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Review Article

Graphene Oxide Nanocarriers for Effective Drug Delivery in Breast Cancer Treatment

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Abstract

Breast cancer is the most commonly diagnosed form of cancer globally, with women having a higher risk of developing the disease. Current treatment approaches, such as surgery, chemotherapy, and radiotherapy, encounter significant difficulties due to the heterogeneous and intricate regulation of tumors. Nanotechnology, especially the utilization of graphene oxide (GO), presents a promising approach to overcoming the limitations of traditional treatments. GO's unique properties, including its two-dimensional structure, functional groups, and high surface area, make it an ideal material for developing multifunctional nanocarriers. Graphene oxide-based nanocarriers have demonstrated immense potential in breast cancer therapeutics by overcoming the limitations and adverse reactions associated with chemotherapy. The functionalization of GO's surface using biocompatible substances like chitosan and polyethylene glycol improves the cytotoxicity of GO. Enhancing the cytotoxicity also improves the ability to treat tumors that have developed resistance to traditional treatments. These findings demonstrate the promising efficacy of GO-based nanocarriers in treating breast cancer and pave the way for the development of more precise and efficient treatment strategies in the future, potentially improving therapeutic outcomes.

Keywords

Breast Cancer, Graphene Oxide, Nanocarrier, Drug Delivery

1. Introduction

On December 15, 2020, the official site of the Universal Office for Investigate on Cancer, a division of the World Wellbeing Organization, distributed worldwide information on cancer predominance. The data revealed that the world witnessed 2.26 million new incidences of breast cancer, surpassing lung cancer and becoming the most commonly diagnosed form of cancer globally [1]. Women have a higher risk of developing breast cancer compared to men, with approximately one in eight women being affected. Moreover, there is a notable disparity in breast cancer patient mortality rates between developed and developing nations [2, 3].

Owing to the heterogeneity and intricate regulation of tumors, biomedical treatments encounter significant difficulties in clinical settings. Presently, primary treatment approaches for breast cancer comprise surgery, chemotherapy, immunotherapy, radiotherapy, and hormone therapy, which may not entirely eradicate the tumor and can lead to adverse side effects [4]. The utilization of nanomaterials facilitates advancements in drug effectiveness, specific toxicity toward cancer cells, and drug delivery [5].

GO has recently captured the attention of researchers due to its exceptional properties. Its controllable two-dimensional

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structure, versatile functional groups, and high surface area make it an intriguing material for various applications. These unique characteristics allow GO to be tailored into multi-functional nanocarriers, opening up a wide range of potential applications [6]. However, the engineering of a drug carrier that can effectively meet all the crucial requirements of a drug delivery system and ultimately advance to clinical trials remains a formidable task. Consequently, this characteristic facilitates the functionalization of GO's surface by incorporating proteins, DNA fragments, and antibodies [7].

Of all the nanostructured materials, GO possesses an exceptionally substantial surface area that exhibits an abundance of oxygenated groups. These oxygenated groups contribute significantly to the material's thermal and chemical stability. Moreover, the existence of oxygenated functional groups, including hydroxyl and epoxy groups, enables the occurrence of biochemical and bioconjugation reactions on GO's structure. Consequently, this characteristic facilitates the functionalization of GO's surface by incorporating proteins, DNA fragments, and antibodies [8]. According to scientific studies, GO demonstrates sensitivity toward various stimuli, including temperature, pH, and near-infrared irradiation (NIR) [9].

2. Breast Cancer

All through the 20th century, there was a worldwide add up to of around 685,000 passings and an evaluated 2.3 million modern cases of breast cancer among ladies [10]. Breast cancer features a lifetime frequency rate of around 1 in 833 among guys [11]. Histological classification is fundamental for directing clinical treatment strategies in cases of intrusive breast cancer. The foremost common sort, bookkeeping for 70–80% of breast cancer cases, is intrusive ductal carcinoma. Taking after that, obtrusive lobular carcinoma constitutes roughly 5 to 15% of cases. Moreover, there are other less common histological varieties, counting papillary tumors. Categorizing breast cancer based on histology makes a difference clinicians create customized approaches to successfully oversee and treat patients. [12, 13].

Breast cancer is influenced by several major risk factors, including reproductive and hormonal factors, lifestyle choices, and genetic predisposition. Reproductive and hormonal factors encompass early age at menarche, late age at menopause, older age at first childbirth, having fewer children, limited breastfeeding, the use of menopausal hormone therapy, and oral contraceptive use. These factors can impact the hormonal balance in the body and increase the risk of breast cancer. Lifestyle risk factors include excess body weight, physical inactivity, and alcohol intake. Obesity and physical inactivity can alter hormone levels and promote the growth of cancer cells. Alcohol consumption, particularly in excessive amounts, can increase estrogen levels and contribute to the development of breast cancer. Genetic predisposition also plays a significant role, with certain individuals carrying germline mutations in high-penetrance genes being more vulnerable to breast cancer. Mutations in genes such as BRCA1 and BRCA2 have been strongly linked to an increased risk of developing the disease [14-16].

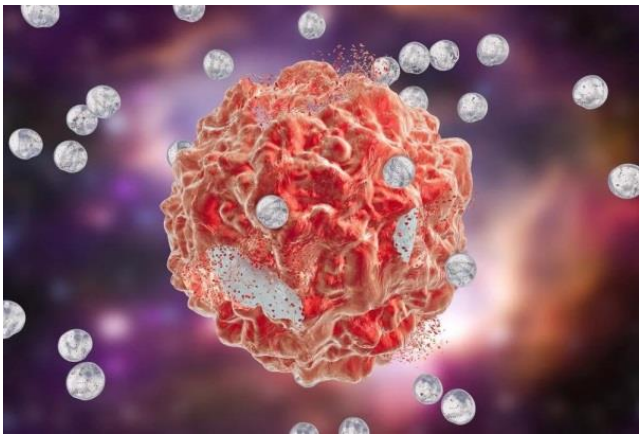

Figure 1. *Breast Cancer Treatment.*

Currently, the three principal strategies employed in the treatment of cancer are surgical procedures, chemotherapy, and radiotherapy. Surgical procedures involve the complete removal of the breast (mastectomy) or the removal of the tumor and surrounding tissues (breast-conserving lumpectomy). Chemotherapy involves the administration of drugs that are designed to target and kill cancer cells. Radiotherapy, on the other hand, uses high-energy waves to destroy cancer cells [17].

Among the available treatment options, chemotherapy is commonly employed for the treatment of various types of cancer. This form of treatment can target and eliminate cancer cells throughout the body. Additionally, chemotherapy can eradicate microscopic diseases that may not be visible during surgical procedures. It also has the potential to be used in combination with other therapies to enhance effectiveness. Nevertheless, it is important to note that chemotherapy is associated with significant side effects [18].

Nanotechnology has indeed revolutionized various fields, including medicine and drug delivery. The utilization of nanoparticle drug delivery in cancer treatments, particularly for breast cancer, has shown great promise. Nanoparticles offer advantages such as high loading capacity, stability, reduced toxicity, efficacy, specificity, and tolerability over conventional chemotherapy drugs. This enables them to effectively deliver anticancer drugs to tumors, either through active or passive means. This development holds significant potential for enhancing the effectiveness of breast cancer treatments [19].

3. Graphene Oxide

Graphene, a two-dimensional structure comprising sp2-

hybridized carbon atoms, possesses a unique honeycomb-like arrangement [20]. Due to its complete structure, high stability, and weak interaction with other substances, graphene is not an ideal choice for drug delivery purposes. However, derivatives of graphene, such as graphene oxide (GO) and reduced graphene oxide (rGO), have been introduced.

Graphene oxide (GO) and reduced graphene oxide (rGO) have surfaces that contain oxygen-based functional groups like carboxyl, epoxy, and hydroxyl groups. These functional groups can be altered chemically to create active sites for potential uses. Unlike other carbon-based materials, graphene oxide (GO) has a much larger surface area. In contrast to the typically hydrophobic nature of graphene, graphene oxide (GO) has both hydrophobic regions and hydrophilic peripheries, making it amphiphilic. However, graphene oxide (GO) has poor biocompatibility and stability in physiological solutions, limiting its use in drug delivery. To overcome these drawbacks, there is a growing interest in modifying the surface of graphene oxide (GO) to enhance its potential. Several studies have shown that the cytotoxicity of graphene oxide (GO) can be reduced by modifying it with biocompatible substances such as chitosan and polyethylene glycol. [25-27].

1) Functional modification of graphene oxide (GO) enhances the utilization of graphene carriers.
2) There are two primary types of methods for functional modification of GO: covalent and non-covalent modifications. Covalent modification involves chemical reactions that alter the oxygen-containing functional groups on the surface of GO. Non-covalent bond modification utilizes pi-pi conjugation, hydrogen bonds, and ionic bonds to modify GO. Functional modification makes GO more dispersible in polar solvents. [28].

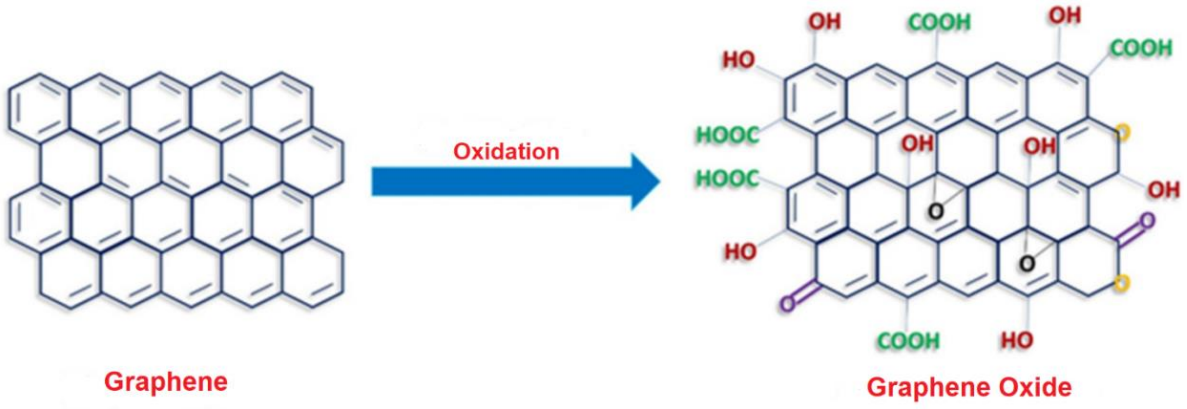

Figure 2. *Chemical structures of graphene and graphene oxide.*

In general, there are two primary types of graphene oxide (GO) synthesis methods: "top-down" and "bottom-up" approaches. The "top-down" methods involve the recovery of graphene derivatives from a carbon source, typically graphite, while the "bottom-up" procedures use basic carbon molecules to create pristine graphene. Both approaches offer viable options for synthesizing GO based on specific requirements [29, 30].

In cases where the targeted tissue is located outside the bloodstream, the requirement for efficient endothelial penetration necessitates the use of small carriers (<200 nm). The mentioned standard is fulfilled by graphene oxide, which has an adjustable lateral size, ranging from several nanometers to tens of microns. This tunability of GO allows for the fabrication of carriers with sizes suitable for effective endothelial penetration in such cases [7, 31, 32].

4. Cancer Therapy

The current state of cancer treatment in the medical field is still relatively nascent, and efforts to develop and apply effective drugs are ongoing. Chemotherapy, alongside surgical procedures, is commonly employed for cancer treatment. However, chemotherapy drugs often cause severe side effects. Thus, further research is necessary to reduce the toxic side effects while maintaining the effectiveness of these drugs. The utilization of carriers as drug delivery systems represents a significant advancement in the field of cancer research [33].

Ideally, nanocarriers should have a size ranging from 30 to 200 nm to enable their retention in blood vessels. Nanocarriers larger than this range tend to aggregate in the spleen or, liver while sizes below this range can be subjected to blood renal filtration, leading to their filtration from the plasma into the urine. Achieving the optimal size range is crucial to ensure the stability and effective circulation of nanocarriers in the bloodstream [34].

GO has demonstrated an excellent capacity for loading chemotherapeutic drugs and other chemical moieties. This ability arises from various interactions such as electrostatic interactions, hydrogen bonding, and π–π interactions [35, 36].

Nanocarriers based on graphene oxide have displayed immense promise in the realm of breast cancer therapeutics by surmounting the constraints and adverse reactions associated with chemotherapy [37].

Rana et al. conducted a study in which they successfully loaded Juniperus squamata root essential oil (JSEO) onto polyvinylpyrrolidone (PVP) functionalized graphene oxide (GO-PVP). They subsequently evaluated the cytotoxic effects of GO-PVP-JSEO on human breast cancer cells. Ultimately, the research yielded a novel and promising finding, indicating that the utilization of a JSEO-loaded GO-PVP nanocarrier shows potential as a platform for breast cancer therapy [38].

Yang et al. introduced a hybrid material combining superparamagnetic graphene oxide (GO) with Fe_3O_4 nanoparticles, known as GO–Fe_3O_4. This hybrid was subsequently loaded with doxorubicin hydrochloride (DXR), a common chemotherapeutic drug. A notable finding was that both the GO–Fe_3O_4 hybrids, whether before or after DXR loading, exhibited good dispersion in aqueous solutions. Furthermore, they demonstrated the ability to aggregate under acidic conditions and respond to an external magnet, enabling controlled movement.

Interestingly, the aggregated hybrid could be redispersed into a stable suspension under basic conditions. These characteristics make the GO–Fe_3O_4 hybrid a promising candidate for controlled and targeted drug delivery [39].

Taiwari et al. conducted a study to examine the effectiveness of a combinatorial anticancer treatment involving the well-established anticancer drugs quercetin and gefitinib. In their research, they compared the combined therapy with separate loading of gefitinib and quercetin onto polyvinylpyrrolidone (PVP)-functionalized graphene oxide (GO-PVP) nanovehicles. The findings suggest that the combined drug system, when loaded onto the GO-PVP nanovehicle, has the potential to outperform individual drug therapies. This is attributed to the synergistic effect of the combinatorial approach, as well as the efficient delivery of the chemotherapeutic agents [40].

Matiyani et al. successfully synthesized polyvinylpyrrolidone-grafted magnetic GO (GO–PVP–Fe_3O_4) as a nanocarrier for the loading and delivery of the anticancer drug quercetin (QSR). The effectiveness of the QSR-loaded GO–PVP–Fe_3O_4 nanocarrier was investigated in terms of cytotoxicity against both non-tumorigenic HEK 293T cells and human breast cancer MDA MB 231 cells. The results revealed that the QSR-loaded GO–PVP–Fe_3O_4 nanocarrier exhibited more pronounced cytotoxic effects on MDA MB 231 breast cancer cells compared to pure QSR alone. Importantly, no significant cytotoxic effects were observed in normal cells. These novel findings suggest that the synthesized magnetic nanocarrier holds promise as a potential candidate for cancer therapy [41]. Folic acid-conjugated graphene oxide (GO-FA) was synthesized as a targeted drug delivery carrier for doxorubicin. GOFA-DOX was integrated into a thermosensitive and biodegradable polymer hydrogel called HACPN for targeted drug delivery. GOFA had a high loading capacity for doxorubicin, allowing efficient intracellular uptake by breast cancer cells, particularly MCF-7 cells. The release of the drug from GOFA-DOX was sensitive to pH changes, improving its therapeutic effect. Tissue biopsy examination and blood analysis showed no evidence of acute toxicity due to the intratumoral administration of doxorubicin using GOFA-DOX/HACPN. The study suggests that GOFA-DOX/HACPN can be considered a safe and effective intratumoral drug delivery system for breast cancer therapy. [42].

The study conducted by Rajaei et al. focused on loading 5-FU onto a pH-sensitive hydrogel composed of chitosan, agarose, and graphene oxide (CS/AG/GO) for in vitro treatment of human breast cancer cells (MCF-7). This nanocarrier, which is biocompatible and consists of two polysaccharides and GO, has the potential to enhance the dosage of 5-FU and facilitate localized delivery to the target site. Therefore, this developed nanocarrier holds significant potential for the targeted release of 5-FU and the effective treatment of breast cancer [43].

Vinothini et al. investigated the potential of a modified graphene oxide-methyl acrylate (GO-g-MA) nanocarrier for the targeted delivery of paclitaxel to breast cancer cells. Based on their collective data, they observed that the GO-g-MA/FA nanocarrier loaded with paclitaxel (PTX) demonstrated inhibitory effects on cell growth in MDA-MB-231 breast cancer cells. Additionally, in breast cancer rats, the nanocarrier led to a reduction in tumor size. Both in-vitro and in-vivo experiments highlight the effectiveness of the GO-g-MA/FA nanocarrier for treating breast cancer. These findings hold promise for the development of more precise and efficient treatment strategies for breast cancer, potentially enhancing therapeutic outcomes in the future [44].

The utilization of specific nanocarriers in combination with multiple anticancer drugs holds great promise for drug delivery. In their research, Tiwari et al. explored the use of potassium-contained graphene oxide (K-GO) as a nanocarrier in a drug delivery system simultaneously delivering two anticancer drugs, gefitinib (GEF) and camptothecin (CPT). Their findings demonstrated that the combined drug-loaded system exhibited superior loading capacity and cytotoxicity compared to the individual drug systems when tested on human breast cancer cells. This highlights the promising efficacy of the nanocarrier-based approach in enhancing drug delivery for breast cancer treatment [45].

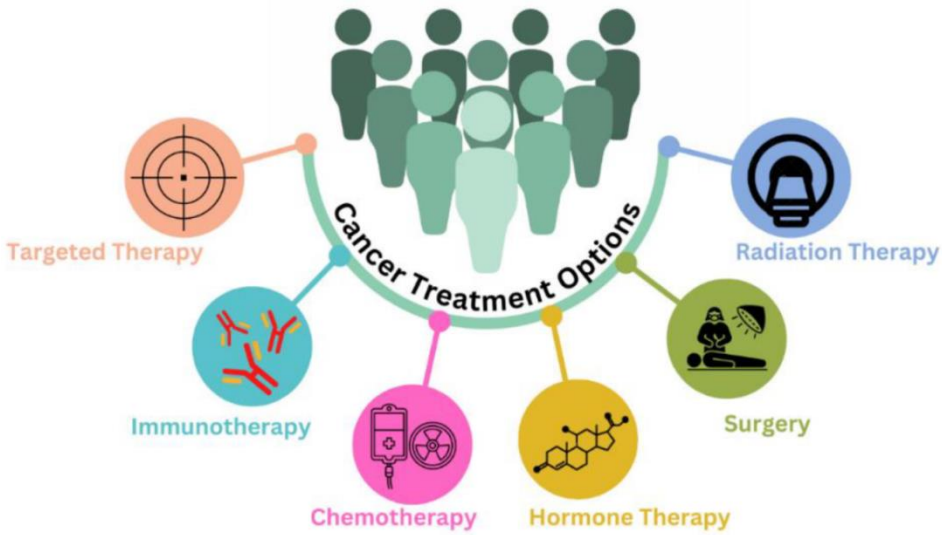

Figure 3. *Cancer Treatment Option.*

5. Conclusions

The development of nanocarriers based on graphene oxide has paved the way for more effective breast cancer therapy. These nanocarriers can deliver chemotherapy drugs to cancer cells, minimizing side effects and overcoming multidrug resistance. The use of biocompatible coatings enhances cytotoxicity against cancer cells, offering an opportunity to enhance patient outcomes. Further research is necessary to optimize the design and delivery of these nanocarriers for successful implementation in breast cancer therapy. However, the results are promising and provide hope for an enhanced approach to treating breast cancer.

Abbreviations

GO Graphene Oxide

Author Contributions

Mahshid Sadeghi is the sole author. The author read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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