Potential Role of Graphene Oxide in Diagnosis and Treatment of Breast Cancer- An overview

Prashant Shahadev Tandale[1], Abhishek Kumar[1], Pavani Sriram[2], Ramesh Kasarla[3], Ashish Suttee[1*]

[1]School of Pharmaceutical Scineces, Lovely Professional University, Punjab, India.
[2]Vaagdevi College of Pharmacy, Kakatiya University. Warangal, Telangana State, India.
[3]Lab of Molecular and Cellular Endocrinology Division of Endocrinology, Diabetes, and Metabolism, Department of Medical Sciences - University of Turin, Corso Dogliotti, 14 - 10126 Turin, Italy.

Corresponding author : Dr. Ashish Suttee (ashish7sattee@gmail.com)

DOI: 10.31838/ecb/2023.12.s1-B.262

ABSTRACT

According to World Health Organization estimations, there are 2.3 million women diagnosed with breast cancer in 2020, with 6,85,000 deaths worldwide and 7.8 million women alive who have been diagnosed with breast cancer in the previous 5 years, making it the world's most prevalent cancer. Breast cancer is a diverse illness on a molecular level. Several critical unsolved clinical and scientific issues persist despite great advancements in the detection and treatment of breast cancer. Graphene-based materials have shown tremendous relevance for detecting/imaging, quality/drug conveyance, malignant growth treatment/finding, and tissue designing/regenerative medication. Indeed, graphene (G) and graphene oxide (GO)-based nano-structures are promising candidates for applications in cancer therapy due to their large surface area, ease of functionalization, high drug loading capacity, and reactive oxygen species induction potentials. For the application of graphene and graphene oxide-based nanosystems in cancer therapy, significant obstacles, recent advancements, and perspectives for the future are discussed.

Keywords: Cancer, breast cancer, graphene oxide, therapies, treatment of cancer, nanomaterials, nanostructures

INTRODUCTION

Every year, about 1.5 million women worldwide are diagnosed with breast cancer.[1-3] Breast cancer cases in the United States have gradually climbed during the last three decades. In the United States, 181,600 new cases of breast cancer have been detected, with 44,190 people dying as a result of the disease.[3,4]

The Breast is made up of adipose tissue, nerves, lymph, lymph vessels, blood vessels, and lymph nodes, all are supplied with adipose tissues. Both male and female breasts have glandular tissue, however, female breasts have more glandular tissue than male breasts. It

typically occurs in lobules and ducts. Lobules are milk-producing glands, and ducts transport milk from the gland to the nipples.[5,6]

It typically develops in areas where the majority of breast tissues are located, such as the top and outer quadrants of the breast[7,8] Breast ductal and lobular epithelium can both develop malignant diseases. This concern (a) prevention (who needs it and when), (b) diagnosis (we need more accurate and sensitive methods), (c) tumor progression and recurrence (what causes it and how to predict it), (d) treatment (who should be treated and how), and (e) therapeutic resistance (how to anticipate, prevent, and overcome it).[9]

Although the majority of breast cancers begin in the ductal epithelium, malignant cells can also form in the lobular (milk-producing) glands.[10] Sarcomas and lymphomas, which are abnormalities of other breast structures, are not typically associated with breast cancer, though some benign disorders, both proliferative and non-proliferative, can raise the risk of breast cancer development.[11]

GLOBAL PREVALENCE OF BREAST CANCER

Among the twentieth century, there were 685 000 fatalities globally and 2.3 million new instances of breast cancer among women. Breast cancer is the most frequent type of cancer in the world, impacting 8.8 million individuals as of 2025.[12] Breast cancer causes more women to lose disability-adjusted life years (DALYs) than other forms of cancer.[13] Breast cancer occurs in every country throughout the world in women after puberty at any age, though rates climb as people age.[14] From the 1930s until the 1970s, there were modest changes in breast cancer mortality.[15] Improvements in survival began in the 1980s in countries with early detection programmes and a variety of treatment techniques to eliminate the invasive disease.[16]

In 2023, women in the United States are expected to be diagnosed with 287,850 new cases of invasive breast cancer and 51,400 new cases of non-invasive (in situ) breast cancer.[17,18] Breast cancer affects approximately 1 in 833 males throughout their lifetime. As of January 2022, there are more than 3.8 million women in the United States who have had breast cancer in the past.[19] Women who have completed therapy and those who are currently undergoing it are both included. Breast cancer is the most common type of cancer among American women. Breast cancer is expected to account for around 30% of newly diagnosed malignancies in women by 2022.[20,21]

PREVALENCE OF BREAST CANCER IN INDIA

Breast cancer is the most common type of cancer in women, accounting for 14% of all cancer cases among Indian women. According to statistics, every four minutes, a woman in India is diagnosed with breast cancer. Breast cancer cases are increasing in both rural and urban India.[22] In 2018, 1,62,468 new instances of breast cancer were identified, with 87,090 fatalities reported.[23] Women in their early thirties to fifties are at a high risk of developing breast cancer because it is the most prevalent type of cancer in Indian women; this risk climbs until it reaches a peak by the time they are 50 to 64 years old.

In India, one in every twenty-eight women would develop breast cancer over her lifetime. It is higher (1 in 22) for urban women than for rural women. (1 in 60). Cancer

accounted for 5% of all disability-adjusted life years (DALYs) among Indians in 2016, according to a study.[24,2] More than half of Indian women have breast cancer in stages 3 or 4, making survival more difficult as the disease develops. Breast cancer patients in India had a post-cancer survival rate of 60%, compared to 80% in the United States.[26] Additionally, poor survival and high mortality were seen in more than 70% of the patients that were in the advanced stage.[27]

Women in less developed countries have somewhat higher cases (883 000) than those in more developed countries. (7,94,000). While India's age-adjusted incidence rate of breast cancer is lower than that of the United Kingdom (95 per 100,000), death rates are comparable. (12.7 vs 17.1 per 100 000).[28,29] India had a mortality rate that was greater than the average for Asia, which was 34%. The average across the world was 30%.[30] Data for breast cancer mortality percentage worldwide was shown in *Figure 1*.

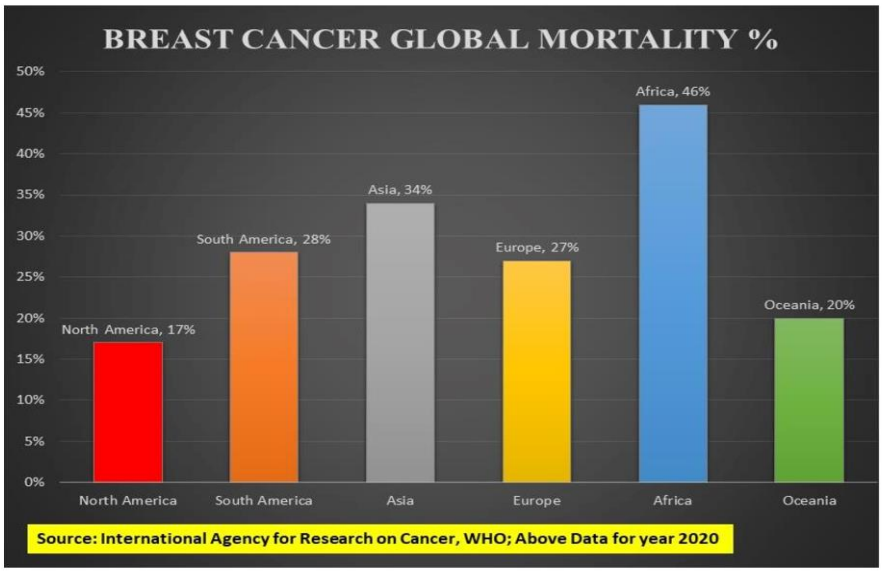

Figure 1. Data for Global Mortality Percentage of Breast Cancer

Lack of sufficient awareness and the absence of screening for the at-risk population are the main causes of India's high mortality rates from breast cancer. These factors may also play a role in late diagnosis. The high mortality rate is due in part to advanced breast cancer diagnosis and general inadequacy of medical infrastructure in India. The age-adjusted rate (AAR) of breast cancer incidence is highest in Kerala, Punjab, Andhra Pradesh, Karnataka, and Telangana in 2020, according to state-specific figures revealed in the Lok Sabha debate on July 22, 2022. The number of breast cancer diagnoses per 100,000 females in the population is referred to as the incidence rate, or AAR.[30]

BREAST CANCER TYPES

- Invasive breast cancer occurs when cancer cells migrate from the ducts and glands into the fat or connective tissue of the breast.[31]
- Invasive Ductal Carcinoma: Breast cancer usually starts in the milk ducts or lobules, which are the glands that produce milk. The most common type of breast cancer is invasive.[32]

- Invasive lobular carcinoma: Invasive lobular carcinomas account for around 10% of all breast tumours. According to Trusted Source, it affects approximately one in every five women in both breasts.[32]
- Breast cancer in situ: Breast cancer is referred to as localized when it is limited to the milk ducts or glands and has not spread to adjacent breast tissue.
- Ductal Carcinoma in Situ (DCIS): DCIS occurs when a mass of abnormal cells begins to grow within the lining of the milk duct. Given that these cancerous cells have not spread to other breast tissue by traveling outside the duct.[32] It is known as a noninvasive or preinvasive cancer.[32,33].
- Lobular Carcinoma in situ: Rarely occurring lobular cancer in situ is characterized by abnormal cells in the milk-producing glands. It is thought to be a harmless condition.[32,34] *Figure 2* pie chart displays the incidence of different forms of breast cancer.

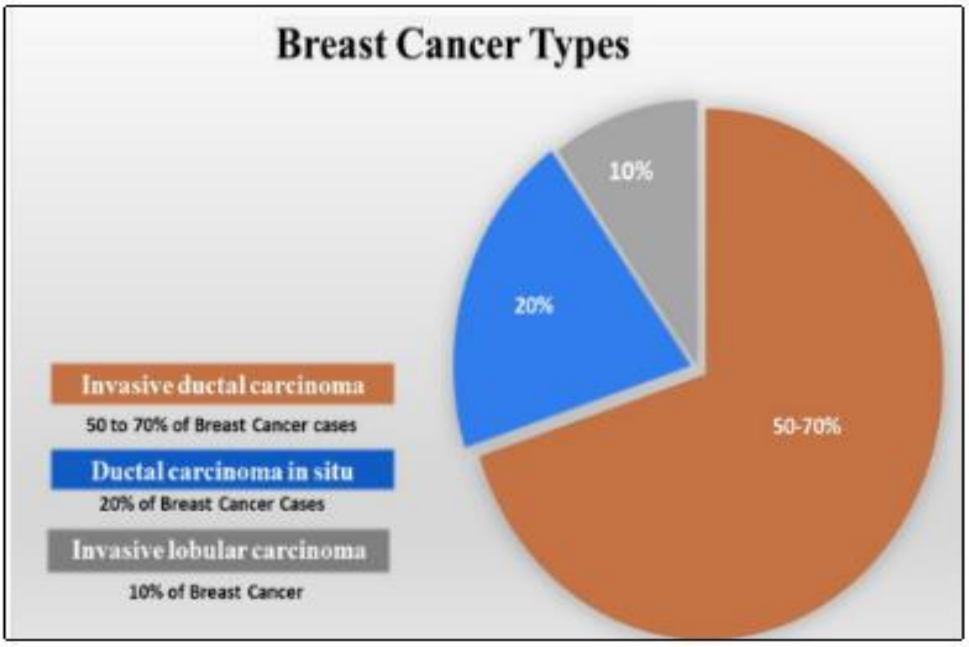

Figure 2. Types of breast cancer

Breast Cancer Subtypes

The four primary subtypes of breast cancer are based on the pathological evaluation of hormone receptors (oestrogen receptor [ER] and progesterone receptor [PR]) and human epidermal growth factor receptor 2 (HER2). Tumors that express their hormone receptors may grow more quickly when oestrogen and progesterone are present. About two out of every three breast tumours test positive for hormone receptors making them particularly common. The HER2 gene produces the HER2 (HER2/neu) proteins, which aid in the regulation of healthy breast cell development, division, and repair. However, HER2 can be linked to aggressive forms of breast cancer if the HER2 gene is amplified (too many protein copies are formed) and the protein is over-expressed (too many HER2 receptors are created). Hormone and HER2 receptor variables can be used to determine disease stage, estimated recurrence, and prognosis treatment response. The following are the four primary subtypes of

breast cancer.[35] The four main subtypes of breast cancer are listed in *Table 1* [35] and the symptoms are given in Fig.3. Breast cancer symptoms are summarized in *Figure 3.*

Table.1 Subtypes of breast cancer

HR+/HER2-	Luminal A	67%
HR-/HER2-	Triple Negative	10%
HR+/HER2+	Luminal B	10%
HR-/HER2+	HER-enriched	4%
Unknown	----	8%

The most common subtype of cancer (HR+/HER2) is 67% more common than triple-negative tumours. According to data from 2012 to 2016, only 14% of instances of both Luminal B and HER2-enriched subtypes combined are HER2-positive.[35]

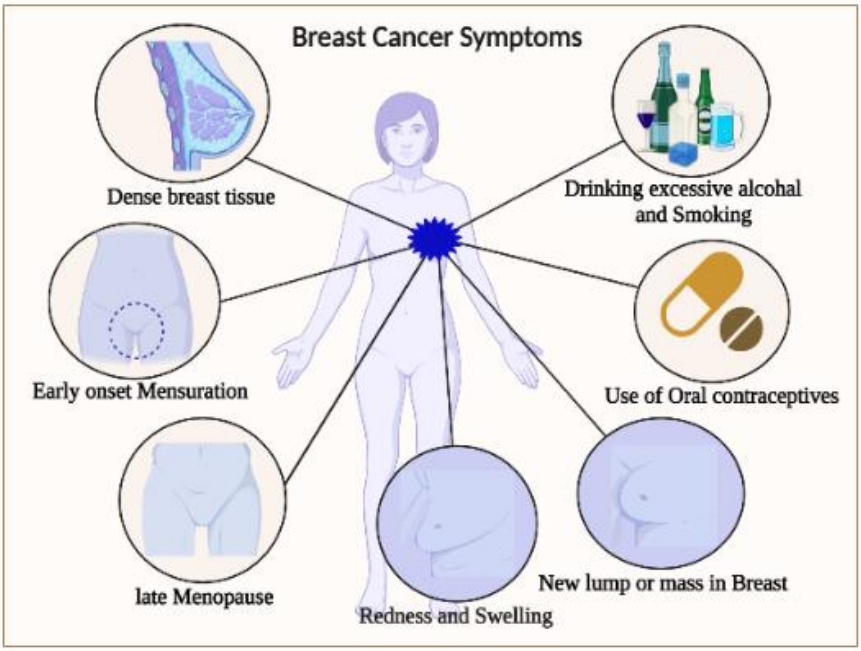

Figure 3. Breast Cancer symptoms

ETIOLOGY OF BREAST CANCER

Breast cancer is caused by genetic abnormalities or DNA damage. They can be connected to oestrogen, inherited genetic defects, or hereditary cancer-causing genes, such as the BRCA1 and BRCA2 genes. The genes that are frequently affected in hereditary breast and ovarian cancer are breast cancer 1 (BRCA1) and breast cancer 2 (BRCA2). Inherited mutations in the BRCA1 and BRCA2 genes contribute to around 3% of breast cancers (7,500 women annually) and 10% of ovarian cancers (2,000 women annually). The BRCA1 and BRCA2

genes are present in everyone in two copies, one from the mother and one from the father. Even if a person has a BRCA1 or BRCA2 mutation from one parent, they will still receive the other parent's gene.

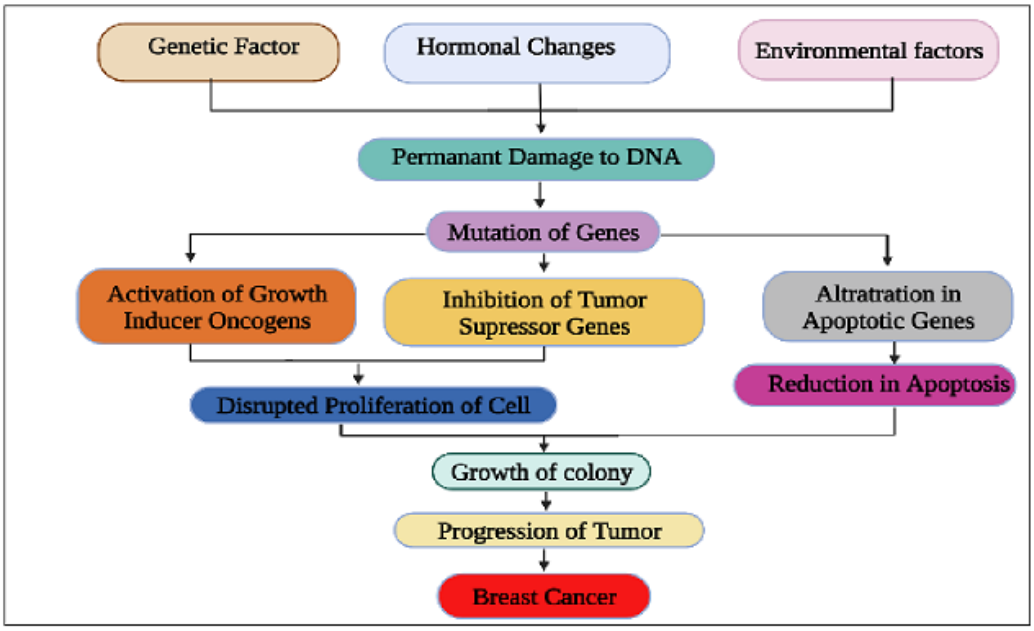

Figure 4. Etiology of breast cancer

At the point when a subsequent transformation happens and affects the healthy copy of the gene, cancer develops because the affected individual no longer has functional BRCA1 or BRCA2 genes. The subsequent mutation, in contrast to the hereditary BRCA1 or BRCA2 mutation, would only be found in the malignant growth tissue and not elsewhere in the person's body. Other than BRCA1 and BRCA2, genetic irregularities in different qualities can likewise bring about bosom and ovarian malignant growth.[36,37] *Figure 4* illustrates the etiology of breast cancer.

Family history

Family background of disease is a significant reason for raising the likelihood of creating malignant growth. This may be inferable from innate and natural likeness between family members. The beginning of breast cancer at a young age is the best indicator of innate inclination. Generally speaking, 10-15% of tumors are brought about by hereditary history, with around half of them brought about by helplessness qualities that are overwhelmingly inherited.[1,38,39]

Reproductive History

Women's risk of developing breast cancer goes up when they are exposed to hormones for longer periods during menstruation before the age of 12 and when they enter menopause after the age of 55.

Diet

- Fat: Dietary fat has received the most attention. High-fat diets increase the frequency of breast cancer in mice and shorten the time it takes for it to occur.[40] It has also been proposed that total energy consumption is more essential than dietary fat intake.[41,42]
- Vitamin A and carotenoids—Carotenoids are potent antioxidants that protect DNA-damaging reactive oxygen species, while retinol control cell division and works well as differentiates in invitro cell systems. Epidemiological studies on the relationship between diet and the risk of breast cancer[43-45] have shown that eating a variety of fruits and vegetables can help lower one's risk.
- Alcohol: Compared to people who don't drink, people who drink 15 g or more of alcohol each day—roughly two to three drinks—run a 50% greater risk. Alcohol-induced increases in plasma oestrone and oestradiol may be the cause of this rise.[46]
- Smoking: Numerous carcinogens in cigarette smoke are attributes of studies showing an increase in risk.[47] Beginning smoking earlier raises the risk of developing breast cancer. Women who first started smoking between the ages of 10 and 14 had a higher risk of developing breast cancer.[48]
- Nutritional factors: An unhealthy diet and gaining weight are two of the many factors that can lead to breast cancer.[48]
- Immune system: Numerous immunological factors that use cytokines like IL-12 and IFN play important roles in the immune system's ability to fight cancer. The immune system is completely capable of doing so. Furthermore, IL-12 is a critical cytokine in the improvement of TH1 cells, which are strong IFN-creating cells.[48]

Radiation therapy

Radiation therapy Women who have received chest or breast radiation before the age of 30 (for example, as part of treatment for Hodgkin's lymphoma) are more likely to develop breast cancer later in life.[49]

Exposure to oestrogen

Oestrogen exposure using birth control pills is linked to an increased risk of breast cancer because of the increased exposure to oestrogen.[50] On the other hand, once the person stop using these hormones for more than ten years, the risk does not go up. Additionally, hormone replacement therapy may increase women's risk of developing breast cancer.[51,52]

SYMPTOMS OF BREAST CANCER

The main side effect of breast cancer is typically a knot or area of thicker tissue in the breast.[53] Armpit pain doesn't change from month to month, like the outer layer of an orange, or variety changes, like redness in the skin of the bosom or a rash around or on one areola,[54,55] secretion from a nipple, possibly with blood.[56] A sunken or inverted nipple; a change in the size or shape of the breast; skin scaling, flaking, or peeling on the breast or nipple.[57] The majority of lumps in the breast are not cancerous. On the other hand, anyone who discovers a breast lump should have it examined by a medical professional.[58] A breast

lump or tumor is common, one of the early signs of breast cancer. These bumps typically do not hurt. A person's menstrual cycle might be the cause of pain in the nipple or breast area.[59,60]

PATHOPHYSIOLOGY OF BREAST CANCER

The malignant tumor is known as breast cancer is formed by breast cells.[61] When breast cancer invades a specific area, it spreads through local lymph nodes, the bloodstream, or both. The lungs, liver, bone, brain, and skin are the most frequently affected organs by metastatic breast cancer. Rare are scalp metastases.[62] Breast cells are what give rise to the cancerous tumor that is known as breast cancer. Due to DNA damage and genetic changes, oestrogen exposure has been experimentally linked to breast cancer. DNA and genetic defects, such as those in the P53, BRCA1, and BRCA2 genes, are passed down to some people. As a result, people who have breast or ovarian cancer in their families are more likely to get breast cancer.[61] Some breast tumors have oestrogen and progesterone receptors, which are nuclear hormone receptors that, when the right hormones attach to them, encourage DNA replication and cell division. As a result, cancers that express these receptors may be effectively treated with medications that inhibit them.

Oestrogen receptor-positive (ER+) tumors make up approximately two-thirds of postmenopausal cancer patients. The incidence of ER+ cancers is lower in premenopausal patients. About 20% of women with breast cancer have over-expressed HER2 receptors. Medication that blocks these receptors is a common treatment for these people. Normally, the immune system searches for and kills cells with DNA damage as well as cancerous cells. Breast cancer could occur if such a robust immune defense and surveillance are not maintained. With stromal and epithelial cells, various growth factors and other mediator signaling systems interact. When these are disrupted, breast cancer may develop.[61]

CANCER THERAPIES

For the treatment of cancer, a wide range of nanoparticles is being investigated. Nanoparticle-based therapeutic systems can be synthesized in a variety of configurations, such as spherical, tubular, or branched structures, using materials like carbon, ceramic, polymers, lipids, and metals. Various nanoparticles' physicochemical properties have been used to treat cancer[63,64]. Alternately, the use of the nanoparticles as "passive" or "active" drug delivery agents has also been investigated. The majority of the studies using graphene for drug delivery focused on cancer chemotherapeutics, according to our search results analysis.

Graphene's hydrophobic chemical structure enables the covalent and noncovalent tethering of a variety of amphiphilic functions, enhancing aqueous dispersibility and making it easier to target cancer cells[65]. Graphene, a carbon nanomaterial with multiple uses, could be used to create platform technologies for cancer treatments. With anticancer drugs and functional groups that target cancer cells and tissues, its surface can be functionalized both covalently and noncovalently to enhance treatment efficacy.

Graphene Oxide Benjamin Brody first made graphene oxide in 1859, a long time before graphene was found. He came up with a way to make graphite oxide. Graphene that has been oxidized is called graphene oxide (GO).[63] Graphite oxidation is a cheap and simple

process that results in a single nuclear-layered substance. It is simple to treat graphene oxide because it dissolves in water and other solvents. Graphene oxide (GO) is a two-dimensional carbon structure in which oxygen-containing functional groups (O, -OH, -O-, -COOH) are bonded to the plane's edges and both sides of the layer.

Like every other 2D carbon material, GO can have a structure with one layer or multiple layers.[66] The structure of graphene oxide is unilayered; A two-layered graphene oxide (GO) has two layers of graphene oxide. Graphene has emerged as a rapidly rising star thanks to its extraordinary physicochemical and structural properties, such as ballistic conductivity, high elasticity and mechanical strength, large surface area, and rapid heterogeneous electron transfer *Figure 5* describes the Graphene oxide structure. It has already sparked a lot of interest in materials science and bio applications. It has been broadly anticipated that the production of creative biosensors, nanocarriers for medication and quality conveyance, cell imaging, and phototherapy for disease will be made conceivable by graphene and its derivatives.[64]

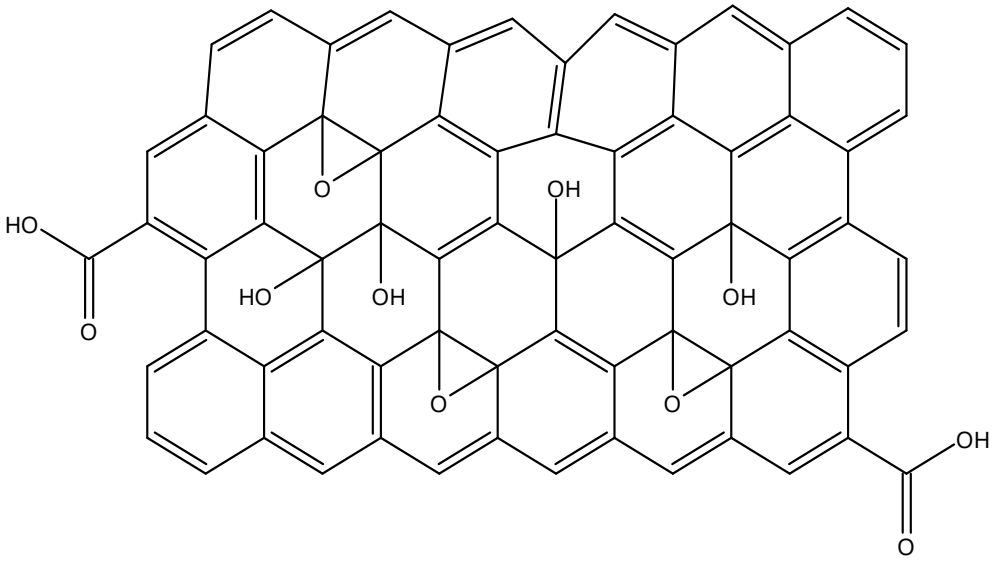

Figure 5 Structure of Graphene oxide

The process of oxidizing graphite to produce graphite oxide and then shedding this graphite oxide to produce GO can result in the formation of GO. The method of synthesis, which determines the quantity and type of oxygen-containing groups in the produced GO, has a significant impact on the properties of the material. Even though GO is hydrophilic, it is relatively simple to make solutions based on water or organic solvents. GO was merely a basic and insignificant step in the reduction-based planning of single- and multi-facet mass designs[67].

PROPERTIES OF GRAPHENE OXIDE

A variety of graphene-based nanocomposites in biosensors that combine metal with biomolecules for increased sensitivity have been created using the properties of graphene oxide (GO). Due to its functional chemical groups and excellent surface-to-volume ratio, GO has enormous capabilities for biomolecule adsorption. GO is made up of layers of graphene with functional groups like hydroxyl, epoxy, and carboxyl on the surface that contain active

oxygen[63-65]. GO has distinct physical and chemical properties, such as its conductivity, small size (20–100 nm), and optical and electrical properties. In addition, graphene is hydrophobic and difficult to dissolve in water, whereas GO is hydrophilic and soluble in water. In GO, which has a sp^2 carbon network that is significantly disordered and has a number of flaws, functional groups serve as insulators.

Thermal conductivity: Synthesized graphite oxide (GO) has a low thermal conductivity of 0.5–1 Wm^{-1} K^{-1}, making it unsuitable for most applications requiring strong thermal properties. On the other hand, graphene has been shown to have one of the highest in-plane thermal conductivities of any known material, ranging from 300 to 5000 $Wm^{-1}K^{-1}$. Consequently, GO reduction is necessary to incorporate GO into polymers and boost their thermal conductivity.[68]

Electrical Properties: Graphene is a two-dimensional sheet of sp2 carbon that is one atom thick. It has a high electron mobility (25 $m^2V^{-1}s^{-1}$) and electrical conductivity (6500 Sm^{-1}), making it an electrically conductive material. Graphene has been shown to significantly increase the electrical conductivity of polymers at low filler concentrations (e.g., 0.1 Sm^{-1} at 1 vol% in polystyrene) (PS). However, when GO is made, the sp2 bonding orbitals of graphene are broken up and a lot of surface groups are added, which makes the material less electrically conductive (1.64 104 m).[68-70]

Mechanical Properties: The advantageous mechanical properties of pure monolayer graphene are well-known. The intrinsic tensile strength is 130.5 GPa, the Young's modulus is 1.0 TPa, and the break strength is 42 N/m. Furthermore, the low fracture of graphene sheets is supported by the examination of graphene's fracture toughness, which may be as low as 4.0 0.6 $MPam^{1/2}$.[68, 69]

Graphene oxide composites: The remarkable capabilities of GO are primarily due to its chemical modifications and interactions with various substances, such as polymers and magnetic nanoparticles[63]. These adjustments help keep up with its effectiveness as well as reduce the harmfulness of the other part in light of the fact that GO will in general gather under physiological settings (on the grounds that to the presence of salts, particles, and proteins).[70] The majority of composites contain chemical components that improve mechanical properties (such as PMMA and PVC), biocompatibility (such as PEG and PVC), thermo/stimuli responsiveness (such as PNIPAM), used to coat the surface of biomaterials (such as dextran and polyamide), and colloidal stability (such as sulfonic acids and oleylamine). Different preparation methods can improve the drug delivery capacity and effectiveness of GO-based composites.[71,72]

Properties of Graphene oxide in Breast cancer treatment

Graphene oxide that is regularly made by means of the Hummers cycle. Graphene oxide is an unpredictable delicate material that joins the properties of polymers, colloid, flimsy, and amphoteric molecules.[73] Graphene oxide has solid water dispersibility because of the overflow of liquor, carboxyl corrosive, and epoxide useful gatherings in it. Covalent bonds are possible, and these categories can be changed easily. Graphene oxide (GO) offers numerous advantages as a drug carrier due to its enormous specific surface area and capacity to adsorb multiple drugs via " π–π " stacking. When oxidized, GO can be easily modified to increase its hydrophilicity and decrease its thickness[74].

The ability of anticancer medications to destroy tumors increases when they are linked to GO, allowing for lower dosages and smart drug-release properties[75,76] GO and RGO have been utilized to make an assortment of graphene-based nanocomposites in biosensors that consolidate metal with biomolecules for expanded responsiveness[77,78].

SYNTHESIS OF GRAPHENE OXIDE (GO)

In general, there are two types of GO synthesis. Both "top-down" methods, in which layers of graphene derivatives are recovered from a carbon source, typically graphite, and "bottom-up" procedures, in which pristine graphene is created using basic carbon molecules, can be used to synthesize GO.[68,69] GO can be made in a number of ways, including the Staudenmaier method and the Modified Hummer method.[70] Although both processes use graphite to oxidize it, their oxidizing agents, mineral acids, preparation times, and washing/drying steps are different. In the original Hummers method, concentrated H_2SO_4 was used to synthesize GO using $KMnO_4$ and $NaNO_3$.

The Modified Hummer's procedure typically utilized Hummer's reagents with $NaNO_3$ added. GO is made by gradually adding pure graphite powder and $NaNO_3$ to a boiling H_2SO_4 solution that has been cooled in an ice bath. $KMnO_4$ must be added gradually to keep the reaction temperature below 20°C and to prevent explosions and overheating.[72]

The Staudenmaier method is an improvement on the Brodie, 1859 method, which used KClO3 to mix graphite slurry with fuming HNO_3; Concentrated HNO_3 and H_2SO_4 are also used as oxidizing agents in the new method. $KClO_3$ would be introduced gradually over the course of a week during the operation. The few modifications make it simple to make highly oxidized GO.[79,80]

Preparation of graphene oxide (GO)

An ice bath was used to submerge a 500 mL reaction flask containing 1 g of graphite, 1.5 g of $NaNO_3$, and 46 mL of H_2SO_4 at 0 °C, agitated for 15 minutes. After that, 6 g of KMnO4 were gradually mixed into the aforementioned solution, and cooling was allowed to occur for 30 minutes. For the next two hours, the suspended solution was agitated continuously. By gradually adding 46 mL of water to the suspension over a 10-minute period at 35 °C, the temperature was raised to 98 °C. After that, the mixture was stirred for twenty minutes. The suspension was diluted with 140 mL of warm water after ten minutes of stirring. After that, 15 mL (30%) H_2O_2 was used to convert the remaining Mg+2 soluble into permanganate while the solution was kept at room temperature. The suspension was filtered through centrifugation, washed with 10% HCL and distilled water, and then dried for 24 h at 70 °C in a vacuum oven to produce GO. (Hummer method)[80,81] *Figure 6* depicted the synthesis of graphene oxide from graphite.

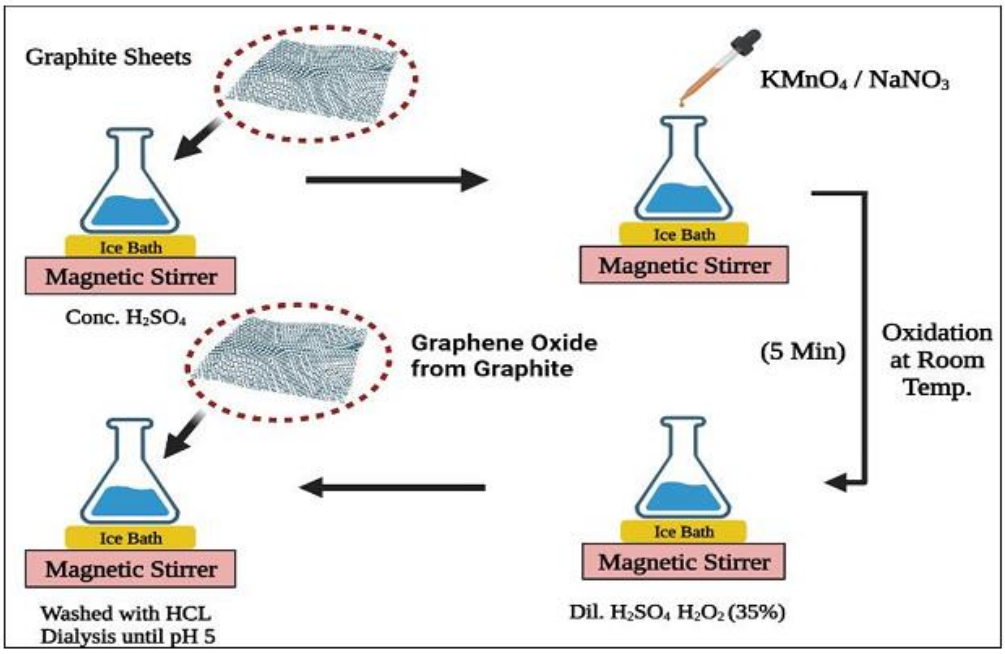

Figure 6. Synthesis of Graphene oxide from Graphite

APPLICATIONS OF GRAPHENE OXIDE

Graphene oxide may play a role in the detection and diagnosis of breast cancer cells, which may effectively increase the accuracy of the detection and diagnosis.[78] The delivery of drugs has sparked interest in graphene oxide. Nanoscale graphene oxide (NGO) was frequently used to load anti-cancer drugs because of its sp2-aromatic structure and abundance of oxygen-containing groups. This resulted in excellent loading efficiency.[67]

Cancer detection and diagnostics using graphene oxide nanosystems with potential benefits are highlighted in *Table. 2*

Table.2 Graphene oxide nanosystems cancer detection and diagnosis with promising advantages

GO based nanosystemes	Applications	Important features	Reference
Graphene oxide	Cancer therapy and drug delivery system	• Sustained-release nano formulation • Improved suppression of cancer cell growth	[124]
Graphene oxide	Anticancer drug delivery; tumour	• Low cytotoxicity • Improved biocompatibility	[189]

	therapy	and biodegradability • High drug release and inhibition of tumour growth	
Modified Graphene oxide	Gene delivery	• Low toxicity • Improved release of DNA • Suitable interaction with DNA and hydrophobic immune adjuvant	[190]
Reduced-Graphene oxide nanostructures	Anticancer drug delivery	• Sustained pH-sensitive drug release • Improved therapeutic efficacy • High drug loading capacity • High hemolytic toxicity to rabbit red blood cells	[191]
Reduced-Graphene oxide nanostructures	Cancer therapy and anti-inflammatory effects	• Anti-proliferative activity with high efficacy	[192]
Chitosan-carboxylated GO	Gene delivery	• High gene transferring properties	[193]

Options for breast cancer treatment with graphene oxide

Chemotherapy and hormone therapy are the primary treatment options for breast cancer because they kill and control cells.[82,83] Chemotherapy medications can be given orally and intravenously, but because they are not specifically designed to attack cancer cells, a variety of side effects, including hair loss.[84] Hormonal therapy, which refers to the suppression of hormones like oestrogen that encourage the growth of cancer cells (ER), is used to treat more than 65 percent of breast cancer patients.

Functionalized graphene oxide (GO) nanoparticles are rapidly being utilized in the design of modern drug delivery systems due to their high level of functionalization, high surface area with remarkable loading capacity, and customizable dimensions. This kind of treatment is dependent on the biological characteristics of the patients as well as the presence of oestrogen receptors (ER+).[85-87]

Due to its intelligent controlled release and gene silencing capabilities, GO is a powerful nanocarrier that enables the targeted delivery of tiny therapeutic molecules, antibodies, nucleic acids, and peptides to the liquid or solid tumor locations. Although graphene oxide nanoplatelets are used to kill cancerous cells, it is important to evaluate their toxicity and biocompatibility because GO-based formulations may cause aggregations or accumulate in healthy tissues while focusing on tumors or cancerous cells.[88,89] They are likewise used to imaging living cells against a foundation of close infrared light (NIR).[85]

Photothermal therapy

Photothermal therapy is essential for the creation of graphene-based multifunctional probes with both medicinal and imaging capabilities. Due to their distinct physicochemical properties, G-based photothermal therapy materials can be used to diagnose and detect breast cancer.[90] For instance, when GO and polyethylene glycol (PEG) were combined, it demonstrated photothermal treatment effects against cancers and tumors by producing a heating effect in macrophages, both in vitro and in vivo. GO-PEG demonstrated excellent thermal stability in addition to having enhanced biocompatibility and a significant photothermal effect[9-93]. The anticancer potential of these photothermal structures was controlled, and interleukin-4 significantly reduced macrophage M2 polarization.

NIR fluorescence and photoacoustic imaging were utilized in conjunction with folic acid and chitosan-functioning GO nanoplatforms for the purpose of photothermal cancer therapy. Laser irradiation completely eliminated the malignant cells in vitro. In vivo research demonstrated that 20 days after the deployment of the targeted nanosystem and laser irradiation, the tumors were completely eradicated without any evidence of recurrence.[124]

. CT is currently an important treatment method for treating a wide range of cancers. Doxorubicin-loaded PEGylated nanographene oxide (NGO-PEGDOX) was developed to enable integrated CT and PTT in a single device. Tumors can be eradicated both in vivo and in vitro by utilizing this functional graphene oxide in conjunction with PTT and CT. Cancer treatment's therapeutic efficacy was significantly improved. Additionally, NGO-photo-thermal PEG can be utilized to enhance photodynamic treatment (PDT) by increasing the intracellular delivery of photosensitizers[94].

The photosensitizer chlorin e6 (Ce6) was loaded further onto NGO-PEG via supramolecular stacking.[92] When excited by light, the generated GO-PEG-Ce6 combination can produce cytotoxic singlet oxygen for PDT and has good water solubility. When graphene was subjected to a near-infrared laser with a low power density, the photothermal effect of graphene was used to encourage the distribution of Ce6 molecules, increasing the PDT's effectiveness against cancer cells.[95,67] *Figure 7* illustrates a summary of Photothermal therapy method.

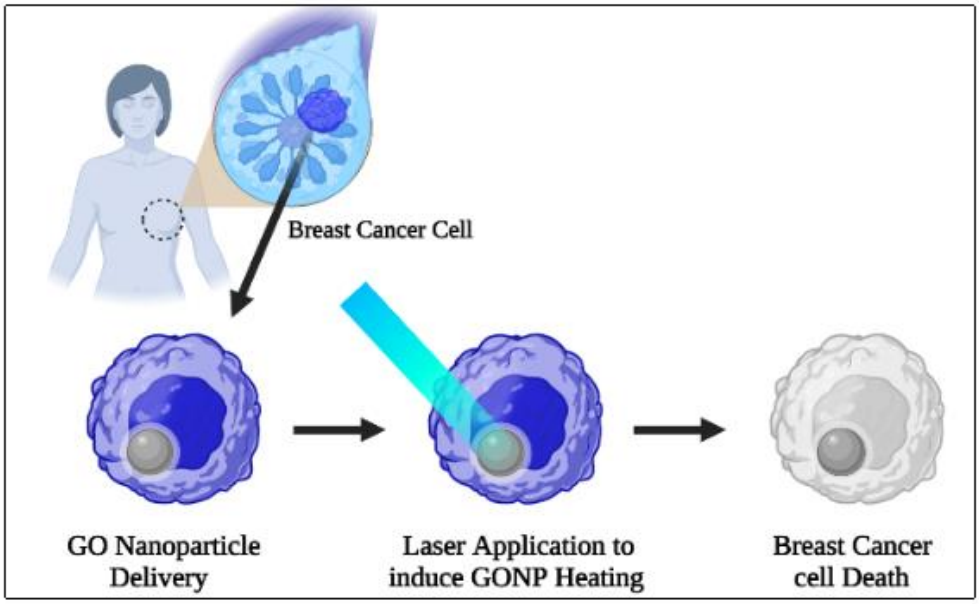

Figure 7. Process of Photo thermal therapy

Photodynamic therapy

Photodynamic therapy (PDT) has been approved by the Food and Drug Administration (FDA) as an effective method for treating cancer.[92,96] Recently, PDT has been used to treat a number of cancers, including breast cancer. In photodynamic therapy (PDT), a photosensitizing medication and light are used to selectively harm the cancer cells that are being treated. A suitable concentration of molecular oxygen is also necessary for cell damage. For total efficacy, careful planning of both medication and light dosimetry is required because there is no impact if any of these components are missing. Despite the fact that the drugs are often given to the whole body, they only have a local rather than a systemic effect because the targeting process mostly involves applying the light with care, which is usually from a laser. Since they affect both PDT's potential as an effective cancer treatment and its potential drawbacks, its local effects should be immediately recognized.[97] Specificity and recurrent therapy are two of its benefits.

In addition, it has been demonstrated that PDT can cause damage to the tumor's vasculature and elicit an immune response. Graphene oxide-based nanomaterials have been recognized as a suitable carrier of photosensitizers (PSs) due to their enormous specific surface area, extremely effective fluorescence quenching capabilities, and variety of surface functional groups. For instance, photosensitizers (PSs) were delivered via a brand-new modified NGO-mPEG made of methoxy-polyethylene glycol (mPEG). Under certain light, X-ray, and microwave irradiation, photosensitizers (PSs) are required to produce reactive oxygen species (ROSs) in order to destroy cancer cells in photodynamic therapy (PDT)[98,99]. Porphyrin, chlorin, or phthalocyanine derivatives, all of which contain tetrapyrrole structures, are examples of photosensitizers (PSs) that have been used therapeutically or in preclinical testing for PDT.[100,101] The carrier may significantly increase PS's biocompatibility and water solubility, as well as its efficient cellular absorption by MCF-7 cells, both of which help to suppress MCF-7 cells through PDT.[102]

Magnetothermal therapy

Magnetothermal therapy (MTT) is a brand-new therapeutic approach to the treatment of breast cancer. The thermal effect of magnetic nanoparticles kills breast cancers by exposing them to an external, alternating magnetic field. For the magnetothermal ablation of breast cancer, the temperature typically rises to between 37 and 45 °C or even higher.[103] GO's compatibility and magnetothermal properties were also improved after it was functionalized with PEI or PEG. Synthetic PEGylated GO was used to bind superparamagnetic IONPs used to kill MCF-7 breast tumor cells in an external magnetic field.

MTT provides the advantages of deep tissue penetration and magnetic selectivity to destroy breast cancer cells without harming the surrounding healthy breast tissues, in contrast to PDT and PTT modalities.[104] In order to address the limited therapeutic effects of standard MTT, magnetothermodynamics (MTD) treatment was devised, which combines MTT with immunological effects associated with ROS. In the absence of anticancer medications, this design significantly improved the magnetic thermal ablation of breast cancer.[106] In a 4T1 cell subcutaneous tumor model, an efficient MTD agent with ferrimagnetic vortex-domain iron oxide nanoring and GO was utilized. The tumor was successfully eliminated at a temperature that is physiologically tolerable through the synergistic interaction of heating effects and ROS-related immune effects.[100]

Delivery of Anticancer agents

Delivery of Anticancer Agents Graphene-based nanostructures made of graphene oxide, graphene quantum dots (GQDs), nanostructures have excellent stability and are effective at administering curcumin to cancer cells. Graphene oxide-curcumin and GQDs-curcumin complexes were tested against the human breast cancer cell lines MDAMB-468 and MCF-7 in various ratios. These samples had cell vitality of more than 75% after 48 h of incubation with the cell lines; however, when curcumin alone (approximately 100 g ml^{-1}) was used, cell viability was only about 40%. At 100 gml^{-1}, the equivalent cell death results were 60, 80, and 95% after 48 hours of treatment, respectively.[107] In addition, targeted fluorouracil (FU) delivery was made possible by a Graphene oxide-based nanosystem. Silver-Graphene oxide nanocomposites (20-100 g ml-1) were tested against malignant cells and demonstrated appropriate cytotoxic effects, but their effectiveness was inferior to that of free silver (Ag) nanoparticles due to their smaller sizes and greater absorption.[108-111]

Nucleotides/Peptides

Graphene's hydrophobic and electrostatic/hydrogen bonding interactions with the major amines of nitrogen bases and the carboxylic and phenolic groups of the graphene sheets are the primary mechanisms by which biomolecules can bind to its surface.[98,112] The transport of oligonucleotides to inter- or intracellular regions via GO nanosheets demonstrated effective protection against enzyme cleavage. Nucleotide/peptide biodevices have been praised for two kinds of therapeutic oligonucleotides, siRNA and antisense DNA, transported using GO in a study. A polyethyleneimine installation that was found to be an efficient GO-based carrier for gene delivery (PEI)[103,112].

It was discovered that combining low-molecular-weight branching PEI with GO to create a hybrid gene carrier improved DNA binding, condensation, and transfection efficiency. This hybrid material also made bioimaging and sensing simpler due to its adaptable electrical and optical properties. Positively charged GO-PEI complexes that were also able to bind plasmid DNA (pDNA) were used to transfect the enhanced green fluorescent protein gene intracellularly into HeLa cells. The GO nanosheets' advantages included dispersibility, colloidal stability, cell absorption, and low toxicity. GO nanosheets made it possible to transport DNA aptamers into live cells while protecting them from enzymatic attack[113,114].

Transferrin (Tf)

Iron that is ingested and released when erythrocytes are destroyed is carried and transported by transferrin (Tf), a hydrophilic single-chain glycoprotein. Tf receptors, which are widely communicated on the layer of bosom malignant growth cells, are utilized to ship iron. Tf is an effective drug for targeting tumors because it is biodegradable, nontoxic, and does not cause an immune response. Tf protein-surface decorating also increased the anticancer efficacy of therapeutic medications and decreased the cytotoxicity to normal breast cells, ensuring its safety and effective use in vivo. Tf-functionalized GBNs have been shown to enhance tumor cell selectivity and significantly increase cytotoxicity to breast cancer cells.[114-116] It has been shown that Tf is a good ligand for going after breast cancer cells. In addition to the potential application of the photothermal effects of GO nanoparticles functionalized with transferrin (Tf) molecules for the treatment of breast cancer.[67,117]

MUC1 ligand

MUC1, a protein with a high glycosylation level and a large molecular weight of approximately 250–500 kDa, is encoded by the MUC1 gene, making it a potential target for tumor bio immunotherapy.[118] The MUCI ligand MUC1 is an essential biomarker for breast cancer that frequently exhibits nonpolar distribution in tumor cells. The mucin 1 receptor immunoglobulin G antibody (antiMUC1 IgG) and the MUC1-binding aptamer (AptMUC1) have both been used as targeted agents, and over 90% of human breast tumors overexpress MUC1 (more than tenfold).[118] The increased multivalent binding affinity of AptMUC1 on the breast cancer cell membrane was facilitated by the extremely high density and great flexibility of GO conjugated with AptMUC1 on its surface.[119] Breast cancer was successfully targeted by GO coupled to anti-MUC1 IgG using a thiol-ene coupling process.

Immunotherapy

The goal of tumor immunotherapy is to stimulate the human immune system and induce an autoimmune response that kills cancer cells.[120] Immunotherapy can effectively eliminate any remaining cancer cells and minuscule lesions after surgery, radiation, and chemotherapy. It can also stop the recurrence and spread of tumors by inhibiting the growth of new cancer

cells. Less unfavorable impacts, worked on organic responsiveness, and a durable resistant reaction are advantages of immunotherapy.[121] There has been an expansion in interest in photoimmunotherapy. *Figure 8* outlines therapies for breast cancer treatment.

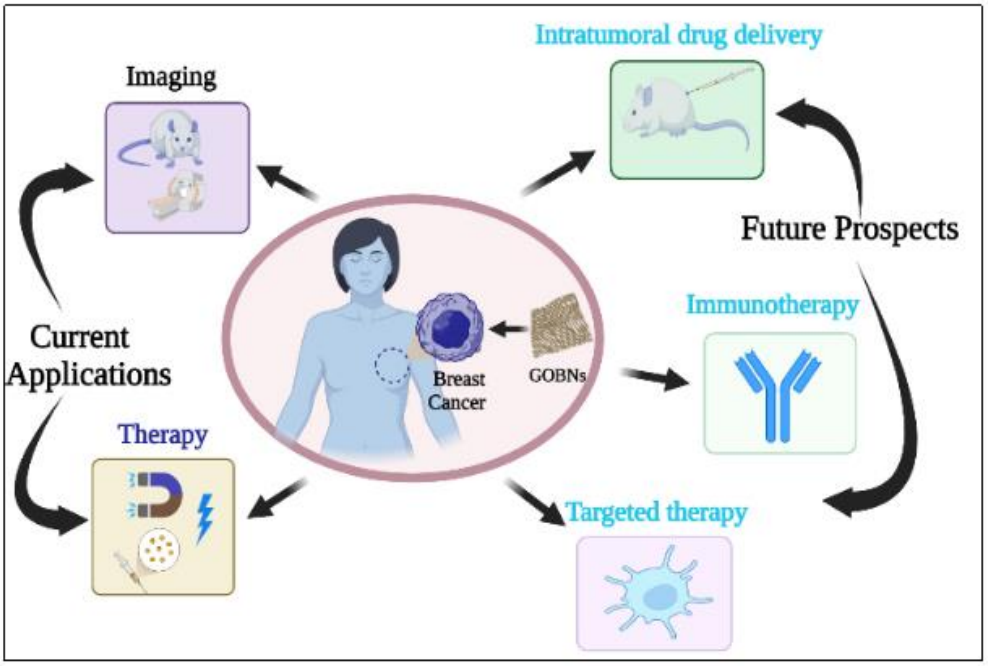

Figure 8. Therapies in the treatment of breast cancer

Intratumoral drug delivery

Intratumoral drug delivery is an intriguing locoregional treatment that involves injecting drugs directly into the tumor via intratumoral injection to increase the immunological memory effect and promote host immunity by recruiting CD8+ T cell infiltration and activating dendritic cells.[101] This method demonstrated to be an effective and secure intratumoral drug delivery method for breast cancer.

In terms of loading and releasing insoluble anticancer medications, this method outperforms conventional intravenous injection. By delivering chemotherapy directly to the breast tumor site, intratumoral administration reduces toxicity and increases medication efficacy by limiting exposure to healthy tissues.[1522,123] Graphene-based intratumoral drug delivery devices may be able to circumvent the limitations due to their controlled drug release properties. Injectable gelling depots are less invasive and more comfortable to inject. Problems with their intratumoral delivery include burst release, inadequate drug loading capacity, implant biocompatibility, and poor drug solubility that affect the release kinetics.[124]

Chitosan gel functioned as an intratumoral delivery system for docetaxel (DTX), which had a higher concentration and a longer residence time in the breast tumor tissues of mice, with no apparent harm to healthy organs[116]. These and other new intratumoral delivery techniques may result in shorter hospital stays and lower healthcare costs for patients, which would be beneficial to the economy.[125]

Graphene-Based biomedical imaging and biosensor

The bioreceptor, transducer, and read-out system are the primary components of biosensors. An enzyme, cell, aptamer, or antibody typically make up the bioreceptor, which responds to the target substance. Because it converts the biological signal into a quantifiable signal, the transducer is another essential component.[77,126] It is essential to identify and monitor carcinoma cells as soon as possible in order to stop the spread of breast cancer. Biomedical imaging technologies as useful tools for diagnosing tumors provide invaluable guidance for tumor therapies. Graphene oxide-based nanomaterials have been extensively studied using a variety of imaging techniques, including computed tomography (CT), photoacoustic imaging (PAI), and near-infrared spectrum (NIR) fluorescence imaging (FLI). It is essential to detect and monitor carcinoma cells as soon as possible in order to stop the spread of breast cancer.[98]

Magnetic resonance imaging

Magnetic resonance imaging applications have both been beneficially utilized GO and graphene-based attractive nanoparticle half breed materials[113]. MRI stands out from other imaging technologies because it can take high-resolution 3D pictures of opaque and soft tissues, making it an essential diagnostic tool[103,106]. For MRI, nanomaterials based on graphene oxide and containing metals that are paramagnetically functionalized are suitable. For MRI applications, the high-temperature thermal decomposition method was used to make Fe3O4-adorned poly (4-styrene sulfonate)-GO.[100,104,105] The functional GO that was produced by the Report on the Development of a Two-Dimensional Nanomaterial Based on GO for T1 MRI CA was well-soluble in water and possessed excellent MRI effects[127,128,129].

Near infrared range (NIR)

A NIR (infrared range) test was made accessible for cell imaging in the close (NIR). NGO-strong PEG's NIR absorption also worked well for photothermal tumor ablation in vivo. Because of the lower foundation signal, decreased photobleaching and phototoxicity, profound tissue entrance (because of low Rayleigh dissipating and low tissue ingestion of NIR light), low Rayleigh dispersing, and low tissue retention of NIR light, two-photon microscopy with a NIR laser is a promising procedure for disease cell imaging.[67,130,131]

Photoacoustic imaging

During the beyond a decade, an original biomedical imaging strategy in view of the utilization of laser-created ultrasound has emerged. Photoacoustic imaging (PA), also known as optoacoustic imaging, is the term for it. It is a hybrid modality that combines optical imaging's spectroscopic specificity with the high spatial resolution of ultrasonic imaging.[132,133] A PA image is, in essence, an ultrasonic image in which the optical properties of the tissue, particularly optical absorption, determine the contrast rather than its mechanical and elastic properties. Fluorescent biosensors Fluorescent nanoparticles and labels are a highly sensitive and selective approach with acceptable spatiotemporal resolution and cheap application cost that may be used for biomolecular imaging and biomarker identification.[132,134,135]

Fluorescent Biosensors

The use of organic dyes, inorganic semiconductor quantum dots (QDs), and carbon nanomaterials as fluorometric indicators has been recorded for a variety of fluorometric diagnostic tests and fluorescent-based biosensors focused on biocatalyst activity. Fluorescent nanoparticles and labels are a highly sensitive and selective approach with acceptable spatiotemporal resolution and cheap application costs that may be used for biomolecular imaging and biomarker identification.[127,136] These biosensors work by using the fluorescence peculiarity, which happens when a fluorophore or particle that has been fluorescently labeled retains the related electromagnetic radiation. The main advantages of fluorescence-based biosensors are their extreme sensitivity, low or no invasiveness, ability to use fluorescence intensity and fluorescence lifespan, and capacity to provide molecular structure and microenvironment.[77]

COMBINATION THERAPIES FOR THE TREATMENT OF BREAST CANCER

Breast cancer is the cancer that kills the most people worldwide. Despite significant advancements in science, the incidence and mortality rates of breast cancer remain high. Some of the current treatments for breast cancer include targeted therapies, cytotoxic chemotherapy, and endocrine therapies. Although monotherapies (such as chemotherapy, targeted therapy, hormone therapy, or immunotherapy) can be effective for some people with breast cancer, their efficacy can sometimes wane over time, and some patients develop treatment resistance. A novel and promising idea is combination treatment, which involves administering two or more medications to treat the condition. Understanding the many combination techniques that are being used in clinical trials or in the clinic is essential for figuring out the best ways to treat patients.[137]

Combination therapy with reduced toxicity and greater targeted advantages through functionalized nanostructures is one area of interest for researchers in the field of cancer treatment. Photothermal therapy and radiotherapy are two examples. A hydrothermal reaction could be used to make Fe_3O_4@Au/reduced GO nanoparticles, which could be used in combination with radiation and photothermal therapy. Chemo-photothermal and chemo-photodynamic therapy were developed by attaching cyclodextrinhyaluronic acid to Fe_3O_4-GO polymers, which resulted in the creation of a nanoplatform. These nanosystems also demonstrated high biocompatibility and acceptable cytotoxicity.[95,138] Combination treatment, which involves administering two or more drugs to treat the condition, is a novel and promising concept. In order to determine the most effective methods for treating patients, it is crucial to comprehend the many combination techniques that are being employed in clinical trials or in the clinic.

Radiotherapy and photothermal therapy: One of the subjects of interest for researchers in the realm of cancer treatment is combination therapy with reduced toxicity and greater targeted advantages through functionalized nanostructures. It was suggested that Fe3O4@Au/reduced GO nanoparticles might be created using a hydrothermal reaction for combined therapy utilising both radiation and photothermal therapy techniques. The

photothermal conversion efficiency was therefore roughly 61%. The oral squamous carcinoma KB cell lines were successfully killed by these nanosystems, which also demonstrated high biocompatibility and acceptable cytotoxicity.[95,138]

Advantages and challenges in the use of combination therapy for breast cancer treatment

Advantages

a) One of the benefits is precise treatment: Certain targets can be targeted with a molecular combination treatment. Many molecular targeting drugs have been studied over the years, and combination therapy makes it possible to precisely target multiple pathways for a precise response.[138,139]

b) Synergistic and additive effects: Certain combination treatments are currently used as first-line or adjuvant treatment for recurrent or metastatic breast cancer in clinical settings. As was discussed throughout this article, molecular combination treatment has the potential to extend survival due to the additive or synergistic effects of using more than one medication.

Challenges

(a) Drug resistance: When compared to combination therapy, single medications may be weaker and more likely to have off-target effects, particularly in complex cancer contexts.[138,140,141] In spite of the fact that combination medications frequently assist patients who are resistant to one or more medications, individuals occasionally develop resistance to them. This might be brought about by different components, including an intricate growth microenvironment, drug efflux, disease undifferentiated organisms, mass cancer cells, and connection across flagging pathways.

(b) Drug–drug interaction (DDI) risks and toxicity: Different breast cancer subtypes can have distinct effects. Any combination of multiple medications increases the risk of DDI. As a direct consequence of this, complications like sarcopenia, liver or kidney failure, thrombocytopenia, brain metastases, malnutrition, and inflammation may emerge.[138,141] With any mix, considering expected secondary effects and poisonousness, very much like with any new medicine is important. A promising potential solution to this problem is the utilization of molecular docking tools to assist in the creation of the most advantageous combination regimens with the least likelihood of DDI.[132,138,141].

Future perspective and important challenges

In general, the use of GO-based materials with high electrical conductivity, mechanical strength, and stiffness in the design and manufacturing of anticancer nanosystems has the potential to provide distinct advantages. However, thorough evaluation of their intracellular uptake, bioaccumulation, multi-drug resistance, biopersistency, cellular long-term immunogenicity, clearance mechanism histopathology, and biopersistency is still required; Researchers have not extensively investigated the effect that particle size has on the viability of cells.[138]

Due to its distinctive physicochemical characteristics, including high surface area, high stability, and biocompatibility, graphene oxide (GO) has become a promising nanomaterial in

the field of cancer therapy. In the treatment of breast cancer, GO has demonstrated significant promise for targeted medication delivery, imaging, photothermal therapy, and photodynamic therapy. However, there are still a number of issues that need to be resolved before using GO as a treatment for breast cancer. Several of these challenges include:

- Biocompatibility: Although GO has been demonstrated to be biocompatible, further toxicity research is still required to ascertain its long-term impacts on human health.
- Targeted medication delivery: Although GO can be functionalized to target particular cancer cells, additional research is still required to improve drug delivery to the tumour site and minimise off-target effects.
- Imaging: GO-based imaging methods for the detection of breast cancer appear promising, but more studies are required to confirm their sensitivity and specificity.
- Production on a big scale: GO's broad use is now constrained by its expensive and time-consuming large-scale manufacture.
- Before GO is authorised for clinical usage, there are regulatory obstacles that must be overcome.[138-141]

Conclusion

Taking everything into account, GO-based materials have been broadly concentrated on throughout recent many years and are especially pertinent to disease treatment. Because of their remarkable physicochemical properties — two-layered planar designs, huge surface regions, high synthetic/mechanical solidness, and critical conductivity — these can deliver or make into different nanostructures, biosensors, nanocarriers for medicine and quality movement, cell imaging, and phototherapy for therapy of bosom disease.

In conclusion, there is gaining evidence that graphene oxide (GO) may have therapeutic promise in the treatment of breast cancer. Anti-cancer effects of GO have been demonstrated, including the potential to induce apoptosis and limit cell proliferation. GO has also been shown to have little toxicity in normal cells and tissues, which is a considerable benefit over conventional chemotherapy drugs.

Studies have also shown that GO is an effective choice for targeted medication delivery since it is easy to functionalize with targeting moieties, such as antibodies or peptides, to deliver it merely to cancer cells. Furthermore, GO is a desirable option for combination therapy with other medications or radiation therapy due to its distinct physicochemical features, such as its large surface area and strong reactivity.

Even though GO has a promising future as a breast cancer treatment, further study is required to completely comprehend its mechanisms of action and maximise its therapeutic efficacy. In order to assess both the safety and efficacy of GO-based medicines and establish suitable dose regimens and delivery strategies, additional preclinical and clinical researchare required. However, recent study data indicates that GO could potentially serve as a potent and secure therapeutic agent for the treatment of breast cancer.

References

1. Sun, Y.-S., et al. Risk factors and preventions of breast cancer. Int J Bio Sci. 2017; 13(11): 1387; doi: 10.7150/ijbs.21635
2. Bray, F., et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68(6):394-424; doi: 10.3322/caac.21492
3. Hortobagyi, G.N. Treatment of breast cancer. N Engl J Med. 1998;339(14): 974-984, doi: 10.1056/NEJM199810013391407
4. Yacoub, N., Molecular events involving p27 § k § i § p¹, p53, HER-2/neu, and ER in multistep progression of breast cancer. 2000. Available from: https://hdl.handle.net/1807/14601
5. Darlington, A.J., Anatomy of the breast, in Digital Mammography. Springer; 2015; pp.3-10.
6. Akram, M., et al. Awareness and current knowledge of breast cancer. Biol Res. 2017; 50(1):1-23, doi: 10.1186/s40659-017-0140-9.
7. Feng, Y., et al. Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. Genes Dis. 2018; 5(2):77-106, doi: 10.1016/j.gendis.2018.05.001.
8. Colombo, M., et al. HER2 targeting as a two-sided strategy for breast cancer diagnosis and treatment: Outlook and recent implications in nanomedical approaches. Pharmacol Res 2010; 62(2): 150-165, doi: 10.1016/j.phrs.2010.01.013.
9. Polyak, K.J.T.J.o.c.i., Breast cancer: origins and evolution. 2007. **117**(11): p. 3155-3163.
10. Guray, M. and A.A.J.T.o. Sahin, Benign breast diseases: classification, diagnosis, and management. 2006. **11**(5): p. 435-449.
11. Kesharwani, P., et al. Recent advances in multifunctional dendrimer-based nanoprobes for breast cancer theranostics. J Biomater Sci Polym Ed. 2022;33(18):2433-2471, doi: 10.1080/09205063.2022.2103627.
12. Ghaffari Sardasht, F., et al. Breast Cancer Screening Behaviors Based on Health Belief Model. J Holist Nurs 2022; 32(2):89-97, doi: 10.32598/jhnm.32.2.2130.
13. Li, N., et al. Global burden of breast cancer and attributable risk factors in 195 countries and territories, from 1990 to 2017: results from the Global Burden of Disease Study 2017. J Hematol Oncol 2019; 12(1):1-12, doi: 10.1186/s13045-019-0828-0..
14. Polyak, K.J. Breast cancer: origins and evolution. J Clin Invest. 2007; 117(11): 3155-3163, doi: 10.1172/JCI33295.
15. Guray, M. and Sahin, A. Benign breast diseases: classification, diagnosis, and management. Oncologist.2006;11(5):435-449.
16. Wyld, L., Audisio,R.A. Poston,G.J. The evolution of cancer surgery and future perspectives. Nat Rev Clin Oncol 2015; 12(2):115-124,doi: 10.1038/nrclinonc.2014.191.

17. Moore, C.D., Mevalonate Pathway Inhibitors Potentiate the Efficacy of Chemotherapeutic Drugs to Limit Breast Cancer Cell Growth. Front Oncol 2019; 11:626971
18. Giaquinto, A.N., et al. Breast cancer statistics, 2022. CA A Cancer J Clin 2022;72(6):524-541, doi.org/10.3322/caac.21754.
19. Lin, R.-H., et al. Application of Deep Learning to Construct Breast Cancer Diagnosis Model. Appl Sci 2022; 12(4):1957, doi.org/10.3390/app12041957
20. Abbasniya, M.R., et al. Classification of breast tumors based on histopathology images using deep features and ensemble of gradient boosting methods. Comp Elec Eng 2022;103: 108382, doi:10.1016/j.compeleceng.2022.108382.
21. Yi, M., et al. Epidemiological trends of women's cancers from 1990 to 2019 at the global, regional, and national levels: a population-based study. Biomark Res 2021;9(1):1-12,doi:10.1186/s40364-021-00310-y.
22. Jeeva, M., E. Padmapriya, and Rajan, R.G. Hybridization of ML techniques for predicting Breast Cancer. in 2022 Third International Conference on Intelligent Computing Instrumentation and Control Technologies (ICICICT). 2022. IEEE.
23. Garg, N., et al. Insights of breast cancer and barriers to its therapy. J Pharm Tech Res Mang 2010; 7(2): 73-86
24. Sinha, L. Role of serum levels of vitamin D in patients of breast Cancer. Intl J Adv Biochem Res 2020; 4(1): 37-41, doi: 10.33545/26174693.2020.v4.i1a.69
25. Debbarma, A., et al., Journal Homepage:-www. journalijar. com.
26. Lortet-Tieulent, J., et al., US burden of cancer by race and ethnicity according to disability-adjusted life years. 2016;**51**(5):673-681.
27. Statistics of Breast Cancer in India.
    Available from: https://cytecare.com/blog/breast-cancer/statistics-of-breast-cancer/.
28. Malvia, S., et al. Epidemiology of breast cancer in Indian women. Asia Pac J Clin Oncol 2017;13(4):289-295, doi: 10.1111/ajco.12661.
29. Srinath, A., et al. Barriers to cervical cancer and breast cancer screening uptake in low-and middle-income countries: a systematic review. Health Policy & Plan 2022; czac104; doi: 10.1093/heapol/czac104.
30. Today, I. Breast cancer: Government data shows fatal disease's increasing prevalence. 2022 19 Aug 2022.
    Available from: https://www.indiatoday.in/diu/story/breast-cancer-government-data-shows-fatal-disease-s-increasing-prevalence-1989694-2022-08-18.
31. prevention, C.f.d.c.a. What is breast cancer. 26 sep 2022. Available from: dc.gov/cancer/breast/basic_info/risk_factors.html.
32. Clinic, C. Breast Cancer. 1/21/2022. Available from: https://my.clevelandclinic.org/health/diseases/3986-breast-cancer.

33. Dekalb surgical associates, p.c. Breast Cancer Terms. 2022; [cited 2023 09/03]
Available from: https://dekalbsurgical.com/our-services/breast-cancer/breast-cancer-glossary/.
34. Conditions, N.-c.b. Lobular Carcinoma in Situ (LCIS). 25 /01/2022; [cited 2023 09/03]; Available from: https://www.cancer.org/cancer/breast-cancer/non-cancerous-breast-conditions/lobular-carcinoma-in-situ.html.
35. Nurses, O. Breast Cancer Pathophysiology. 09 Sep 2019 [cited 2023 06/01/2023]; Available from: https://oncologynurse-ce.com/breast-cancer-pathophysiology/
36. Prevention, C.o.d.c.a. The BRCA1 and BRCA2 Genes. [cited 2023 18/02]; https://www.cdc.gov/genomics/disease/breast_ovarian_cancer/genes_hboc.htm#:~:text=Normally%2C%20the%20BRCA1%20and%20BRCA2,%2C%20ovarian%2C%20and%20other%20cancers.
37. Pelttari, L.M., et al. RAD51C is a susceptibility gene for ovarian cancer. Hum Mol Genet 2011;20(16):3278-3288, doi: 10.1093/hmg/ddr229.
38. De Silva, S., et al. Overview of the genetic basis toward early detection of breast cancer. Breast Cancer 2019:71-80, doi: 10.2147/BCTT.S185870.
39. Peto, J. and Mack, T.M. High constant incidence in twins and other relatives of women with breast cancer. Nat Genet 2000;26(4):411-414, doi:10.1038/82533.
40. Hulka, B.S. and Stark, A.T. Breast cancer: cause and prevention Lancet. 1995; 346(8979):883-887, doi: 10.1016/s0140-6736(95)92713-1.
41. Bojková, B., Winklewski,P.J., and Wszedybyl-Winklewska, M.J. Dietary fat and cancer—which is good, which is bad, and the body of evidence. Int J Mol Sci 2020;21(11): 4114, doi:10.3390/ijms21114114Woutersen,
42. R.A., et al., Dietary fat and carcinogenesis. 1999. **443**(1-2): p. 111-127.
43. Smith-Warner, S.A., et al. Intake of fruits and vegetables and risk of breast cancer: a pooled analysis of cohort studies. JAMA 2001;285(6):769-776, doi: 10.1001/jama.285.6.769.
44. Niranjana, R., et al. Carotenoids modulate the hallmarks of cancer cells. J Fun Foods 2015; 18: 968-985.
45. Palozza, P., et al., Prooxidant effects of β-carotene in cultured cells. Mol Aspects Med 2003;24(6):353-362, doi: 10.1016/s0098-2997(03)00031-1.
46. Al-Sader, H., et al., Alcohol and breast cancer: the mechanisms explained. J Clin Med Res 2009; 1(3):125, doi: 10.1016/s0098-2997(03)00031-1.
47. BS Hulka., A.S., Breast Cancer: Cause and Prevention. The lancet. 1995; 8979:883-887, doi:10.1016/S0140-6736(95)92713-1
48. Ataollahi, M., et al., Breast cancer and associated factors: a review. J Med Life. 2015; 8(Spec Iss 4):6.
49. prevention, C.f.d.c.a. What Are the Risk Factors for Breast Cancer? 26 September 2022 [cited 2023 18/02].

50. Parsa, P. and Parsa, B.J.P Effects of Reproductive Factors on Risk of Breast Cancer: A. Asian Pac J Cancer Prev 2009;10(4):545-550.
51. Colditz, G.A. Relationship between estrogen levels, use of hormone replacement therapy, and breast cancer. J Natl Cancer Inst 1998;90(11):814-823, doi: 10.1093/jnci/90.11.814.
52. Vassilopoulou-Sellin, R., et al., Estrogen replacement therapy after localized breast cancer: clinical outcome of 319 women followed prospectively. J Clin Oncol 1999; 17(5):1482-1487.
53. Charishma, G.C.G., et al., Review on breast cancer and its treatment. Indi Her Drugs 2020;21-26.
54. Lawton, G., Mustn't Grumble: The surprising science of everyday ailments and why we're always a bit ill. 2021: Hachette UK.
55. Miltenburg, D.M., Speights V.J. Benign breast disease. Obstet Gynecol Clin North Am 2008;35(2):285-300.
56. Abu-Naser, S.S. and B.G. Bastami, A proposed rule based system for breasts cancer diagnosis. Aug Repo 2016.
57. Supriya, M. and A.J.H.c.m.s. Deepa, A novel approach for breast cancer prediction using optimized ANN classifier based on big data environment. Health Care Manag Sci 2020;23(3):414-426, doi: 10.1007/s10729-019-09498-w
58. Bukhari, M.H., et al., Use of fine-needle aspiration in the evaluation of breast lumps. 2011. Patholog Res Int 2011;689521, doi: 10.4061/2011/689521.
59. Morrow, M.J.A.f.p., The evaluation of common breast problems. Am Fam Physician 2000; 61(8):2371.
60. Sharma, G.N., et al. Various types and management of breast cancer: an overview. J Adv Pharm Technol Res 2010;1(2):109-26.
61. Net, N.-M. Breast Cancer Pathophysiology. 2023 26 Feb 2019 [cited 2023 06 Jan 2023]; Available from: https://www.news-medical.net/health/Breast-Cancer-Pathophysiology.aspx#:~:text=Breast%20cancer%20is%20a%20malignant,experimentally%20linked%20to%20estrogen%20exposure.
62. Manual, M. Breast Cancer. 2022 March 2022; Sep 2022:[Available from: https://www.msdmanuals.com/en-in/professional/gynecology-and-obstetrics/breast-disorders/breast-cancer.
63. Seal, M.D. and S.K.J.T.C.J. Chia, What is the difference between triple-negative and basal breast cancers? Cancer J 2010;**16**(1):12-16.
64. Nurses, O. Breast Cancer Pathophysiology. 09 Sep 2019 [cited 2023 06/01/2023]; Available from: https://oncologynurse-ce.com/breast-cancer-pathophysiology/.
65. Jiříčková, A., et al., Synthesis and applications of graphene oxide. Materials. 2022:15(3):920, doi.org/10.3390/ma15030920.
66. scientific, B. Graphene Oxide. [cited 2023 18/02]; Available from: https://www.biolinscientific.com/blog/what-is-graphene-oxide%20(GOC1).

67. Feng, L., L. Wu, and X.J.A.M. Qu, New horizons for diagnostics and therapeutic applications of graphene and graphene oxide. Adv Mater 2013;25(2):168-186, doi: 10.1002/adma.201203229.
68. Smith, A.T., et al., Synthesis, properties, and applications of graphene oxide/reduced graphene oxide and their nanocomposites. Nano Mat Sci 2019; 1(1): 31-47.
69. Anwar, A., T.-P. Chang, and C.-T.J.C.L. Chen, Graphene oxide synthesis using a top–down approach and discrete characterization techniques: A holistic review. 2022. **32**(1):1-38.
70. Krishnamoorthy, K., et al., The chemical and structural analysis of graphene oxide with different degrees of oxidation. Carbon 2013;**53**:38-49.
71. Shahriary, L. and A.A.J.I.J.R.E.E.E. Athawale, Graphene oxide synthesized by using modified hummers approach. Graphene 2014;**2**(01):58-63.
72. Material, A. Graphene Oxide. Nov 21,2017 [cited 2023 18/02]; Available from: https://www.acsmaterial.com/blog-detail/graphene-oxide.html.
73. Study.com. Breast Anatomy and function | What is Physiology of Breast. 2022 [cited 2022 18 Oct]; Available from: https://study.com/academy/lesson/breast-anatomy-function-physiology.html.
74. Cui, G., et al., Graphene-based nanomaterials for breast cancer treatment: promising therapeutic strategies. J Nano Biotech 2021;**19**(1):1-30.
75. Liu, L., et al., Recent progress of graphene oxide-based multifunctional nanomaterials for cancer treatment. Cancer Nanotech 2021;**12**(1):1-31.
76. Zaaba, N., et al., Synthesis of graphene oxide using modified hummers method: solvent influence. 2017;**184**:469-477, doi.org/10.1016/j.proeng.2017.04.118.
77. Pourmadadi, M., et al., Properties and applications of graphene and its derivatives in biosensors for cancer detection: a comprehensive review. Biosensors 2022;**12**(5):269.
78. Li, T., et al., Detection of breast cancer cells specially and accurately by an electrochemical method. Biosens Bioelectron 2010;**25**(12):2686-2689.
79. Chua, C.K., Z. Sofer, and M.J.C.A.E.J. Pumera, Graphite oxides: effects of permanganate and chlorate oxidants on the oxygen composition.Chemistry 2012;18(42):13453-13459, doi: 10.1002/chem.201202320.
80. Alam, S.N., N. Sharma, and L.J.G. Kumar, Synthesis of graphene oxide (GO) by modified hummers method and its thermal reduction to obtain reduced graphene oxide (rGO). Graphene 2017;6(1):1-18, doi: 10.4236/graphene.2017.61001
81. Fadhil, H.A., et al., Synthesis, characterization, and in vitro study of novel modified reduced graphene oxide (RGO) containing heterocyclic compounds as anti-breast cancer. 2022;4:1156-1170, doi: 10.22034/ecc.2022.345188.1484.

82. Yildiz, G., M. Bolton-Warberg, and F.J.A.B. Awaja, Graphene and graphene oxide for bio-sensing: General properties and the effects of graphene ripples. Acta Biomater 2021;131:62-79, doi: 10.1016/j.actbio.2021.06.047.
83. Citron, M.L., et al., Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clini Oncol 2003; 21(8):1431-1439, doi: 10.1200/JCO.2003.09.081.
84. Muazim, K., Z.J.M.S. Hussain, and E. C, Graphene oxide—A platform towards theranostics. Mater Sci Eng C Mater Biol Appl 2017; 76:1274-1288, doi: 10.1016/j.msec.2017.02.121.
85. Saeed, N., I. Hamzah, and S. Mahmood. The applications of nano-medicine in the breast cancer therapy. in Journal of Physics: Conference Series. 2021. IOP Publishing.
86. Goldhirsch, A., et al., Meeting highlights: international consensus panel on the treatment of primary breast cancer. J Clin Oncol 2001;19(18):3817-3827, doi: 10.1200/JCO.2001.19.18.3817.
87. Lindley, C., et al., Quality of life and preferences for treatment following systemic adjuvant therapy for early-stage breast cancer.J Clin Oncol 1998; 16(4): 1380-1387, doi: 10.1200/JCO.1998.16.4.1380.
88. Grilli, F., P. Hajimohammadi Gohari, and S.J.I.J.o.M.S. Zou, Characteristics of Graphene Oxide for Gee Transfection and Controlled Release in Breast Cancer Cells. Int J Mol Sci 2022;23(12): 6802, doi: 10.3390/ijms23126802.
89. Hossen, S., et al., Smart nanocarrier-based drug delivery systems for cancer therapy and toxicity studies: A review. J Adv Res 2019;15:1-18, doi: 10.1016/j.jare.2018.06.005.
90. Sainz-Urruela, C., et al., Graphene-based sensors for the detection of bioactive compounds: A review. Int J Mol Sci 2021;22(7):3316.
91. Li, M., et al. Using graphene oxide high near-infrared absorbance for photothermal treatment of Alzheimer's disease. Adv Mater 2012;24(13)1722-1728, doi: 10.1002/adma.201104864.
92. Tian, B., et al., Photothermally enhanced photodynamic therapy delivered by nano-graphene oxide. ACS Nano 2011;5(9):7000-7009, doi: 10.1021/nn201560b.
93. Wang, L., et al. PEGylated reduced-graphene oxide hybridized with Fe 3 O 4 nanoparticles for cancer photothermal-immunotherapy. 2019;7(46):7406-7414.
94. Zhu, X., et al., Functionalized graphene oxide-based thermosensitive hydrogel for near-infrared chemo-photothermal therapy on tumor. J Biomater Appl 2016; 30(8):1230-1241, doi:10.1177/0885328215619583.
95. Ardakani, T.S., et al. Fe3O4@ Au/reduced graphene oxide nanostructures: Combinatorial effects of radiotherapy and photothermal therapy on oral squamous carcinoma KB cell line. Cere Int 2020;46(18):28676-28685.

96. Lee, Y. and E.D. Baron. Photodynamic therapy: current evidence and applications in dermatology. in Seminars in cutaneous medicine and surgery. 2011. WB Saunders
97. Brown, S.B., E.A. Brown, and I.J.T.l.o. Walker, The present and future role of photodynamic therapy in cancer treatment. Lancet Oncol 2004;5(8):497-508, doi: 10.1016/S1470-2045(04)01529-3.
98. Liu, L., et al. Recent progress of graphene oxide-based multifunctional nanomaterials for cancer treatment. Cancer Nanotech 2021;12:1-31.
99. Abrahamse, H. and M.R.J.B.J. Hamblin, New photosensitizers for photodynamic
therapy. Biochem 2016;473(4):347-364, doi: 10.1042/BJ20150942.
100. Liu, X., et al. Graphene oxide-grafted magnetic nanorings mediated magnetothermodynamic therapy favoring reactive oxygen species-related immune response for enhanced antitumor efficacy. ACS Nano 2020;14(2):1936-1950, doi: 10.1021/acsnano.9b08320.
101. Yu, X., et al., Inhibiting metastasis and preventing tumor relapse by triggering host immunity with tumor-targeted photodynamic therapy using photosensitizer-loaded functional nanographenes. ACS Nano 2017;11(10):10147-10158, doi: 10.1021/acsnano.7b04736
102. Huang, X., et al. Delivery of MutT homolog 1 inhibitor by functionalized graphene oxide nanoparticles for enhanced chemo-photodynamic therapy triggers cell death in osteosarcoma. Acta Biomater 2020;109:229-243, doi: 10.1016/j.actbio.2020.04.009.
103. Kumar, C.S. and F.J.A.d.d.r. Mohammad, Magnetic nanomaterials for hyperthermia-based therapy and controlled drug delivery. Adv Drug Deliv Rev 2011;63(9):789-808, doi: 10.1016/j.addr.2011.03.008.
104. Sangnier, A.P., et al. Targeted thermal therapy with genetically engineered magnetite magnetosomes@ RGD: Photothermia is far more efficient than magnetic hyperthermia. J Control Release 2018; 279:271-281, doi: 10.1016/j.jconrel.2018.04.036.
105. Xu, X., et al. Formation of graphene oxide-hybridized nanogels for combinative anticancertherapy.NanoMed2018;14(7):2387-2395,doi:10.1016/j.nano.2017.05.007
106. Alhasan, A.H., et al., Polymeric reactor for the synthesis of superparamagnetic-thermal treatment of breast cancer. Mol Pharm 2019;16(8): 3577-3587, doi: 10.1021/acs.molpharmaceut.9b00433.
107. De, D., et al., Curcumin complexed with graphene derivative for breast cancer therapy. ACS Appl Bio Mater 2020;3(9):6284-6296, doi: 10.1021/acsabm.0c00771.
108. Khorrami, S., et al., An improved method for fabrication of Ag-GO nanocomposite with controlled anti-cancer and anti-bacterial behavior; a comparative study. Sci Reports 2019;9(1):9167.

109. Hou, C., et al., Facile synthesis of water-dispersible Cu 2 O nanocrystal–reduced graphene oxide hybrid as a promising cancer therapeutic agent. Nanoscale 2013; 5(3):1227-1232.
110. Ashjaran, M., et al., Stimuli-responsive polyvinylpyrrolidone-NIPPAm-lysine graphene oxide nano-hybrid as an anticancer drug delivery on MCF7 cell line. Artif Cells Nanomed Biotechnol 2019;47(1):443-454, doi: 10.1080/21691401.2018.1543198.
111. Singh, G., et al., Fabrication of chlorambucil loaded graphene-oxide nanocarrier and its application for improved antitumor activity. Biomed Pharmaco 2020;129: 110443, doi: 10.1016/j.biopha.2020.110443.
112. Suriyakala, G.,Plumeria pudica Jacq. flower extract-mediated silver nanoparticles: characterization and evaluation of biomedical applications. 2021;126:108470, doi: 10.1016/j.inoche.2021.108470
113. Wani, A.A., et al., Recent advances and future perspectives of polymer-based magnetic nanomaterials for detection and removal of radionuclides: a review. 2022:119976
114. Tang, M., et al., Ferritinophagy/ferroptosis: Iron-related newcomers in human diseases. J Cell Physio 2018;233(12):9179-9190, doi: 10.1002/jcp.26954.
115. Nasrollahi, F., et al., Targeted delivery of docetaxel by use of transferrin/poly (allylamine hydrochloride)-functionalized graphene oxide nanocarrier. ACS Appl Mater Interfaces 2016; 8(21):13282-13293, doi: 10.1021/acsami.6b02790.
116. Cui, G., et al. Graphene-based nanomaterials for breast cancer treatment: Promising therapeutic strategies. J Nanobiotech 2021;19:1-30.
117. Li, J.-L., et al., A review of optical imaging and therapy using nanosized graphene and graphene oxide. Biomaterials 2013;34(37):9519-9534, doi: 10.1016/j.biomaterials.2013.08.066.
118. Nath, S. and P.J.T.i.m.m. Mukherjee, MUC1: a multifaceted oncoprotein with a key role in cancer progression. Trends Mol Med 2014;20(6):332-342, doi: 10.1016/j.molmed.2014.02.007.
119. Rubio, N., et al. Solvent-free click-mechanochemistry for the preparation of cancer cell targeting graphene oxide. ACS Appl Mater Interfaces 2015;7(34):18920-18923, doi:10.1021/acsami.5b06250.
120. Huang, R.-C., et al., Multivalent aptamer/gold nanoparticle–modified graphene oxide for mass spectrometry–based tumor tissue imaging. Sci Reports 2015;5(1):1-10.
121. Chen, D.S. and I.J.i. Mellman, Oncology meets immunology: the cancer-immunity cycle. Immunity 2013; 39(1):1-10, doi: 10.1016/j.immuni.2013.07.012.
122. Li, C., et al., Efficacy, pharmacokinetics, and biodistribution of thermosensitive chitosan/β-glycerophosphate hydrogel loaded with docetaxel. AAPS PharmSciTech 2014;15:417-424, doi: 10.1208/s12249-014-0077-z.

123. van Herpen, C.M., Intratumoral administration of interleukin-12 in head and neck cancer. Immune effects on the primary tumor and lymph nodes. Clin Cancer Res 2004;(10)8: 2626-35 doi: 10.1158/1078-0432.ccr-03-0304
124. Wu, W., et al., A novel doxorubicin-loaded in situ forming gel based high concentration of phospholipid for intratumoral drug delivery. Mol Pharm 2014;11(10):3378-3385, doi: 10.1021/mp500019p.
125. Zhu, X., et al., Functionalized graphene oxide-based thermosensitive hydrogel for near-infrared chemo-photothermal therapy on tumor. J Biomater Appl 2016;30(8):1230-1241, doi: 10.1177/0885328215619583.
126. Ferrari, M., R. Bashir, and S. Wereley, BioMEMS and Biomedical Nanotechnology: Volume IV: Biomolecular Sensing, Processing and Analysis. 2006: Springer.
127. Mulder, W.J., et al., Magnetic and fluorescent nanoparticles for multimodality imaging. Nanomed 2007;2(3):307-24, doi: 10.2217/17435889.2.3.307.
128. Shen, J., et al., One step synthesis of graphene oxide− magnetic nanoparticle composite. J Phys Chem 2010;114(3):1498-1503, doi: 10.1021/jp909756r.
129. Liang, W., et al., β-Cyclodextrin–hyaluronic acid polymer functionalized magnetic graphene oxide nanocomposites for targeted photo-chemotherapy of tumor cells. Polymers 2019;11(1):133, doi: 10.3390/polym11010133.
130. Hong, G., A.L. Antaris, and H.J.N.b.e. Dai, Near-infrared fluorophores for biomedical imaging. Nat Biomed Eng 2017; 1(1):0010, doi: 10.1038/s41551-016-0010
131. Li, J.L., et al., Graphene oxide nanoparticles as a nonbleaching optical probe for two-photon luminescence imaging and cell therapy. Angew Chem Int Ed Engl 2012;51(8):1830-1834, doi: 10.1002/anie.201106102.
132. Beard, P.J.I.f., Biomedical photoacoustic imaging. Interface Focus 2011;1(4): 602-631, doi: 10.1098/rsfs.2011.0028.
133. Nyayapathi, N. and J.J.J.o.b.o. Xia, Photoacoustic imaging of breast cancer: a mini review of system design and image features. J Biomed Opt 2019;24(12): 121911-121911,doi: 10.1117/1.JBO.24.12.121911.
134. Tromberg, B.J., et al., Assessing the future of diffuse optical imaging technologies for breast cancer management. Med Phys 2008;35(6Part1):2443-2451, doi: 10.1118/1.2919078.
135. Kruger, R.A., et al., Photoacoustic angiography of the breast. Med Phys 2010;37(11):6096-6100, doi: 10.1118/1.3497677.
136. Kaczmarski, J.A., et al., Structural and evolutionary approaches to the design and optimization of fluorescence-based small molecule biosensors. Curr Opin Struct Biol 2019;57:31-38, doi: 10.1016/j.sbi.2019.01.013.
137. Fares, J., et al., Landscape of combination therapy trials in breast cancer brain metastasis. MedComm 2020;147(7):1939-1952, doi: 10.1002/mco2.118.

138. Shafiee, A., S. Iravani, and R.S.J.M. Varma, Graphene and graphene oxide with anticancer applications: Challenges and future perspectives. Int J Cancer 2022;3(1): e118., doi: 10.1002/ijc.32937
139. Bedard, P.L., et al., Small molecules, big impact: 20 years of targeted therapy in oncology. Lancet 2020;395(10229):1078-1088, doi: 10.1016/S0140-6736(20)30164-1.
140. Tan, A.C., et al., Systematic review of combinations of targeted or immunotherapy in advanced solid tumors. J Immunother Cancer 2021;9(7), doi: 10.1136/jitc-2021-002459
141. Kommineni, N., et al., Cabazitaxel and thymoquinone co-loaded lipospheres as a synergistic combination for breast cancer. Chem Phys Lipids 2019;224:104707, doi: 10.1016/j.chemphyslip.2018.11.009.