



NANOTECHNOLOGY-DRIVEN APPROACHES TO BREAST CANCER: DIAGNOSIS AND TREATMENT

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Abstract: Cancer is a group of diseases that involves abnormal growth of cells, with the potential to occupy or spread to different parts of the body. Breast cancer is one of the most common malignant tumours in women worldwide, endangering both their physical and mental well-being. Usually, the cancer treatment involves chemotherapy and radiotherapy, but they consist of a great deal of several drawbacks like increasing toxicity, unselectively, and comparative lack of solubility in targeted cells. Nowadays, the application of nanotechnology in treatment of breast cancer received more attention. Basically, the tumours can be targeted or cured using nanoparticles. Nanoparticles like liposomes, polymeric nanoparticles, micelles, solid lipid nanoparticles, and gold nanoparticles are introduced in the targeted cell to cure the breast cancer. Nanoparticles consist of unique physio-chemical properties, which enhance drug delivery systems and sustained release of the drugs. They basically activate the immune cell against the tumours. Currently, the major type of breast cancer seen among the women is triple-negative breast cancer (TNBC), which is nothing but the absence of estrogen, progesterone, and epidermal growth factor type 2 receptor; for this, the use of nanoparticles is preferred. As well, there are numerous advantages to the nanotechnology-based targeted drug delivery system over chemotherapy, which helps in the treatment of cancer and in building a quality life. A combination of phytochemical and chemotherapeutic agents with nanotechnology will have a greater impact on the treatment of breast cancer in the future. In this review, we have been given the outline and clinical use of nanoparticles in therapy and diagnosis of breast cancer and also various studies categorized for breast cancer cell lines into the different groups that complicate our comprehension of cell line classification.

Index Words: malignant, chemotherapy, radiotherapy, nanotechnology.

1. INTRODUCTION:

Breast cancer is the most common cancer and the leading cause of cancer-related death. in women (1). Despite several treatment options and targeted therapies, the mortality rate remains high. (1). Female Breasts are composed of fatty tissue called adipose tissue (2). Female Breasts consist of approximately 20 lobes or lobules connected via the milk ducts. Adipose tissue consists of blood vessels, lymph vessels, and lymph nodes, as well as fibrous connective tissue and ligaments (2). As such, there are various risk factors that can induce various types of breast cancer according to the site and destruction of the receptors. Breast cancer can be divided into two types: in situ and invasive carcinomas (3). A) In situ carcinoma/non-invasive carcinoma: will not spread all over the body; remains where it is situated. For example, ductal carcinoma in situ and lobular carcinoma in situ. B) invasive carcinoma in which cancer cells passes through the breast and spreads all other parts of the body through systematic circulation. For ex. Infiltrating lobular carcinoma; IDC; medullary, mucinous, and tubular carcinoma. Inflammatory breast cancer may arise from a swollen breast

with broad ridges due to blocking of lymph channels by cancer cells in the skin of the breast. (4) Breast cancer is usually classified based on the type of receptor that is enhanced by the presence of cancerous cell membranes. Includes PR, ER, and HER2 receptors. Breast cancer, which shows the presence of enhanced receptors, is called ER-, PR, or HER2 positive depending upon the overexpression of receptors. Patients with ER, PR, and HER2 are referred to as triple-positive breast cancer, and those that do not show these three are called triple-negative breast cancer. Breast cancer is recognized in the field of medicine, with the greatest presence of nanotechnological therapeutic agents in clinics (5). Nanotechnology is a branch of science and engineering devoted to designing, producing, and using structures, devices, and systems by manipulating atoms and molecules at the nanoscale level. Various treatments or therapies can be used to treat breast cancer, such as surgery, radiation therapy, and chemotherapy. Hormone therapy, immunotherapy, targeted therapy, nanotechnological therapeutic agents Nanotechnological approaches have been used to improve delivery of nano-therapeutic agents to cancer cells with the goal of minimizing toxic effects on health tissue while maintaining antitumour efficacy (6)

2. NANOTECHNOLOGY IN CANCER BIOLOGY:

Materials and devices smaller than 100 nm are used in nanotechnology for the synthesis, characterization, and engineering of several applications across numerous domains. Numerous diseases can now be diagnosed, screened, and treated more quickly thanks to medical applications of nanotechnology. Nanotechnology has several uses in cancer biology, including tumour detection, the identification of cancer biomarkers, and therapeutic enhancement. (8) According to their transport characteristics and other attributes, nanoparticles are tiny molecules. Since Professor A.D. Bangham of the United Kingdom discovered lipid-based nanoparticles in 1960, researchers have been particularly interested in nanoparticles. Additionally, by bypassing numerous biological barriers and having fewer or no side effects than chemotherapy and radiation, nanoparticles provide a platform for efficient and targeted drug delivery. (9) Additionally, the nanotechnology-based drug delivery system is a novel approach that targets cancer cells specifically. It offers many advantages over traditional chemotherapy, including improved drug distribution and bioavailability, a longer shelf life, and the ability to administer both hydrophobic and hydrophilic molecules through oral, parental, nasal, and intracellular routes. Thus, the field of cancer research has a fresh hope thanks to the advancements in nanotechnology-based cancer treatments. (21)

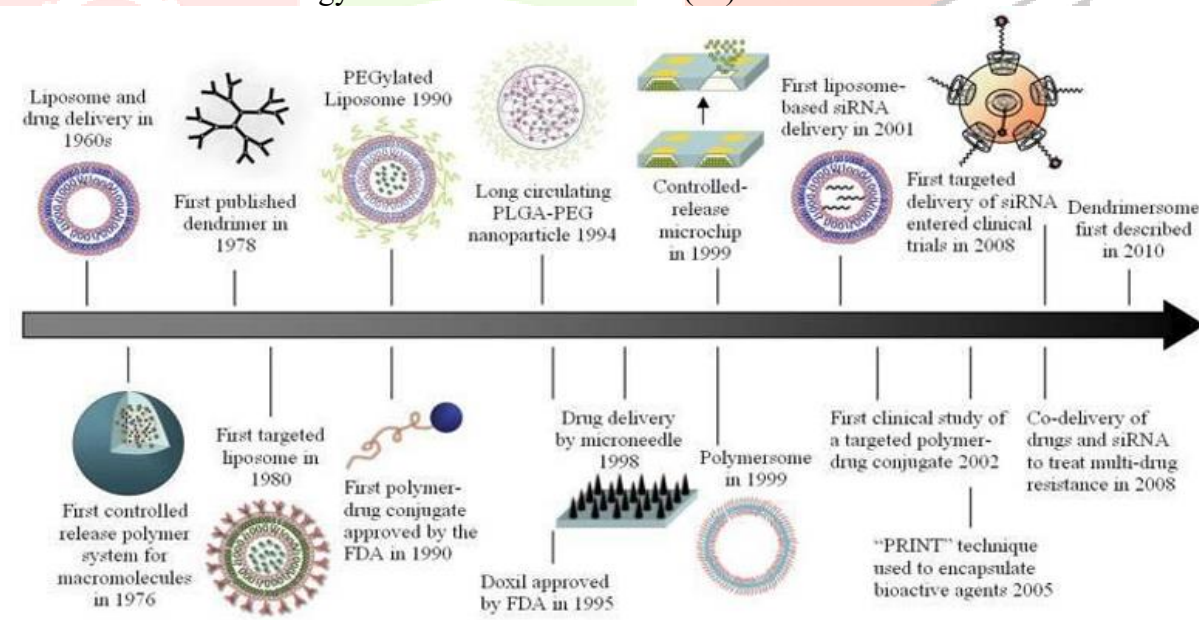


Figure 1: Development of nanotechnology-based drug delivery (21)

3. DIAGNOSIS AND IMAGING OF TUMOUR:

Hormone-receptor expression in breast cancer is directly linked to hormonal therapy benefits. Immunohistochemistry is used for determining hormone-receptor expression, but its use is limited. (29) Nanoparticles offer more accurate and sensitive quantification and profiling of biomarkers, offering advantages over immunohistochemistry in detecting different receptor proteins. The remarkable sensitivity of these particles and their capacity to detect targets that are found in cancer cells at low concentrations. Nanoparticles, composed of cobalt, nickel, or ferric oxide, are used in T2-weighted images as magnetic resonance contrast agents. These nano-agents are less harmful, biocompatible, and more rapidly absorbed by target tissue. High-resolution, non-invasive tumour imaging in vivo is possible when paired with quantum dots. (11,13) Super magnetic nanoparticles, such as ultrasmall superparamagnetic iron oxide [USPIO] nanoparticles, significantly enhance MRI by producing a magnetic field that influences tissue and amplifies scan signal. (12) Quantum dots can be conjugated to specific antibodies, allowing simultaneous detection and quantification of tissue protein spectra. These dots have enhanced photostability, allowing long-term fluorescence emission, and increased diagnostic sensitivity. (10)

3.1 BIOMARKER PROFILING:

Molecular profiling techniques are crucial in oncology due to the increasing use of targeted medicines. The expression of specific proteins or genes in cancer cells determines the effectiveness of targeted therapies. For example, hormone-receptor expression is closely correlated with the effectiveness of endocrine therapy in breast tumors. Immunohistochemistry is the conventional technique for determining hormone receptor expression. (14) Immunofluorescent staining methods can visualize targets, but organic dye molecules like fluorescent tags have limitations. Quantum dots have unique optical properties, exceptional photostability, and can be easily detected and quantified with spectrometry, overcoming these limitations. 17 Quantum dots, conjugated nanoparticles, can increase sensitivity and selectivity in molecular target labeling. They can identify targets in cancer cells at low levels due to their strong fluorescence. Studies have shown their colocalization with cytoskeletons in fibroblasts, and their optical and physical properties can be distinguished through electron microscopy. (15, 16). A quantum dot-based technique that enables the quantitative identification of ERBB2, progesterone receptor, and estrogen receptor in paraffin-embedded human breast cancer cells was created by Yezhelyev and associates. Multiple quantum dots, which were directly bioconjugate to targeting antibodies for the estrogen receptor, progesterone receptor, and ERBB2, were stained simultaneously with breast cancer cell lines that were known to exhibit differential expression of these three proteins (e.g., MCF-7, BT474, and MDA-231 cells). Using these conjugates and spectrometry, the quantitative expression of the breast cancer biomarkers was concurrently found on single samples of breast cancer cell lines. This was correlated with semiquantitative western blotting and traditional immunohistochemical analysis. Furthermore, the estrogen receptor, progesterone receptor, and ERBB2 have been identified and measured on human breast tumors embedded in paraffin. Automated image analysis and immunohistochemistry techniques can accurately measure biomarkers in clinical breast cancer tissues, but they are not widely available. Detecting proteins on single tumor specimens can be challenging due to antibodies requiring different antigen retrieval techniques. An assay that can measure multiple cancer-related proteins simultaneously could be beneficial. (14, 15, 16, 17)

3.2 TUMOUR IMAGING:

Magnetic nanoparticles are used in MRI due to their ability to provide contrast, reduce toxicity, and offer biologic flexibility. Bismuth nanoparticles are used as a contrast factor for CT, while superparamagnetic nanoparticles (0-10 nm) are used for MRI. These nanoparticles have a nonspecific distribution, quick pharmacokinetics, and can absorb a wide range of x-rays. (18, 19) They can survive in blood for up to two hours. Conjugated nanoparticles containing specific antibodies can diagnose and treat cancer simultaneously. Streptavidin and biotin can conjugate target ligands, creating a nanoshell. (20, 21) This system consists of a silica-based nanoparticle, a dielectric core, and a gold film. With near-infrared transmission, the nanoshells transform light into thermal energy, enabling thermal tumor elimination or surgery. The nanoparticles' efficiency is one million times higher than colored molecules. Targeted nanoshells can permanently remove breast tumors in vivo by producing heat that is too high to cause tissue damage and cell death. (18). Nanoparticles, composed of cobalt, nickel, or ferric oxide, are used in T2-weighted images as magnetic resonance contrast agents. They are less harmful, biocompatible, and faster absorbed by target tissue. High-resolution non-invasive tumor imaging in vivo is possible when paired with quantum dots, which are useful for tumor blood vessel labeling. Additionally, by bypassing numerous biological barriers and having fewer or no side effects than chemotherapy and radiation, nanoparticles provide a platform for efficient and targeted

drug delivery. Additionally, the nanotechnology-based drug delivery system is a novel approach that targets cancer cells specifically. It offers many advantages over traditional chemotherapy, including improved drug distribution and bioavailability, a longer shelf life, and the ability to administer both hydrophobic and hydrophilic molecules through oral, parental, nasal, and intracellular routes. Thus, the field of cancer research has a fresh hope thanks to the advancements in nanotechnology-based cancer treatments. 10 Superparamagnetic nanoparticles, composed of anti-Her-2 antibodies and a magnetic metal core, can enhance breast cancer imaging by enabling in vivo tumor detection and metastasis detection when used with targeted ligands. (10)

3.3 CONCURRENT IMAGING AND THERAPEUTIC TARGETING:

In order to enable subcellular imaging technologies in vivo, nanoparticles can be bio conjugated to various affinity ligands and employed as contrast agents. Conjugated to a targeted antibody, nanoparticles allow for the simultaneous diagnosis and therapy of cancer. The promise of this strategy has been demonstrated by preliminary in vitro and in vivo investigations. Using biotin and streptavidin linkers is one method for bio conjugated targeted ligands to nanoparticles. Using this method, an antiERBB2 has been coupled to a modified metal nanoparticle to create nano shells. The structure consists of a thin gold shell enclosing a spherical silica dielectric core nanoparticle. These near-infrared-emitting nanoshells have been employed to provide thermal tumour ablation by converting light into thermal energy. Compared to similar dyes, thermal induction following near-infrared exposure with these nanoparticles is more than a million times more effective. after bioconjugation with compounds that are antiERBB2. These magnetite nanoparticles were specifically labelled to ERBB2-positive SK-BR-3 breast cancer cells by Ito and colleagues. These conjugated nanoshells produced hyperthermia in response to near-infrared light, with an average temperature significantly higher than what is required to cause irreversible tissue damage and tumour-cell death. Therefore, localized, irreversible photothermal ablation of breast tumours in vivo can be accomplished using targeted nano shells. (6,14)

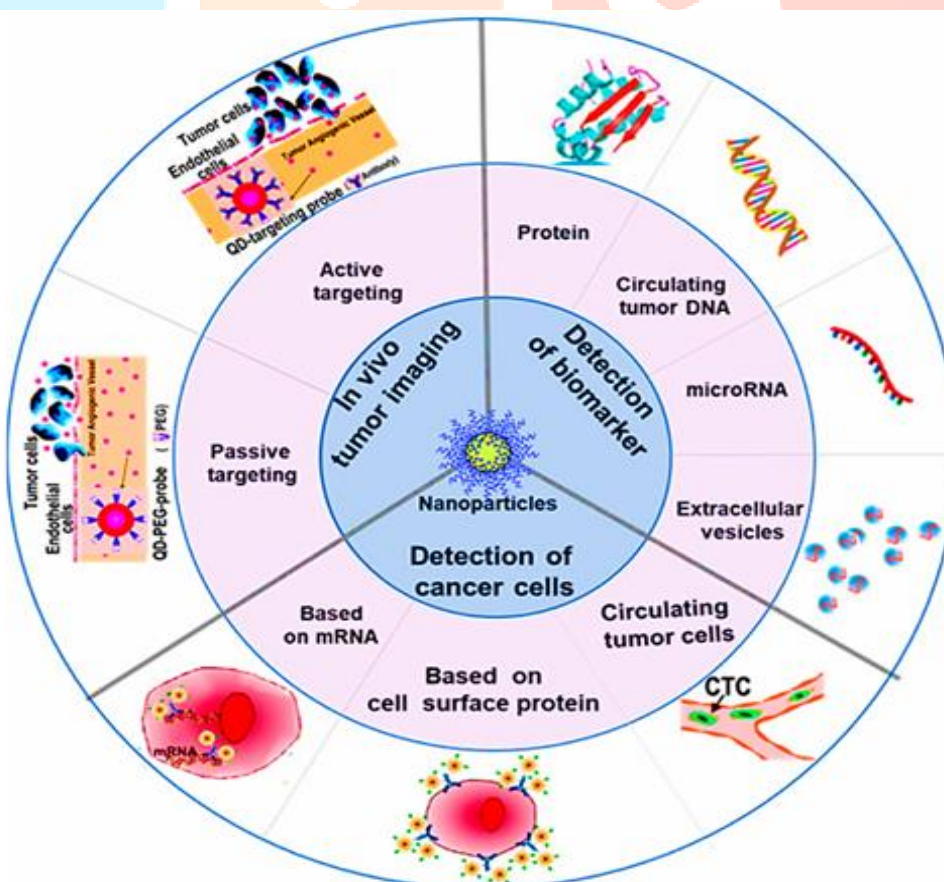


Figure 2: Presenting detection and imaging of tumour cells in breast cells. (29)

3.4 THERMAL ABLATION:

A thin gold shell encircles a silica core in nanoshells. The particle generates thermal energy that causes local tissue ablation once its surface thickness is precisely adjusted to be activated by near-infrared irradiation. The nanoshells should gather in the intended target tissue when coupled to a particular targeting antibody in order to localize the destruction of cancer cells.(22,23) Anti-HER2 conjugated nanoshells have been used in animal models to show targeted thermoablation of breast cancer cells.(24,21) When treated with in vitro breast cancer cell lines and coupled with IGF1R and HER2 antibodies, nanotubes tube structures with walls that are one carbon molecule thick have demonstrated a comparable thermoablative activity.(22)

4. NANOCARRIERS: A NOVEL APPROACH OF DRUG DELIVERY:

The concept of nanocarriers emerged from Paul Ehrlich's observation that selective targeting of pathogens allows for the delivery of toxic agents. Nanomaterials have been designed for drug delivery, but site-specific targeting is necessary for diagnostic or therapeutic effects. Nanotechnology-based carriers have been used for high drug load and sustainable release, avoiding biological obstacles and targeting drugs effectively.(25,26) Major organic and inorganic biomaterials have been discovered as drug carrier polymers, such as PEG, polyglutamic acid (PGA), polylactic acid (PLA), polycaprolactone(PCL), poly-D,L-lactide-co-glycolide (PLGA), and N-(2-hydroxypropyl)-methacrylamide copolymer (HPMA).(27,28) Improvements in polymeric nanoparticles encumbered with drugs have been made since Langer and Folkman recognized the first organized release of macromolecules by polymers(25,28).

Nanoshells as active targeting molecules:

Nanoshells are promising candidates for cancer diagnosis and treatment due to their unique properties, such as angiogenesis, high vascular density, and macromolecule extravasation in plasma. Polymeric drugs accumulate in tumours due to plasma diffusion facilitated by vascular epidermal growth factor (VEGF). Endothelial factors accumulate nutrients and oxygen, allowing plasma components to penetrate blood vessel walls, promoting rapid growth. However, nanoshells have limitations due to less penetration and targeting tumour sites. Gold nanoshells in the near infrared region can heat up tumours irreversibly, causing irreversible damage. Nano shell treatment also includes bio-recognition sites that dock with cancer cell receptors. Endoscopic procedures help focus Near Infrared (NIR) radiation at increasing depths. (25)

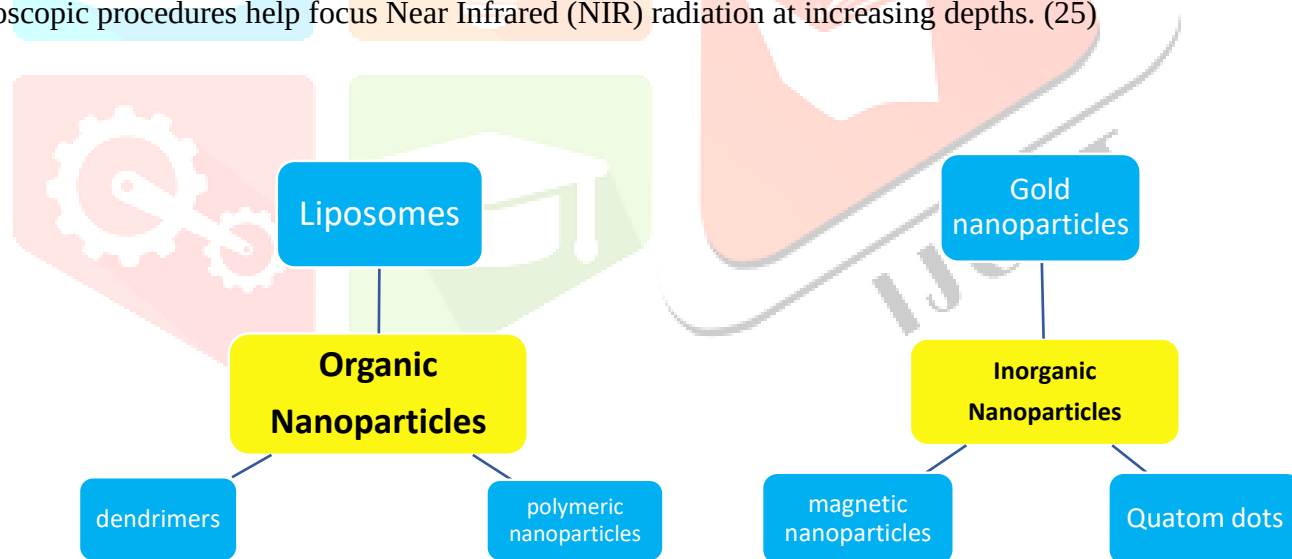


Figure 3: types of nanoparticles

4.1 LIPOSOMES:

Liposomes, developed by Bangham and Horne in 1964, are spherical vesicles with a phospholipid outer layer. They are used for targeted drug delivery due to their biocompatible, biodegradable, and non-immunogenic properties. Liposomes can pass through vascular pores and accumulate in tumours. They also increase rhodamine retention in MCF-7/P-gp cells. Liposomes have been used for anticancer drug delivery to breast cancer cells since 1965. A paclitaxel-nanoliposome formulation was developed using phosphatidylcholine and cholesterol, demonstrating significant cytotoxicity in MCF-7 breast cancer cells. PEGylated liposomal doxorubicin (PLD) showed a 1500-fold higher area under the curve (AUC) in a breast cancer model compared to non-liposomal doxorubicin. pH-sensitive polymer-liposome complexes were also studied for their potential in anticancer therapies. Liposomes have also been developed to combine two anticancer drugs, such as co-loaded liposomes with paclitaxel and rapamycin. These liposomes were found to be more cytotoxic to 4T1 breast cancer cell lines than the free drug in vitro. (4) Liposomes, vesicles with hydrophilic

and hydrophobic groups, are utilized as drug carriers in chemotherapy for human cancers like breast cancer, as they can encapsulate hydrophobic and hydrophilic molecules. (30) Doxorubicin, a drug with a liposome delivery system, is approved for treatment of refractory ovarian cancer and Kaposi's sarcoma in the USA. Nanoparticle albumin-bound paclitaxel is also approved for metastatic breast cancer. (6) Liposomes, self-assembling, have a colloidal structure with a lipid bilayer and a central aqueous area. They can be surface functionalized via PEGylation, promoting receptor-mediated endocytosis and increasing circulation half-life. (7) Liposomes, composed of synthetic or natural phospholipids, have physical and chemical properties based on their constituent phospholipids. They close in on themselves through interactions with water molecules.

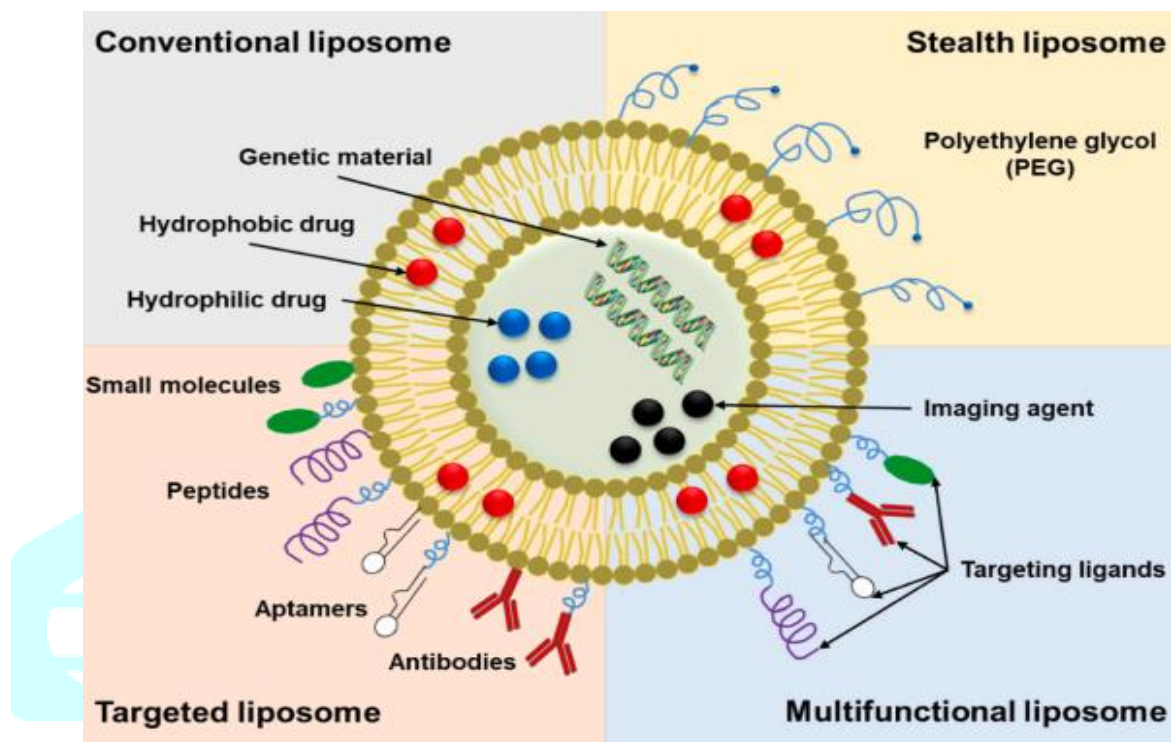


Fig. 4. Simplified representation of conventional, PEGylated, targeted, and multifunctional liposomes. (32)

and hydrophobic phosphate groups. Drug loading into liposomes can be achieved through liposome formation, organic solvents, lipophilic drugs, and pH gradient methods. Liposomes can target specific tissues through active and passive targeting strategies. Due to their size liposomes are rapidly cleared by the MPS system. Liposomal formulations of anticancer drugs are available for human use. Doxil is a liposomal version of doxorubicin, an anthracycline drug, used to treat cancer in AIDS-related Kaposi sarcoma and multiple myeloma. This formulation offers better effectiveness and reduced heart-related side effects compared to regular doxorubicin. (31) Liposomes made only of phospholipids have a short shelf-life and struggle to keep drugs inside due to high leakage. To improve this, sterols like cholesterol are added to enhance membrane stability. Liposomes protect drugs from environmental and chemical changes, impacting pH, temperature, and ion levels. Other materials like vitamin E and polymers can also improve the stability and distribution of liposomes. Liposomes offer many benefits as drug delivery systems, including self-assembly, the ability to hold various types of compounds, improved solubility, and low toxicity. Advancements allow liposomes to respond to different stimuli and target specific sites, reducing drug toxicity and improving distribution. Currently, four liposome-based cancer treatments are approved: Doxil®/Caelyx®, Myocet, Lipodox®, and Lipusu®. Doxil®/Caelyx® is a PEGylated system used for several cancers and is known for reducing free drug levels while increasing circulation time. Myocet is non-PEGylated and has been used in Europe for treating metastatic breast cancer since 2000, with a special status granted in the U. S. for HER2-positive cases. Lipodox® was used in 2012 as a substitute during a shortage of Doxil® in the USA and is now seen as a generic equivalent. Lipusu® is a non-PEGylated liposomal system that encapsulates PTX, a chemotherapy drug from the Pacific Yew tree, often given as Taxol® for ovarian and breast cancers. To reduce Kolliphor-EL toxicity, various nano-based drug carriers have been created, including polymeric micelles and liposomes. Although Lipusu® is approved in China for HER2-metastatic breast cancer, its composition is not publicly available. DaunoXome®, a heat-activated liposome with daunorubicin, has been studied for metastatic breast cancer but is not yet clinically approved. (32)

4.2 DENDRIMERS

Dendrimers are unique polymers with a nanoscale branched system, synthesized from monomers using step growth polymerization. They have three main regions: surface, complex branching system, and core molecule. Dendrimers are stable and ideal nano drug carriers, with anticancer drugs either encapsulated or sticking to them. They attach to polyamidoamine, poly (ethylene glycol), chitin, and chitosan. Dendrimers are involved in drug delivery and gene delivery. (33) Dendrimers, a type of liposome, are used for siRNA delivery in tumours. Studies have shown that an antisense oligo attached to dendrimers can decrease tumour vascularization in TNBC xenograft mice. A novel dendrimer, G4PAMAM, was used for tumour imaging and drug delivery, demonstrating its potential as a nanocarrier and targeted diagnostic and therapeutic agent. (34) Dendrimers, including poly-lysine, polypropylene imine, phosphorus, and carbosilane, are used in biomedical applications, particularly in oncology. Polylysine (PLL) is an amphiphilic dendrimer with a branched structure, making it easier to internalize. Dendrimers and micelles have shown therapeutic efficacy in breast cancer treatment, resolving drug resistance, decreasing toxicity, and increasing solubility. They have been loaded with various anticancer agents, enhancing their effectiveness. (35) Dendrimers, large spherical molecules, are used in Magnetic Resonance Imaging (MRI) as contrast agents to detect pathological processes. Made from natural or synthetic elements, they have an external surface, internal dendritic structure, and central core.(30)

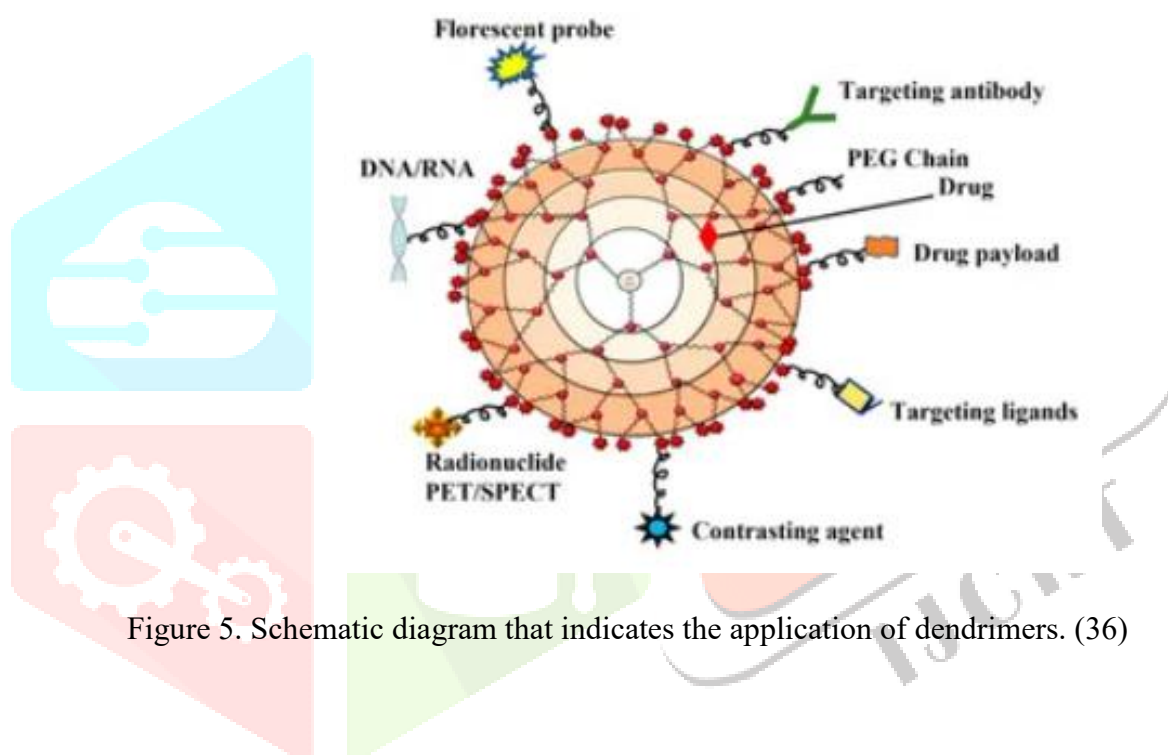


Figure 5. Schematic diagram that indicates the application of dendrimers. (36)

4.3 POLYMERIC NANOPARTICLES

Polymeric nanoparticles, also known as polymersomes, are micelles that self-assemble from either natural or manufactured polymers. Polymersomes have great stability and specificity. Natural polymers including chitosan, cellulose, alginate, and gelatine, as well as synthetic polymers like poly-Lactide (PLA), poly-Caprolactone (PCL), and poly(lactic-glycolic acid) (PLGA)] can be utilized to produce nanoparticles. The delivery of therapeutic drugs to breast cancer cells via polymeric nanoparticles. Polymeric nanoparticles have been developed for the delivery of anticancer drugs to breast cancer cells. These nanoparticles, which are a promising treatment for breast cancer, have shown significant improvements in tumour weights and volumes in BALB/c mice treated with psoralen-polymeric nanoparticles. Tamoxifen nanoparticles, which contain tamoxifen, showed greater accumulation in tumours and systemic circulation compared to the control group. Other studies have also explored the use of PLGA and DSPE-polyethylene glycol 2000 for breast cancer therapies. (4) Synthetic polymers like polylactide (PLA), poly (D, L-lactide-co-glycoside) (PLGA), and polyethylene glycol (PEG) are biodegradable and hydrolysed in vivo. They can be combined to form co-polymers, such as PLA-block-PEG co-polymers, which can be activated by ligands. Polymeric nanoparticles, still in the preclinical phase, have the potential for targeted delivery of cancer drugs due to their ease of attachment to ligands. (31)

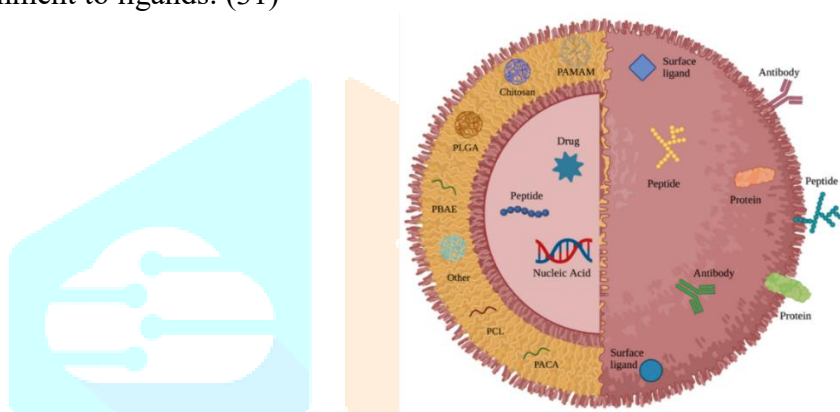


Figure 6. General structure of a polymeric nanoparticle. (37)

4.4 GOLD NANOPARTICLES

Breast cancer is diagnosed, imaged, and treated with gold nanoparticles (AuNPs). (30) Gold nanoparticles, with their inert, non-toxic, and below 150 nm size, are being explored for their biocompatibility, potential for radio sensitization, and photothermal therapy. (4) These particles are used as medication carriers and contrast agents. AuNP conjugation has the potential to improve precise targeting, stability, and biocompatibility of different peptides. There are multiple steps in the body's mechanism of action for AuNPs. (38) AuNPs first bind to their respective receptors. After that, when they come into contact with light or radiofrequency pulses, they oscillate. Consequently, heat is released by AuNPs and light is absorbed. As a result, the cell's surroundings are heated. (39) Consequently, there is irreversible thermal cellular damage. Gold nanoparticles were functionalized with zinc phthalocyanine and a lactose derivative, producing water-dispersible nanoparticles that generate singlet oxygen and cause cell death upon radiation. The targeting ability of lactose was studied in vitro on breast cancer cells, showing its potential as a targeting agent. Antibody-conjugated gold nanoparticles were used for surface-enhanced Raman spectroscopy imaging of tumour biomarkers in MCF-7 breast cancer cells. (40) Chloroquine gold nanoparticles showed anticancer activity in MCF-7 cells, with concentration-dependent uptake and cytotoxicity. Docetaxel gold nanoparticles showed 2.5-fold higher efficacy than docetaxel alone. Inulin-coated gold nanoparticles were prepared for selective delivery of doxorubicin to breast cancer cells, increasing anticancer activity. (4)

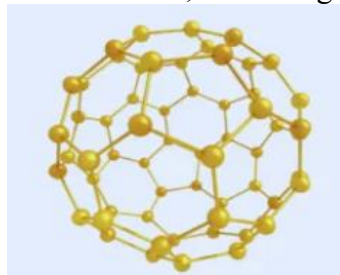


Figure 7- structure of gold nanoparticle (4)

4.5 MAGNETIC NANOPARTICLES

MNPs are nanocarriers with diameters ranging from 1 to 1000 nm, primarily composed of iron, cobalt, nickel, and their oxides like chromium dioxide, hematite, cobalt ferrite, or ferric oxide.(41) Organically coated magnetic nanoparticles can be used in cancer treatment and cell trafficking research, serving as a magnetic resonance agent for iron oxide.(30) Super magnetic nanoparticles contain a metal core (e.g., iron, cobalt, or nickel) that is magnetically active and are used as contrast enhancement agents to improve the sensitivity of MRI. Magnetic particles, when coated with an organic outer layer, can also be conjugated to biomolecules and used as site-specific drug-delivery agents for cancer treatment. Iron-oxide-based magnetic materials have been used widely in clinical practice as magnetic resonance agents and in studies of gene expression, angiogenesis imaging, and cellular trafficking. Metal nanoparticles in combination with fluorescent active molecules can be used for combined optical and magnetic imaging. (14) Magnetic drug delivery systems can work with loaded drugs to reach tumour sites more localized under an external magnetic field. These systems can be synthesized and functionalized in different sizes and structures, with strategies including magnetite or maghemite core shell structures and functional groups attached via cross links. (42)

4.5.1 IRON OXIDE NPs

Magnetic nanoparticles (MNPs) are used in oncological studies due to their ability to target specific side effects, limiting systemic circulation, encapsulating drugs, and improving dissolution. (25) These nanoparticles can be modified with compounds like dextran, polyethylene glycol, and poly(vinylpyrrolidone) to reduce opsonization and overcome clumping. MNPs contain medications like mitoxantrone, tamoxifen, cefradine, doxorubicin, daunorubicin, cisplatin, gemcitabine, paclitaxel, and Adriamycin. (43) When coated with water-dispersed oleic acid pluronic, NPs produced sustained drug release at a concentration dependent on anti-proliferative significance. MNP-induced hyperthermia has been established as a promising therapeutic approach for cancer treatment. (25,44)

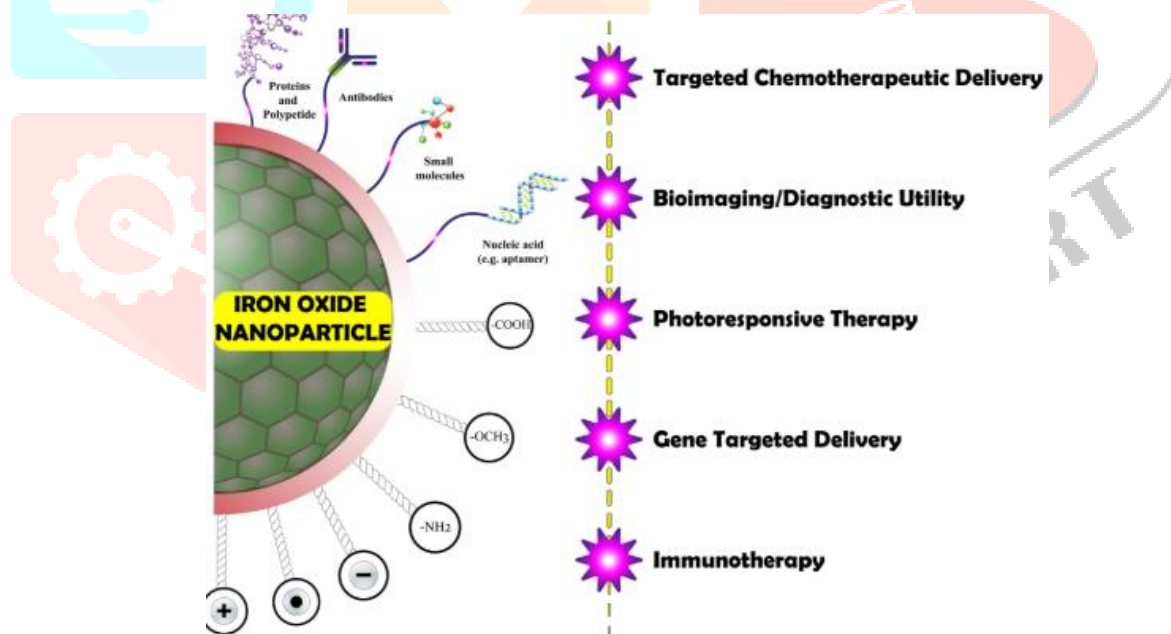


Figure 8-structure of iron oxide representing various applications in diagnosis and treatment of cancer.

4.5.2 COBALT [CO] NPS

Cobalt nanoparticles (NPs) can be synthesized as cobalt oxide, coupled with biological polymers or organometallic compounds. By altering their surface, cobalt oxide nanoparticles can increase their anticancer efficacy. (25,45) Cobalt is known to function as a contrast agent in biomedicines through magnetic resonance imaging (MRI), conjugating with platinum, graphite, iron, and gold; Additionally, it has been examined for the therapy of cancer, particularly breast cancer using the MCF 7 cell line. Additionally, their environmentally friendly characteristics make them a suitable candidate for biological applications. (25,46)

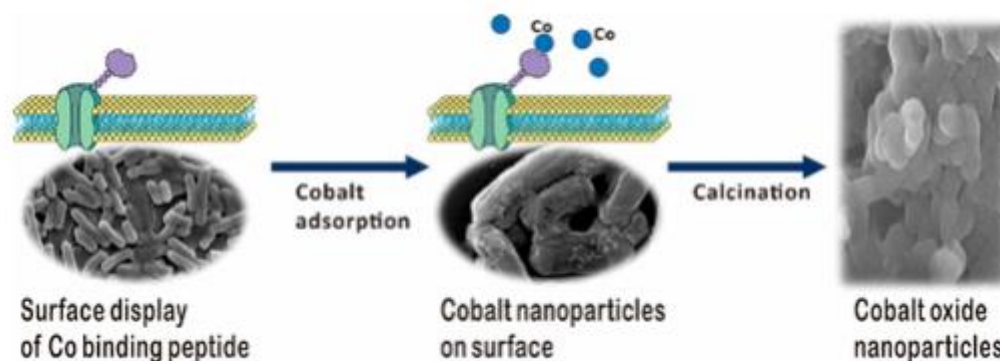


Figure 9. Schematic illustration of the microbial synthesis of cobalt oxide nanoparticles by cell surface display.

4.5.3 NICKEL NPS

Catalysis and sensing make extensive use of nickel nanoparticles that are generated by several methods. Current research shows that Ni NPs may be used in biomedicine, including both cancer diagnosis and treatment. Ni nanowire causes ROS, which causes human pancreatic adenocarcinoma cancer cells and human breast cancer MCF-7 cells to undergo apoptosis. (25,47) Following NP exposure, mRNA levels are increased and the caspase-3 enzyme is activated. Effective cytotoxicity against leukemic cancer cells was demonstrated by Ni NPs coupled with daunorubicin. In a model organism, verbascoside, an anticancer medication linked to Ni NPs, causes K562 cells to undergo apoptosis, preventing the formation of tumours. Following a 24-hour treatment with Ni NPs, MCF-7 human breast cancer cells also shown cytotoxicity. (25,48)

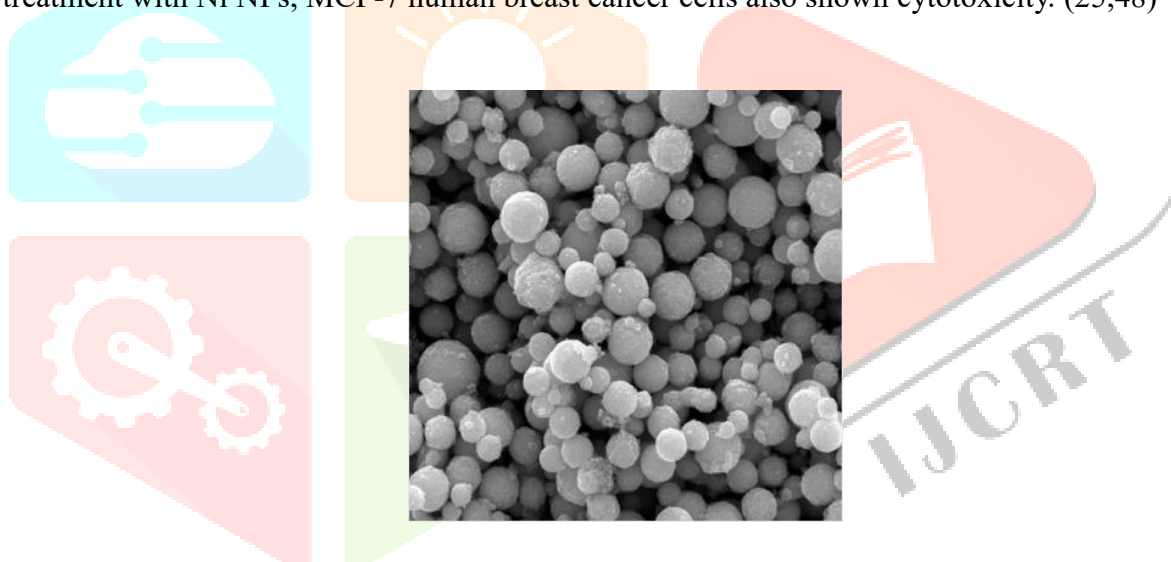


Figure 10- microscopic structure of nickel nanoparticle powder.

4.6 QUANTAM DOTS

Quantum dots are fluorescent nanoparticles with a central core of various elements, including cadmium selenide and zinc sulphide, surrounded by an amphiphilic polymer and ligand. However, their use in therapeutic and imaging applications is limited due to toxic influences. (30) Quantum dots, photodynamic semiconductor nanocrystals with multicolour labelling properties, are used in receptor profiling due to their photostable nature, allowing long-term fluorescent light emission without rapid decline. Quantum dots, when used as fluorescent tags, provide brighter and more stable signals, facilitating the detection and quantification of tumour receptors. (10) Quantum dots (QDs) are inorganic nanocrystals 1-10 nm in diameter with semiconductor properties. Synthesized using Cd, Se nano-particles, QDs can load large amounts of drugs without altering their therapeutic properties. They are useful in biological imaging, cancer diagnosis, and treatment due to their fluorescent emission and photo stability. However, QDs have limitations, including toxicity and excretion pathways, with Cadmium being a potential toxicity factor. (33) Quantum dots arrays can control super-radiance, improving breast cancer hyperthermia by minimizing damage to healthy tissues. Recent studies show fullerenes can be used for diagnosis and treatment of breast cancer. (49)

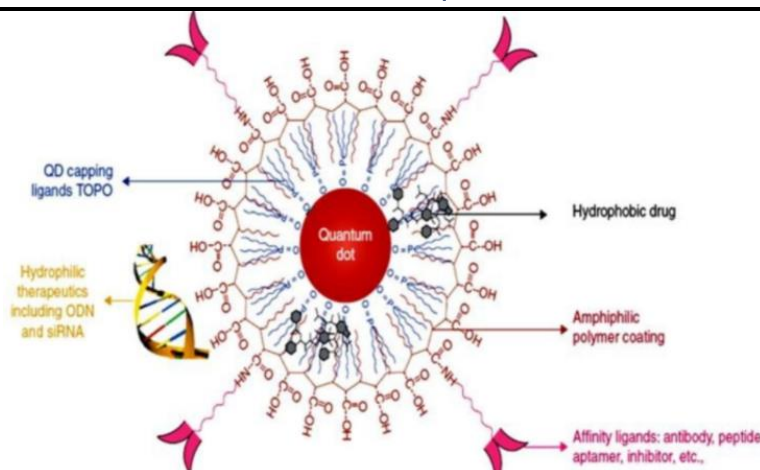


Figure 11 – structure representing the quantum dot nanoparticle.

TABLE 1- Representing drugs combined with the different nanoparticles with their chemotherapeutic effects.

DRUG	NANOPARTICLE	OUTCOME	REFERENCE
Doxorubicin	Poloxamer 407, holo-transferrin	Overcome chemotherapy drug-resistant	(52)
Paclitaxel	Polyethoxylated castor oil (Cremophor)	Treatment of patients with advanced breast cancer	(52)
Rapamycin, Piperine	PLGA	Superior treatment of breast cancer via co-delivery	(52)
Curcumin	Bovine serum albumin	Treatment of breast cancer	(52)
AXT050 (collagen-IV derived bio mimetic peptide)	PLGA-PEG nanoparticle	Enhanced anticancer activity	(52)
Docetaxel	PLGA, PEG, super-paramagnetic iron oxide	Outstanding drug delivery strategy for breast cancer	(52)
Doxorubicin	Poly-(methacrylic acid), Polysorbate 80 grafted-Starch	Targeting brain metastases of breast cancer	(52)
Tamoxifen citrate	PLGA	Enhanced permeation into breast cancer cells	(52)
Curcumin	N-isopropylacrylamide, Methacrylic acid	Breast cancer treatment	(51)
Simvastatin	Cholic acid, PLGA	Breast cancer chemotherapy	(51)
Cisplatin, paclitaxel	Poly(2-oxazoline)	Improved chemotherapy of ovarian and breast cancer; potential for clinical translation	(51)

Docetaxel	PLGA (polymer hybrid nanoparticle)	Advanced therapeutics to combat breast cancer	(51)
Dasatinib	Poly(cyclohexene phthalate)	Controlled drug delivery for breast cancer treatment	(51)
5-fluorouracil (5-FU)	5-FU-glutathione-GNP	Higher anticancer effect compared with non-conjugated 5-FU	(53)
Cyclophosphamide (CPA)	Folate-GNP	A higher sensitivity of α HFR-positive breast cancer cells to cyclophosphamide treatment.	(53)
doxorubicin (DOX) and 2-deoxy- D glucose	Iron oxide (IONP)	enhanced chemotherapeutic actions in breast cancer cells via targeting	(54)
Daunorubicin	Iron oxide (IONP)	Used for treatment of brain glioma	(54)
Cadmium sulfide (CdS)	Quantum dots	Used for drug delivery in tumour	(55)
Cadmium telluride (CdTe)	Quantum dots	Used to load large amounts of drugs without altering their therapeutic properties.	(55)

5. RECENT ADVNCEMENTS

Nanoparticles are frequently utilized in the treatment of cancer and hold significant promise for drug delivery. Numerous benefits have been demonstrated by nanoparticles, including great encapsulation, good stability, and the capacity to include both hydrophilic and hydrophobic medications. However, there have also been some possible hazards associated with nanoparticles. In addition to having additional intricate colloidal structures, solid-lipid nanoparticles (SLNs) have poor drug loading capabilities. The cationic lipids found in liposomes have the potential to be poisonous and degrade quickly in the body. The USFDA has only approved a small number of nanomedicines to yet, with Doxil and Abraxane being the two most effective ones for treating breast cancer in clinical settings. In recent years, a number of different formulations are in the clinical trial stage, and several more promising nanocarrier-assisted targeted deliveries of synthetic and natural compounds have been studied. In recent years, nanomedicine has demonstrated some benefits in assisting in overcoming the challenges associated with conventional BC treatments. At least one dimension of operation in materials ranging in size from 1 to 100 nm is made possible by nanotechnology. For instance, nanoparticles (NPs), which are defines technologically as one-dimensional particles less than 100 nm, were primarily created for targeted medicine administration. . By preventing the distribution of pharmaceuticals in healthy tissues, the NPs not only enhance the biological distribution of medications and direct active molecules to diseased tissues, but they also save healthy tissues. Small size, high surface-to-volume ratio, physical and chemical properties that can be adjusted, the capacity to load large amounts of drugs, prolonged circulation time, high uptake and retention, tumour-targeting efficacy, sustained release of the chemotherapeutic payload, biocompatibility, bioavailability, longer circulation time, and the ability to overcome multidrug resistance are some of NPs' special qualities. Additionally, because of their small size, nanoparticles can penetrate biological barriers like the blood-brain barrier, opening the door to treating BC patients who have brain metastases. (36) Biocompatible silk-sericin-tagged inorganic nanohybrids were created by Riham M. et al. for effective cancer cell imaging and treatment. The produced nanocarriers are expected to maintain the

luminous properties of ZnO quantum dots (QDs), enhance the colloidal stability of layered double hydroxides (LDHs), and stop the premature release of the chemotherapeutic drug pemetrexed (PMX). In conclusion, LDH-sericin nanohybrids coupled to ZnO QDs 135 and loaded with PMX demonstrated promise as a cancer theragnostic nanomedicine. The most recent study used N-doped graphene quantum dots (N-GQDs)-decorated tin sulphide nanosheets (SnS₂) to design and construct an enzyme-free sensor for in situ monitoring of H₂O₂ generated by human BC cells. The N-GQDs@SnS₂ electrode was utilized to successfully monitor H₂O₂ generated from mouse fibroblasts and BC cells in real time. (50)

CONCLUSION: Research on nanoparticles for the treatment of breast cancer has grown significantly in recent years, with a primary focus on employing targeting ligands to obtain high accumulation with tumours. HER2 is one of the most prevalent cell surface receptors on breast cancer cells, and conventional anticancer medications like doxorubicin, docetaxel, and paclitaxel work well against this receptor. Compared to nanoparticles without targeting ligands, treatment efficacy is raised and toxicity in healthy cells is prevented when targeting ligands are used in the nanoparticle production process. Nanoparticles are therefore a promising treatment option for breast cancer as well as other cancers in the future

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