Gold nanoparticles as a potential treatment for breast cancer: a review.

Pooja Pandey*, Shakshi Yadav, Reetu Pandey, Manoj Kumar Mishra

Shambhunath Institute of Pharmacy, Prayagraj, Uttar Pradesh, India.

Abstract

Despite remarkable achievements in the treatment of breast cancer, some obstacles still remain. Gold nanoparticles may prove valuable in addressing these problems owing to their unique characteristics, including their enhanced permeability and retention in tumor tissue, their light absorbance and surface plasmon resonance in near-infrared light, their interaction with radiation to generate secondary electrons, and their ability to be conjugated with drugs or other agents. Herein, we discuss some basic concepts of gold nanoparticles, and early results from studies regarding their use in breast cancer, including toxicity, side effects alongwith potential clinical applications.

Keywords: Gold nanoparticle, Breast cancer, Theranostics, Nanotechnology.

Accepted on March 03, 2021

Introduction

Intensive screening and advanced treatment modalities have reduced the incidence of breast cancer and the rate of breast cancer–related mortality [1]. A relatively new concept of breast cancer as a "chronic disease" reflects not only increased survival rates but also the importance of patients' quality of life. Courtesy of gene expression profiling having prognostic or predictive significance personalized therapy enables tailored treatment avoiding chemotherapy in subgroups unlikely to have much benefit. In addition, minimally invasive approaches to treating early-stage breast cancer now consider the patient's cosmetic appearance and minimize the lifelong sequelae of lymphedema. However, many challenges in treating breast cancer patients remain, including reducing treatment-related adverse events, managing triple-negative breast cancer despite poor outcomes and the lack of a therapeutic target, and balancing treatment toxicity with quality of life in patients with metastatic cancer who have already received extensive therapy.

Breast Cancer

Usually, cancer is named after the body part in which it originated; thus, breast cancer refers to the erratic growth and proliferation of cells that originate in the breast tissue [2].

The breast is composed of two main types of tissues i.e., glandular tissues and stromal (supporting) tissues. Glandular tissues house the milk-producing glands (lobules) and the ducts (the milk passages) while stromal tissues include fatty and fibrous connective tissues of the breast. The breast is also made up of lymphatic tissue-immune system tissue that removes cellular fluids and waste [3].

There are several types of tumors that may develop within different areas of the breast. Most tumors are the result of benign (non-cancerous) changes within the breast. For example, fibrocystic change is a non-cancerous condition in which women develop cysts (accumulated packets of fluid), fibrosis (formation of scar-like connective tissue), lumpiness, and areas of thickening, tenderness, or breast pain [4]. Most breast cancers begin in the cells that line the ducts (ductal cancers). Some begin in the cells that line the lobules (lobular cancers), while a small number start in the other tissue.

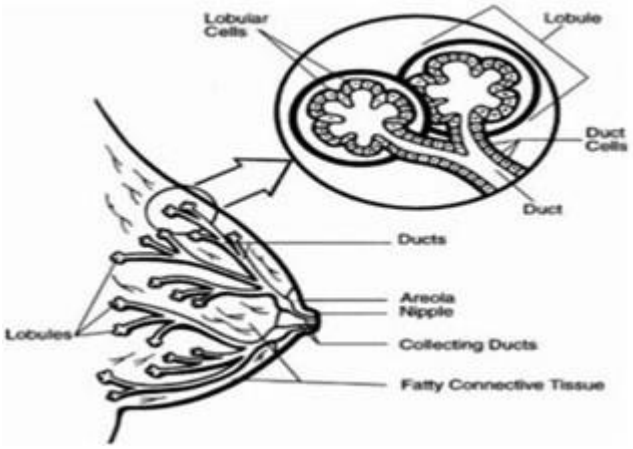

Figure 1. *Structure of breast*

Types of Breast Cancer

According to site

Non-Invasive Breast Cancer cells that are confined to the ducts and do not invade surrounding fatty and connective tissues of the breast. Ductal carcinoma in-situ (DCIS) is the most common form of non-invasive breast cancer (90%). Lobular carcinoma in-situ (LCIS) is less common and considered a marker for increased breast cancer risk.

Invasive Breast Cancer cells that break through the duct and lobular wall and invade the surrounding fatty and connective tissues of the breast. Cancer can be invasive without being metastatic (spreading) to the lymph nodes or other organs [5].

Frequently Occurring Breast Cancer

Lobular carcinoma *in situ* (LCIS, lobular neoplasia): The term, "in-situ," refers to cancer that has not spread past the area where it initially developed. LCIS is a sharp increase in the number of cells within the milk glands (lobules) of the breast.

Ductal carcinoma *in situ* (DCIS): DCIS, the most common type of non-invasive breast cancer, is confined to the ducts of the breast. For example, ductal comedo carcinoma.

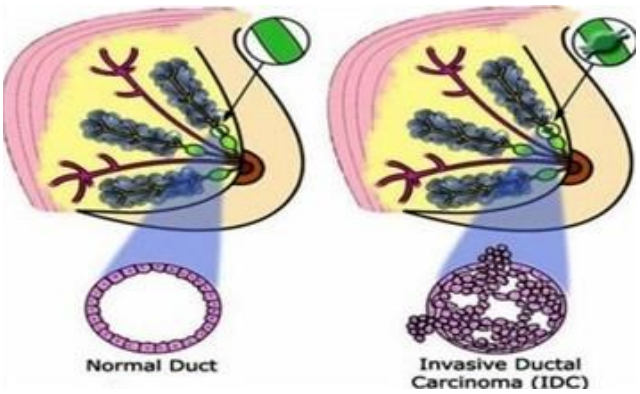

Figure 2. *Typical structure associated with ductal carcinoma*

Infiltrating Lobular Carcinoma (ILC)

ILC is also known as invasive lobular carcinoma. ILC begins in the milk glands (lobules) of the breast, but often spreads (metastatizes) to other regions of the body. ILC accounts for 10% to 15% of breast cancers.

Infiltrating Ductal Carcinoma (IDC)

IDC is also known as invasive ductal carcinoma. IDC begins in the milk ducts of the breast and penetrates the wall of the duct, invading the fatty tissue of the breast and possibly other regions of the body. IDC is the most common type of breast cancer, accounting for 80% of breast cancer diagnoses [6].

Less Commonly Occurring Breast Cancer

Medullary Carcinoma: Medullary carcinoma is an invasive breast cancer that forms a distinct boundary between tumor tissue and normal tissue. Only 5% of breast cancers are medullary carcinoma.

Mutinous Carcinoma: Also called colloid carcinoma, mutinous carcinoma is a rare breast cancer formed by the mucus-producing cancer cells. Women with mutinous carcinoma generally have a better prognosis than women with more common types of invasive carcinoma.

Tubular Carcinoma: Tubular carcinomas are a special type of infiltrating (invasive) breast carcinoma. Women with tubular carcinoma generally have a better prognosis than women with more common types of invasive carcinoma. Tubular carcinomas account for around 2% of breast cancer diagnoses.

Inflammatory Breast Cancer: Inflammatory breast cancer is the appearance of inflamed breasts (red and warm) with dimples and/or thick ridges caused by cancer cells blocking lymph vessels or channels in the skin over the breast. Though inflammatory breast cancer is rare (accounting for only 1% of breast cancers), it is extremely fast-growing.

Paget's Disease of The Nipple: A rare form of breast cancer that begins in the milk ducts and spreads to the skin of the nipple and areola, Paget's disease of the nipple only accounts for about 1% of breast cancers.

Phylloides Tumor: Phylloides tumors (also spelled "phyllodes") are can be either benign (non-cancerous) or malignant (cancerous). Phylloides tumors develop in the connective tissues of the breast and may be treated by surgical removal. Phylloides tumors are very rare; less than 10 women die of this type of breast cancer each year in the United States [7].

Causes of Breast Cancer

A previous history of breast cancer: A woman who has had breast cancer has an increased risk of getting breast cancer in the other breast.

Significant Family History

If several members of patient's family have had particular types of cancer, patient may have an increased risk of developing breast cancer (8,9).

Genetic Causes

Family history has long been known to be a risk factor for breast cancer. Both maternal and paternal relatives are important. The risk is highest if the affected relative developed breast cancer at a young age, had cancer in both breasts, or if she is a close relative. First-degree relatives, (mother, sister, daughter) are most important in estimating risk. Several second-degree relatives (grandmother, aunt) with breast cancer may also increase risk. Breast cancer in a male increases the risk for all his close female relatives. BRCA1 and BRCA2 are abnormal genes that, when inherited, markedly increase the risk of breast cancer to a lifetime risk estimated between 40% and 85%. Women who have the BRCA1 gene tend to develop breast cancer at an early age [10].

Hormonal Causes

Alteration in hormonal level may precipitate breast cancer. It could be attended by starting and stopping of periods (Menstrual Cycle), Pregnancy in early age, Hormonal replacement therapy, Use of oral pills etc [11].

Life Style and Dietary Cause

Sedentary life style, high dietary intake of fat obesity particularly in postmenopausal women may cause breast cancer. The use of alcohol is also another one cause of breast cancer. The risk increases with the amount of alcohol consumed. Women who consume two to five alcoholic beverages per day have a risk about one and a half times that of nondrinkers for the development of breast cancer [12].

Environmental Cause

There is known to be a slight increase in risk in ladies who work with low doses of radiation over a long period of time-for example, X-ray technicians [13].

Breast Cancer Signs and Symptoms

Knowing how your breasts normally look and feel is an important part of breast health. Although having regular screening tests for breast cancer is important, mammograms do

not find every breast cancer. This means it's also important for you to be aware of changes in your breasts and to know the signs and symptoms of breast cancer.

The most common symptom of breast cancer is a new lump or mass. A painless, hard mass that has irregular edges is more likely to be cancer, but breast cancers can be tender, soft, or round. They can even be painful. For this reason, it's important to have any new breast mass, lump, or breast change checked by an experienced health care professional.

Other possible symptoms of breast cancer include:

- Swelling of all or part of a breast (even if no lump is felt)
- Skin dimpling (sometimes looking like an orange peel)
- Breast or nipple pain.
- Nipple retraction (turning inward)
- Nipple or breast skin that is red, dry, flaking or thickened
- Nipple discharge (other than breast milk)

Swollen lymph nodes (Sometimes a breast cancer can spread to lymph nodes under the arm or around the collar bone and cause a lump or swelling there, even before the original tumor in the breast is large enough to be felt.)

Initiation of Breast Cancer

Most breast cancers begin in the ducts that carry milk to the nipple (ductal cancers); Some start in the glands that make breast milk (lobular cancers); there are also other types of breast cancer that are less common like phyllodes tumor and a small number of cancers start in other tissues in the breast. These cancers are called sarcomas and lymphomas and are not really thought of as breast cancers.

Although many types of breast cancer can cause a lump in the breast, not all do. See Breast Cancer Signs and Symptoms to learn what you should watch for and report to a health care provider. Many breast cancers are also found on screening mammograms, which can detect cancers at an earlier stage, often before they can be felt, and before symptoms develop.

Illustration showing breast anatomy from front and side views/ includes the chest wall, muscle, ducts, areola, nipple, lobules, stroma, ribs and lymph nodes.

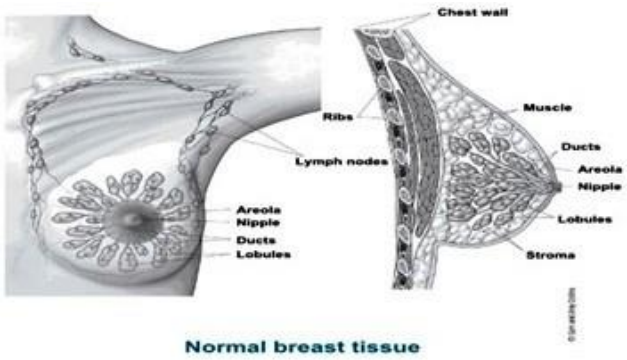

Figure 3. *Normal breast tissues*

Spreading of Breast Cancer

Breast cancer can spread when the cancer cells get into the blood or lymph system and are carried to other parts of the body.The lymph system is a network of lymph (or lymphatic) vessels found throughout the body that connects lymph nodes (small bean-shaped collections of immune system cells). The clear fluid inside the lymph vessels, called lymph, contains tissue by-products and waste material, as well as immune system cells. The lymph vessels carry lymph fluid away from the breast. In the case of breast cancer, cancer cells can enter those lymph vessels and start to grow in lymph nodes. Most of the lymph vessels of the breast drain into:

- Lymph nodes under the arm (axillary nodes)
- Lymph nodes around the collar bone (supraclavicular [above the collar bone] and infraclavicular [below the collar bone] lymph nodes)
- Lymph nodes inside the chest near the breast bone (internal mammary lymph nodes)

Illustration showing the supraclavicular, infraclavicular, axillary and internal mammary lymph nodes in relation to the breast.If cancer cells have spread to your lymph nodes, there is a higher chance that the cells could have traveled through the lymph system and spread (metastasized) to other parts of your body. The more lymph nodes with breast cancer cells, the more likely it is that the cancer may be found in other organs. Because of this, finding cancer in one or more lymph nodes often affects your treatment plan. Usually, you will need surgery to remove one or more lymph nodes to know whether the cancer has spread.

Still, not all women with cancer cells in their lymph nodes develop metastases, and some women with no cancer cells in their lymph nodes develop metastases later (14,15).

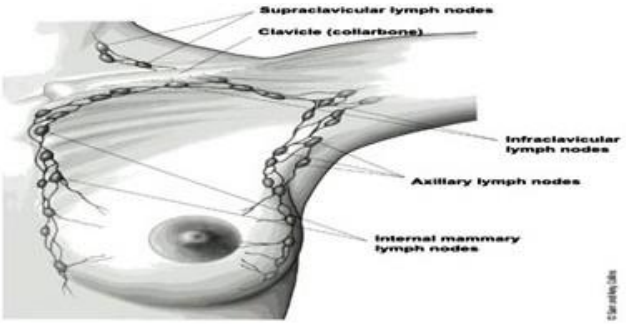

Figure 4. *Lymph node in relation to the breast*

Burden of Breast Cancer In Indian Population

According to Globocan 2012, India along with United States and China collectively accounts for almost one third of the global breast cancer burden. India is facing challenging situation due to 11.54% increases in incidence and 13.82% increase in mortality due to breast cancer during 2008-2012 [16]. The main reasons for this observed hike in mortality is due to lack of inadequate breast cancer screening, diagnosis of disease at advanced stage and unavailability of appropriate

medical facilities. Breast cancer attains top rank even in individual registries (Mumbai, Bangalore, Chennai, New Delhi and Dibrugarh) in females during the period of 2012-2014 (Table 1). The relative proportion of breast cancer in different registries varied from 30.7% in Chennai to 19% in Dibrugarh (Table 1) [17]. Increasing urbanization and westernization associated with changing lifestyle and food habits has lead breast cancer to attain top position in all major urban registries, whereas in Barshi rural registry still cervical cancer is at top position in females and cancer of breast holds second position. Breast cancer crude rate (CR) among different registries showed highest rate in Thiruvananthapuram 43.9 (per 100 000) followed by Chennai (40.6), New Delhi (34.8) and Mumbai (33.6). Among all the PBCR's top four places were occupied by Delhi with AAR 41.0 (per 100,000), Chennai 37.9, Bangalore 34.4 and Thiruvananthapuram District 33.7 (Table 1 and Fig. 5). A total district wise minimum age adjusted incidence rate per 100 000 for India is shown in Fig 6. AAR more than 20 per 100 000 has been reported for districts Chandigarh (39.5), Panchkula (34.6), Aizwal (36.2) and Goa (36.8).

†Relative proportion; ‡Rank; §Crude rate; ϕAge adjusted rate

City name	Breast %†	R‡	CR§ per 100 000	AARϕ per 100 000
Mumbai	28.8	1	33.6	33.6
Bangalore	27.5	1	29.3	34.4
Chennai	30.7	1	40.6	37.9
Thiruvananthapuram	28.5	1	43.9	33.7
Dibrugarh	19	1	12.7	13.9
New Delhi	28.6	1	34.8	41
Barshi Rural	20	2	13.2	12.4

Table 1. *Ranking and rates for breast cancer*

Mortality/incidence ratio (MIR) is another novel measure to evaluate cancer mortality in relation to incidence. It is used to identify whether a region has a higher mortality than might be expected based on its incidence. Barshi rural has MIR as high as 66.3 projecting a very high mortality rate inspite of low incidence of breast cancer in rural India (Table 1). However, Delhi registry had a low MIR of 8.0 despite having high incidence (28.6%), possibly due to high literacy, more awareness and availability of better medical facilities in metropolitan cities. In rural areas, cancer patients are diagnosed at late or advanced stages of disease with a higher proportion of them having widespread metastasis suggesting for need of more attention in terms of awareness, treatment and facilities for early diagnosis.

Age-Wise Breast Cancer Trends

The survey carried out by Indian Council of Medical Research (ICMR) in the metropolitan cities during 1982 to 2005 has shown that incidence of breast cancer has almost doubled.Indian women having breast cancer are found a decade younger in comparison to western women suggesting that breast cancer occurs at a younger premenopausal age in India [18]. Cancers in the young tend to be more aggressive. Studies from various registries have revealed increasing AAR for the breast cancer patients with age intervals (viz. 15-34, 35-44, 45-54, 55-64, and >64 years). The youngest age group consisting of 15-34 years had an APC of 4.24%, 1.60% and 0.80% in Nagpur, Mumbai and Chennai, respectively. For 35-44 age group, the APC ranged from 0.37% to 2.97% in these registries. However, oldest age group comprising of patients >64 years, the APC ranged from 0.53% to 2.64% [19]. Studies suggest that the disease peaks at 40-50 years in Indian women [20]. Many of these cancers are HER2 positive and ER/PR negative, or HER2/ER/PR all three negative, and have a poor prognosis. Trends for 5- year age distribution among different registries showed a peak relative proportion between 45 and 49 years in all registries except in north eastern registries where the peak is seen in even 10- year younger age group-35-39 [21] (Fig. 7]. In India, majority of patients present at locally advanced or at metastatic stages at the time of diagnosis. According to various studies, majority of carcinoma breast cases in the west report in stages I and II of disease, whereas in India 45.7% report in advanced stages [22]. Disease presentation in such conditions results in increased mortality in India. Data from UK cancer registry showed an increasing trend for breast cancer from age 30 to 35 achieving highest peak during age 60–65 years (Fig. 8), suggesting that an average woman in India under the age of 40 has a considerably higher chance of developing the disease unlike United Kingdom.

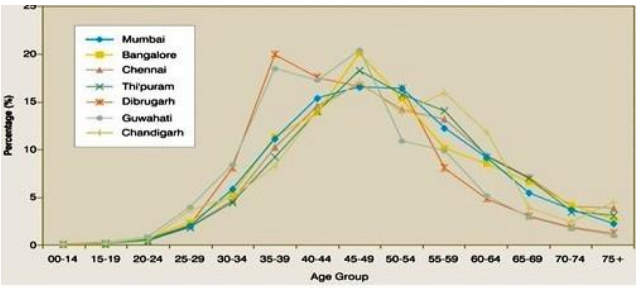

Figure 5. *Epidemiology of breast cancer in Indian women*

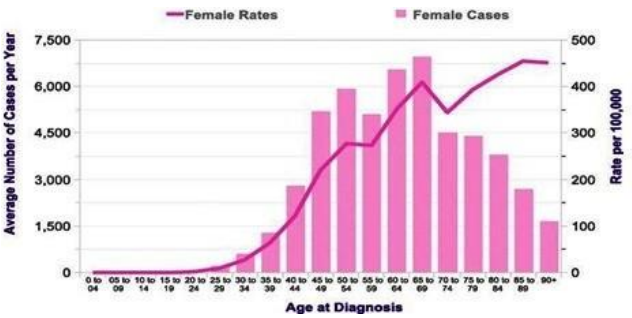

Figure 6. *Annual breast cancer cases in India*

Gold Nanoparticles in Breast Cancer

To overcome these obstacles, researchers have introduced the use of nanotechnology in breast cancer diagnosis and treatment

[23]. In this context, nanotechnology involves the use of nanoparticles that are small bits of matter of about 1-100 nm in two or three dimensions, according to the American Society for Testing and Materials. Matter on the nanoscale often offers unique properties not seen in bulk matter or in solutions, and their interaction with body tissues differs from that of drugs or transplants. Several technological advances now make it possible to design and characterize nanoparticles by using a large variety of organic and inorganic materials to obtain the desired properties. The research literature on cancer nanotechnology has exploded over the last decade. Our focus here is on one of the more promising variants for the treatment of breast cancer are gold nanoparticles. In this review, we summarize the characteristics of gold nanoparticles, their contributions to tumor destruction, their toxicity, and their potential in breast cancer treatment.

Characteristics of Gold Nanoparticles

Physical Attributes

Gold nanoparticles can vary in size, shape, and structure (Fig. 7), and researchers have developed diverse formulations of gold nanoparticles for different treatment purposes. Gold nanospheres (AuNPs), which are produced by the reduction of chloroauric acid, are solid balls of gold that range in diameter from only a few to more than 100 nm and are useful for imaging and radiation dose enhancement. Gold nanoshells (AuNSs) are spherical structures comprising a silica core and thin layer of gold, 50–150 nm in size. Their optical properties can be tuned by modifying the core diameter and shell thickness. Gold nanorods (AuNRs) are synthesized from chloroauric acid with a gold seed and a stabilizing agent, usually cetyltrimethylammonium bromide (CTAB) [24]. The absorption wavelength of AuNRs has two peaks depending on the orientation of the particle to an incident beam of light. Size of AuNRs is typically 25–45 nm in longest dimension, and manipulating these plasmonic particles' length-to-diameter ratio (i.e., aspect ratio) changes their peak absorbance wavelength. Depending on their surface charge and functional groups, AuNRs can have higher cellular uptake [25]. Nanocages and hollow gold nanospheres are other forms of gold nanoparticles that have excellent plasmonic photothermal activities. Depending on the nature of preclinical or eventual clinical application, these differences in size, shape and surface properties of gold nanoparticles are exploited by researchers for specific cancer therapy scenarios. In addition to presence of an inorganic metallic substrate, this tenability to create spheres, shells, rods, and cages of varying sizes and shapes distinguishes gold nanoparticles from other commonly used non-metallic nanoparticles such as liposomes and polymers.

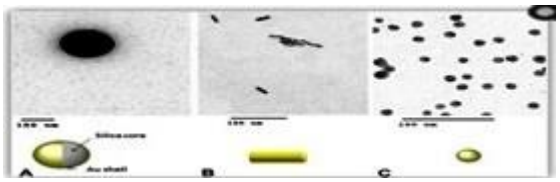

Figure 7. *Use of gold nanoshells and nanorods to treat breast cancer.*

Passive and Targeted Accumulation In Tumors

Gold nanoparticles can easily permeate tumor vasculature and remain in tumors owing to the enhanced permeability and retention (EPR) effect, as gaps in tumor vasculature, whose sizes range from 100 nm to 2 μm, are larger than the gaps in the endothelial lining of normal capillaries. Gold nanoparticles easily pass through these gaps and, because tumors lack lymphatic clearance and have a disordered extracellular matrix, are able to remain in the tumor tissue. However, the tumor uptake of gold nanoparticles *in vivo* is significantly lessened by the opsonization of the nanoparticles with plasma proteins and their subsequent phagocytosis by reticuloendothelial system (RES) components such as monocytes and macrophages. Thus, most injected gold nanoparticles are eventually sequestered in the liver and spleen. Coating the nanoparticles with the polymer polyethylene glycol (PEG) [26] acts like a "stealth" cloak, preventing the uptake of nanoparticles by the RES, thus prolonging their circulation time and increasing their concentration in tumor tissue.

Gold nanoparticles can accumulate in tumor across the blood-brain barrier in brain tumor models, as contrasted with normal brain tissue [27]. Furthermore, conjugated gold nanoparticles can be delivered into brain parenchyma using a carrier-mediated influx of endothelial cells [28]. Such mechanisms can be used to carry drugs to specific targets within the central nervous system. In larger tumors, hypovascular cores confine the neovasculature's leakage of gold nanoparticles to the periphery of the tumor; gold nanoparticle-loaded macrophages and T cells can be used to overcome the difficulties of treating the hypovascular area.

Hyperthermic Effect

Gold nanoparticles such as AuNRs or AuNSs have optical properties of light absorbance and scattering in near-infrared (NIR) wavelengths (650-900 nm) [29]. With exposure to electromagnetic radiation, especially an NIR laser, gold nanoparticles can generate heat *via* the surface plasmon resonance effect (Fig. 8) because its peak absorbance wavelength is in the visible range (450-600 nm), NIR light is transmitted through normal tissue components with minimal absorption [30].Therefore, gold nanoparticles stimulated with NIR laser illumination can induce hyperthermia [31]. In tumor tissue with little damage to normal tissues. In a pivotal study of mice with subcutaneously implanted colon cancer cells, intravenous administration of AuNS-PEG conjugates resulted in the passive accumulation of the AuNSs within the tumors, and subsequent illumination of these tumors with an 808 nm NIR laser successfully ablated the tumors. Compared with mock treatment, this treatment extended the survival of mice. The NIR laser-induced skin reaction in the AuNS-treated mice was no different from that in mice undergoing mock treatment, except that the AuNS-treated mice had a greater skin reaction at the tumor site [32].

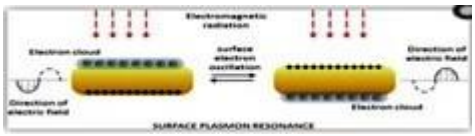

Figure 8. *Interaction of light with gold nanorods*

Radio Sensitizer Properties

Owing to the high atomic number of gold, gold nanoparticles can also be used as imaging contrast agents and radio sensitizers [33]. Several studies have shown that nanoparticles can be used to enhance the effects of radiation [34]. This dose-enhancement effect results from several sources, including the nanoparticles' increased absorption of ionizing radiation energy and their production of secondary electrons that trigger the creation of reactive oxygen species, which cause additional damage to the tumor cell DNA [35]. These effects may not be limited to the DNA but also to the cell membrane and mitochondria [36].

Cellular uptake, pharmacokinetics, clearance, and toxicity concerns The cellular uptake and localization of gold nanoparticle in tumor cells varies according to particle type, size, and/or surface molecule. In one study, smaller (2- or 6-nm) AuNPs coated with tiopronin were found in both the cytoplasm and nucleus, whereas 15- nm particles were found only in the cytoplasm [37]. In another study employing sequential transmission electron microscopy (TEM) of MDA-MB-2 [31] cells, AuNRs were taken up by receptor-mediated endocytosis and formed endocytotic vesicles that evolved into lysosomes and autophagosomes. Reuptake of the eliminated particles was observed after exocytosis [38].

Gold nanoparticles used for imaging and therapeutic research tend to have diameters of at least 5 nm; like bulk gold, these larger gold particles are generally assumed to be chemically inert. One study found that molecules 4 or 10 nm in diameter, which were more easily absorbed than molecules 28 or 58 nm in diameter, accumulated in the liver, kidney, spleen, and other organs, including the brain [39]. Various factors, such as surface charge and size, are associated with the clearance of these molecules from the body. A positive surface charge stimulates the molecules' binding to plasma protein, resulting in RES sequestration or impeding renal excretion owing to the larger hydrodynamic diameter. Particles with hydrodynamic diameters of less than 5-6 mm show enhanced renal clearance. Coating the particles with materials smaller than PEG (e.g. cysteine [40]. Dithionate polyaminocarboxylate to neutralize the surface charge might be one solution to enhancing the renal clearance of nanoparticles [41]. Although numerous studies have investigated the toxicity of gold nanoparticles in animals, the toxicity of gold nanoparticles in humans has not been thoroughly assessed. One phase I trial for dose escalation studied the use of one type of conjugated gold nanoparticle: CYT-6091, a pegylated 27-nm AuNP with recombinant human tumor necrosis factor alpha (rhTNF) [42]. Patients with solid tumors nonresponsive to conventional treatment were enrolled, and possible tissue samples were collected. Twenty-four hours after they were administered, the AuNPs were found in tumor tissue. AuNPs were not found in normal parenchyma in breast cancer patients but were found in normal liver tissue in patients with liver tumors.

Gold nanoparticles cannot be effectively absorbed by oral entry. In contrast, 90% of intravenously delivered nanoparticles remain in the circulation for at least 1 week, and more than 70% of the particles eventually accumulate in the liver. From a toxicity standpoint, these particles' persistence in the body is particularly pertinent because their large surface area-to-mass ratio may render them more active biologically [43]. However, in a study of repeated AuNPs treatments. The proportions of the accumulated amounts decreased as the dose increased, suggesting the activation of a clearance mechanism.

The findings of previous studies suggest that gold nanoparticles have little toxicity. In one such study, AuNPs of various sizes (4 nm, 12 nm and 18 nm) coated with cystein, citrate, biotin, or CTAB were incubated with human leukemia cells. The nanoparticles did not influence cellular mortality, but the CTAB was found to be cytotoxic [44]. Another experiment revealed that incubating human blood cells with 30-nm AuNPs resulted in concentration-dependent hemolysis but no platelet aggregation or change in ROS generation [45]. In rabbits, AuNPs did not produce evidence of acute toxicity within 24 h, nor was any organ observed [46].The findings of another *in vivo* study indicated that exposure to silver nanoparticles, but not gold nanoparticles, resulted in the malformation and death of zebrafish embryos.In recent animal studies of the biodistribution and long-term toxicity of AuNSs, dogs injected with AuNSs had transient weight loss, which recovered within 37 days, and no significant abnormalities in blood chemistry and hematologic analysis. Pathologic evaluations performed 10 months later revealed black pigmentation (indicating gold accumulation) in the Kupffer cells in the liver, in the red pulp of the spleen, and in the lymph nodes. The intensity of the pigment accumulation was mild in the low-dose group and moderate in the high-dose group [47]. The toxicity of AuNRs may result from unbound CTAB. Potential substitutes for CTAB include transferrin, polyacrylic acid, polystyrene sulfonate, and PEG.

Conclusion

cancer nanotechnology brings various perspectives beyond conventional breast cancer treatment that are potentially safer and more efficacious. Several nanoparticulate-based systems have been approved by FDA or are in clinical trials for the delivery of chemotherapeutics (such as liposomes, polymeric nanoparticles and nab paclitaxel). To promote the treatment of breast cancer with nanotherapies, there are still many scientific contributions that can be made. For instance, there is a need to improve the treatment outcome of breast cancer types with higher recurrence rates and mortality rates such as HER2-positive or triple negative breast cancer. HER2 targeting nanotherapies based on HER2 targeting ligand such as trastuzumab, pertuzumab and lapatinib significantly increase the efficacy of HER2-positive breast cancer treatments.

Emerging anticancer mechanisms have also attracted attention in reference to RNAi and PTA. RNAi focuses on the treatment of cancer at gene level by degrading mRNA or suppressing RNA translation in cancerous cells when antibodies or inhibitors cannot target successfully. Immune-related side effects are the caveats of RNAi therapeutic research since hormone receptors are involved. With nanoparticle-mediated PTA, cancer cells are eradicated by the noninvasive treatment, which is beneficial for patients that are irresponsive to chemotherapeutic or radiation treatment. The versatility of nanoparticulates allows for the delivery of multiple active agents with the ability to target various types of cancer. This leads to improved efficacy and advancements in both diagnosis and treatment. These unique properties make nanomedicine challenging to study, but at the same time, appealing to the scientific community aiming to improve patient outcome.

Acknowledgments

We all thank to the management of Shambhunath Institute of Pharmacy, Prayagraj, Uttar Pradesh, India for the needful technical support.

References

1. Desantis C, Siegel R, Bandi P, et al. Breast cancer statistics. Cancer J. Clin. 2011; 61[6]:409-18.
2. Khuwaja GA, Abu-Rezq AN, Bimodal breast cancer classification system. Pattern analysis and application. 2004; 7:235-42.
3. Moore JE, Bertram CD. Lymphatic system flows. Annu. Rev. Fluid Mech. 2018; 50[1]: 459-82.
4. Breast Cancer: Statistics on incidence, survival, and screening. Imaginis Corporation. 2006.
5. Martin TA, Ye L, Sanders AJ, et al. Cancer invasion and metastasis: molecular and cellular prospective. In: Madame Curie Bioscience, Austin (TX): Landes Bioscience; 2000-2013.
6. Kestagar M, Davidson T, Pigott K, et al. Current Status and advances in management of early breast cancer. Int. J. Surg. 2010; 8[3]: 199-202.
7. Nguyen NT, Maciolek LM, Qui S, et al. Malignant phyllodes tumor of the breast in a 26-year-old woman. Cureus. 2020, 12[1], e6590.
8. Hartmann LC, Sellers TA, Frost MH, et al. Benign breast disease and the risk of breast cancer. N. Engl. J. Med. 2005; 353[3]:229-237.
9. Eberl MM, Sunga AY, Farrell CD, et al. Patients with a family history of cancer: identification and management. J Am. Board Fam Pract. 2005; 18[3]:211-7.
10. Mehrgou A, Akouchekian M. The importance of BRCA1 and BRCA2 genes mutations in breast cancer management. Med. J. Islam Repub. Iran 2016; 30:369.
11. Olsson HL, Olsson ML. The menstrual cycle and risk of breast cancer: A review. Front. Oncol. 2020; 10[1]:21.
12. Liu Y, Nguyen N, Colditz GA. Links between alcohol consumption and breast cancer: A look at the evidence. Womens Health (Lond Engl), 2015; 11[1]: 65-77.
13. Vaiserman A, Koliada A, Zabuga O, et al. Health impacts of low-dose ionizing radiation: Current scientific debates and regulatory issues. Dose response, 2018; 16[3]: 1559325818796331.
14. Henry NL, Shah PD, Haider I, et al. Chapter 88: Cancer of the Breast. In: Niederhuber JE, Armitage JO, Doroshow JH, Kastan MB, Tepper JE, eds. Abeloff's Clinical Oncology. 6th ed. Philadelphia, Pa: Elsevier; 2020.
15. Sopik V, Narod SA. The relationship between tumour size, nodal status and distant metastases: on the origins of breast cancer. Breast Cancer Res. Treat. 2018; 170[3]:647-56.
16. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int. J. Cancer 2015; 136[5]: E359-86.
17. Malvia S, Bagadi SA, Dubey US, et al. Epidemiology of breast cancer in Indian women. Asia Pac J Clin Oncol. 2017; 13[4]:289-95.
18. Surakasula A, Nagarjunapu GC, Raghavaiah KV. A comparative study of pre- and post-menopausal breast cancer: Risk factors, presentation, characteristics and management. J. Res. Pharm. Pract. 2014; 3[1]:12-8.
19. Murthy NS, Agarwal UK, Chaudhry K, et al. A study on time trends in incidence of breast cancer: Indian scenario. Eur. J. Cancer Care (Engl) 2007; 16[2]:185-6.
20. Manoharan N, Nair O, Shukla NK, et al. Descriptive epidemiology of female breast cancer in Delhi, India. Asian Pac. J. Cancer Prev. 2017; 18[4]:1015-8.
21. Sreedevi A, Jadev R, Dinesh A. Epidemiology of cervical cancer with special focus in India. Int. J. Womens Health. 2015; 7:405-14.
22. Rangarajan B, Shet T, Wadasadawala T, et al. Breast cancer: An overview of published Indian data. South Asian J. Cancer. 2016; 5[3]:86-92.
23. Yezhelyev MV, Gao X, Xing Y, et al. Emerging use of nanoparticles in diagnosis and treatment of breast cancer. Lancet Oncol. 2006; 7[8]:657-667.
24. Sau TK, Murphy CJ. Seeded high yield synthesis of short Au nanorods in aqueous solution. Langmuir, 2004; 20[15]: 6414-20.
25. Hauck TS, Ghazani AA, Chan WC. Assessing the effect of surface chemistry on gold nanorod uptake, toxicity, and gene expression in mammalian cells. Small. 2008; 4[1]: 153-9.
26. Kah JC, Wong KY, Neoh KG, et al. Critical parameters in the pegylation of gold nanoshells for biomedical applications: an in vitro macrophage study. J. Drug Target. 2009; 17[3]:181-93.
27. Hainfeld JF, Smilowitz HM, O'Connor MJ, et al. Gold nanoparticle imaging and radiotherapy of brain tumors in mice. Nanomed. (Lond.) 2013; 8[10]:1601-9.
28. Prades R, Guerrero S, Araya E, at al. Delivery of gold nanoparticles to the brain by conjugation with a peptide that

recognizes the transferrin receptor. Biomaterials. 2012; 33[29]:7194-205.

29. Shimizu T, Teranishi T, Hasegawa S, et al. Size evolution of alkanethiol-protected gold nanoparticles by heat treatment in the solid state. J. Phys. Chem. B. 2003; 107[12]:2719-24.
30. Day ES, Morton JG, West JL. Nanoparticles for thermal cancer therapy. J. Biomech. Eng. 2009; 131[7]:074001.
31. Huang X, Jain PK, El-Sayed IH, et al. Plasmonic photothermal therapy (PPTT) using gold nanoparticles. Lasers Med. Sci. 2008; 23[3]:217-28.
32. O'Neal DP, Hirsch LR, Halas NJ, et al. Photo-thermal tumor ablation in mice using near infrared-absorbing nanoparticles. Cancer Lett. 2004; 209[2]:171-6.
33. Lal S, Clare SE, Halas NJ. Nanoshell-enabled photothermal cancer therapy: impending clinical impact. Acc. Chem. Res. 2008; 41[12]:1842-51.
34. Zhang SX, Gao J, Buchholz TA, et al. Quantifying tumor-selective radiation dose enhancements using gold nanoparticles: a monte carlo simulation study. Biomed. Microdev. 2009; 11[4]:925-33.
35. Zheng Y, Hunting DJ, Ayotte P, et al. Radiosensitization of DNA by gold nanoparticles irradiated with high-energy electrons. Radiat. Res. 2008; 169[1]:19-27.
36. Prise KM, Schettino G, Folkard M, et al. New insights on cell death from radiation exposure. Lancet Oncol. 2005; 6[5]:520-8.
37. Huang K, Ma H, Liu J, et al. Size-dependent localization and penetration of ultrasmall gold nanoparticles in cancer cells, multicellular spheroids, and tumors in vivo. ACS Nano. 2012; 6:4483–4493.
38. Zhang W, Ji Y, Wu X, et al. Trafficking of gold nanorods in breast cancer cells: uptake, lysosome maturation, and elimination. ACS Appl. Mater. Interfaces. 2013; 5[19]: 9856-65.
39. Longmire M, Chokye PL, Kobayashi H, Clearance properties of nano-sized particles and molecules as imaging agents: Considerations and caveats. Nanomedicine (Lond) 2008; 3[5]:703-17.
40. Jokerst JV, Lovovkina T, Zare RN, et al. Nanoparticle PEGylation for imaging and therapy. Nanomedicine (Lond), 2011; 6[4]:715-28.
41. Alric C, Miladi I, Kryza D, et al. The biodistribution of gold nanoparticles designed for renal clearance. Nanoscale. 2013; 5:5930-9.
42. Libutti SK, Paciotti GF, Byrnes AA, et al. Phase I and pharmacokinetic studies of CYT-6091, a novel PEGylated colloidal gold-rhTNF nanomedicine. Clinical Cancer Res.: An Off. J. Am. Assoc. Cancer Res. 2010; 16[24]:6139-49.
43. Oberdorster G, Oberdorster E, Oberdorster J. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. Environ. Health Perspect. 2005; 113[7]:823-39.
44. Connor EE, Mwamuka J, Gole A, et al. Gold nanoparticles are taken up by human cells but do not cause acute cytotoxicity. Small. 2005; 1[3]:325-27.
45. Love SA, Thompson JW, Haynes CL. Development of screening assays for nanoparticle toxicity assessment in human blood: preliminary studies with charged Au nanoparticles. Nanomedi. (Lond.), 2012; 7[9]:1355-64.
46. Glazer ES, Zhu C, Hamir AN, et al. Biodistribution and acute toxicity of naked gold nanoparticles in a rabbit hepatic tumor model. Nanotoxicology. 2011; 5[4]:459-68.
47. Gad SC, Sharp KL, Montgomery C, et al. Evaluation of the toxicity of intravenous delivery of auroshell particles (gold-silica nanoshells) Int. J. Toxicol. 2012; 31[6]:584-94.

*Correspondence to

Pooja Pandey

Shambhunath Institute of Pharmacy

Uttar Pradesh

India

E-mail: ppoojapandey141998@gmail.com