomes are a non-viral, synthetic delivery technique for nucleic acids; although they have a low immunogenicity, they often have difficulties with delivery effectiveness (Fan et al., 2018).

AuNPs are not only easy to alter and have a huge specific surface area, but they are also very inexpensive. They have the potential to serve as an ideal transfection reagent due to their ability to load a high concentration of nucleic acid while simultaneously controlling their surface charge, increasing their water disposability, increasing the effectiveness of transfection, and decreasing their toxicity.(Saber et al., 2017). Mitra et al. employed a monoclonal antibody that targets the epithelial cell adhesion protein to bind PEI-modified AuNPs (EpCAM). The results showed that RB cells may be infiltrated by siRNA-loaded AuNPs, which dramatically reduced their viability (34). When compared to non-antibody modified siRNA-AuNPs, targeted siRNA-AuNPs significantly reduced EpCAM gene expression in RB cells in both main and secondary tests.

To control gene expression, Ghosh et al. used cysteine-modified AuNP-miRNAs, which are 10–20 times more effective at releasing miRNAs than liposomes. (Lu et al., 2014). The nucleic acid aptamer is an excellent option for anti-tumor research because of its specificity. In a similar study the transfection efficiency of liposomes with AuNPs, Ryou et al. discovered that the former were superior at delivering RNA ligands for the nuclear factor b-catenin.(Cui et al., 2016). The findings demonstrated a nearly complete inhibition of b-nuclear catenin's transcriptional activity as well as a decrease in the levels of the oncogenes cyclin D and c-myc mRNA. Additionally, they joined AuNPs to the RNA aptamer that targets the NF-kB p50 transcription factor. The outcomes showed that AuNPs may successfully trigger apoptosis in human lung cancer A549 cells by loading aptamers into these cells.

4.6. Other applications of AuNPs in tumor management

Other drug carriers, such liposomes, can also be stabilized with the help of AuNPs, which similarly increases the effectiveness of the drug delivery. There is a risk of the medication leaking into the plasma and other organs, which severely limits how often it can be used (J.-W. Liu et al., 2018). Gelation at the liposome adsorption site was found to be a possible outcome of phospholipid adsorption onto nanoparticles, as discovered by Wang et al.Within 50 days of the solution, the nanoparticle-modified liposome exhibits no visible leakage since the nanoparticles occupy 25% of the lipid's outer surface(Luna-Gutiérrez et al., 2012).

Yang et al. used AuNPs to prevent the droplets of an oil-in-water emulsion from separating. They managed to make a droplet of oil-in-water emulsion with particles smaller than 100 nm and a net negative charge. Through electrostatic contact, the positively charged AuNPs affix to it and operate as a "bridge" to shield it from the force's strong attraction to AuNPs. The results demonstrated that the interaction of the AuNP-emulsion and AuNP-transferrin significantly increased the emulsion's droplet stability. (Silva et al., 2016; Su et al., 2015).

Additionally, AuNPs can be employed to encourage the release of medications. Using the photothermal action of the AuNPs, an et al. inserted into the center of the liposome bilayer to stimulate drug release, the liposome bilayer was induced to transition into a new phase.(Mitra et al., 2013).

5. Conclusion

AuNPs are appropriate for use in the diagnosis and treatment of cancer due to a number of characteristics. AuNPs are ideal for usage as targeted delivery agents due to their tiny size and ability to attach to a variety of medicines and proteins. Although this paper's focus is on cell and animal research, the imaging and radio sensitization studies using AuNPs offer novel methodologies and ideas for precise radiation treatment and early diagnosis. Although there is still much to learn about AuNPs, there are already pressing issues that need to be resolved, such as how to increase their biological stability while lowering their toxicity to living things. Numerous promising applications for AuNPs exist in the context of cancer diagnosis and treatment. We anticipate a growing role for AuNPs in cancer therapy.

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