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RESEARCH PAPER

# An Update on Functionalized Graphene Nanosheets as an Electrochemical Nano-Biosensors for Breast Cancer Detection: A Review

***Afonin Georgiy Alekseevich [1]*, Laila Kalimoldina [2], Murat Nurushev [3], Nodirjon Ruzimurodov Fazliddinovich [4], Safarova Tumaris Rustamkulovna [5], Gavxar Zokirova [6], Eshmamat Khurramov [6], I.B. Sapaev [7,8,9], Makhmudova Lazokat Toirjan kizi [10], Khodjieva Gulirano Sayfullaevna [11], Gavkhar Abdullayeva [12], Mamatov Shukurllo Shermat ugli [13], Ergashov Umarbek Shukrat ugli [14]***

[1] *Department of Oncology, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan*

[2] *Department Chemistry, Faculty of Food Technologies, Chemical Technology and Ecology Almaty, Kazakhstan*

[3] *High School of Natural Sciences, Astana International University, Astana, Kazakhstan*

[4] *Institute of Immunology and Human Genomics, Academy of Sciences, Uzbekistan*

[5] *Department of social science, Tashkent State University of Economics, Tashkent, Uzbekistan*

[6] *Termez State University, Termez, Uzbekistan*

[7] *Tashkent Institute of Irrigation and Agricultural Mechanization Engineers National Research University, Tashkent, Uzbekistan*

[8] *University of Tashkent for Applied Sciences, Tashkent, Uzbekistan*

[9] *Western Caspian University, Baku, Azerbaijan*

[10] *Faculty of Philology of Uzbek and Russian language of the Kokand Pedagogical Institute, Uzbekistan*

[11] *Department of Propaedeutics, Internal Medicine of the Bukhara State Medical Institute, Uzbekistan*

[12] *Chirchik State Pedagogical University, Uzbekistan*

[13] *Faculty of Foreign Languages of the Jizzakh State Pedagogical University, Uzbekistan*

[14] *Department of Urology and Oncology, the Fergana medical institute of Public health, Fergana, Uzbekistan*

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## ABSTRACT

This review presents an extensive examination of the progress made in the development of functionalized graphene nanosheets as electrochemical nano-biosensors for breast cancer detection. The distinctive characteristics of graphene, such as its substantial surface area and superior electrical conductivity, render it a highly suitable material for biosensing applications. Recent research has illustrated the efficacy of these biosensors in identifying specific biomarkers linked to breast cancer, including the BRCA1 gene and CA 15-3, demonstrating remarkable sensitivity and minimal detection limits. For example, a cutting-edge sensing platform that employs graphene oxide and ionic liquid composites has achieved a detection limit of 1.48 μg/mL for the BRCA1 gene, highlighting the potential of these materials in clinical diagnostics. Additionally, the review underscores the significance of optimizing sensor performance through various factors, such as ionic liquid concentration and hybridization time, to improve detection capabilities. Despite the encouraging findings, challenges persist regarding the reproducibility and stability of graphene materials, which call for further investigation to overcome these issues. The review also stresses the necessity for standardization in manufacturing processes and the investigation of additional biomarkers to expand the applicability of these biosensors. In summary, this manuscript highlights the transformative potential of functionalized graphene nanosheets in the early detection of breast cancer, setting the stage for future advancements in diagnostic technologies.

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* *Corresponding Author Email: afoningeorgiyalekseevich@hotmail.com*

## INTRODUCTION

Breast cancer ranks as one of the most prevalent and potentially fatal malignancies, exhibiting the highest incidence rate in the female population [1]. The early identification of oncomarkers associated with breast cancer is regarded as the most effective approach for its detection and subsequent treatment [2, 3]. The incorporation of functionalized graphene nanosheets into electrochemical biosensors marks a notable progress in the early identification of breast cancer, which remains a predominant cause of cancer-related deaths among women [4-8]. Conventional diagnostic techniques, despite their efficacy, frequently necessitate invasive procedures and incur substantial costs, potentially delaying timely diagnosis and subsequent treatment [9, 10]. In contrast, electrochemical biosensors present a non-invasive and economically viable alternative, capable of delivering swift and precise results, thereby proving particularly beneficial for the assessment of cancer biomarkers such as CA 15-3 [11-13]. The distinctive characteristics of graphene, which include exceptional electrical conductivity, extensive surface area, and favorable biocompatibility, significantly enhance the efficacy of these biosensors, facilitating greater sensitivity and specificity in the detection of cancer biomarkers [14-17]. This review seeks to examine the most recent advancements in the application of functionalized graphene nanosheets as electrochemical nano-biosensors, emphasizing their transformative potential in breast cancer diagnostics.

The timely identification of breast cancer greatly enhances survival probabilities, underscoring the importance of efficient screening techniques [18, 19]. Electrochemical biosensors possess the capability to identify biomarkers at minimal concentrations, thereby aiding in the early diagnosis and management of the disease [20-23]. Graphene exhibits distinctive physicochemical characteristics, including exceptional conductivity and an extensive surface area, which significantly improve the performance of sensors [24-27]. The functionalization of graphene facilitates enhanced immobilization of bioreceptors, thereby increasing both specificity and sensitivity. Recent research has illustrated the effective utilization of graphene-based biosensors for the detection of CA 15-3, highlighting their analytical capabilities and prospective clinical applications [28-30]. The incorporation of nanocomposites with graphene has significantly enhanced detection signals, resulting in reduced detection thresholds and increased precision. Functionalized graphene nanosheets present considerable benefits in the advancement of electrochemical biosensors aimed at breast cancer detection, largely attributable to their distinctive physicochemical characteristics [30-32]. These attributes improve the sensitivity, selectivity, and overall efficacy of biosensors, rendering them appropriate for the early diagnosis of cancer. The subsequent sections will delineate the primary advantages associated with the application of functionalized graphene nanosheets in this field. Functionalized graphene nanosheets demonstrate remarkable electrical conductivity, a characteristic that is essential for the swift movement of electrons during electrochemical reactions [33-38]. This attribute facilitates enhanced signal amplification, thereby improving the detection thresholds for cancer biomarkers, including HER2 and CA 15-3 [39-41]. The extensive surface area of graphene nanosheets enhances the immobilization of bioreceptors, including antibodies and aptamers, which contributes to heightened sensitivity. Additionally, the process of functionalization introduces reactive groups that augment the binding efficiency of these bioreceptors, thereby facilitating the development of more effective biosensor designs. The straightforward functionalization and modification of graphene nanosheets facilitate the creation of a variety of biosensor platforms designed for particular biomarkers. These biosensors typically exhibit low production costs and can be fabricated through uncomplicated synthesis techniques, thereby enhancing their accessibility for extensive clinical application.

Functionalized graphene nanosheets offer a variety of benefits; however, challenges including variability between batches and issues with reproducibility persist. It is crucial to tackle these obstacles to ensure the reliable use of these materials in clinical applications. In addition, although there have been significant advancements in the development of graphene-based electrochemical biosensors, several challenges persist, including issues related to reproducibility and the necessity for standardized fabrication techniques. Tackling these challenges is essential for the broader implementation of these technologies in clinical environments. Fig.

1 shows important issue of detection of breast cancer using electrochemical nano-biosensor in recent years. This review paper will examine recent original research articles, providing an in-depth analysis of functionalized graphene nanosheets as electrochemical nano-biosensors for the detection of breast cancer.

## LITERATURE REVIEW

In 2024, Shi and colleagues introduced an innovative electrochemical sensor that utilizes a reduced graphene oxide nanocomposite in conjunction with a zirconium-based metal-organic framework featuring terephthalic acid as a ligand [42]. This sensor demonstrates exceptional sensitivity and selectivity in detecting gemcitabine, a chemotherapy agent employed in the treatment of breast cancer, through the Zr-MOF-rGO modified graphene paste electrode. The integration of the robust structural properties and active sites of Zr-MOF with the extensive surface area and electrical conductivity of rGO enhances the sensor's electron transfer efficiency and GEM adsorption capabilities. It surpasses existing GEM sensors, exhibiting a broad linear detection range of 0.5–490 µM and a low detection limit of 0.008 µM. The sensor's long-term analytical performance is validated through stability and reusability assessments, achieving accuracy rates exceeding 94% and relative standard deviation values below 4.21% in recovery experiments conducted with spiked human blood serum and urine samples. Collectively, the findings of this study indicate that the Zr-MOF-rGO/GrPE electrode holds significant promise as a viable platform for the detection of gemcitabine in breast cancer patients. The implications of this research for patient care and treatment results are considerable. Our sensor offers a rapid, economical, and user-friendly approach to monitoring gemcitabine concentrations, which could facilitate more accurate dosing and enhanced management of adverse effects, ultimately resulting in better patient outcomes. Additionally, the capability to track gemcitabine levels in real-time may permit prompt modifications to treatment strategies, potentially increasing the efficacy of chemotherapy and improving survival rates among breast cancer patients.

In 2024, Sadrabadi et al. introduced an innovative microRNA biosensor utilizing magnetic rod carbon paste electrodes for the detection of breast cancer, employing a relatively novel metal-organic framework (MOF) structure as its substrate [43]. The primary objective of developing such biosensors, intended for clinical diagnostics, is to accurately quantify trace amounts of microRNA 155 in complex biological matrices. To enhance the electrode's surface-to-volume ratio and promote efficient electron transfer, a combination of materials was employed, including carbon nanofibers, CuBTC-AIA (CuMOF), and Fe@rGO. The binding of microRNAs to the electrode surface was facilitated by the use of 1-pyrenebutyric acid N-hydroxysuccinimide ester. The hybridization process occurring on the modified electrode was analyzed through techniques such as cyclic voltammetry, electrochemical impedance spectroscopy, and differential pulse voltammetry, within a potential range where the accumulated hematoxylin exhibited electroactivity. Under optimal experimental conditions, the biosensor achieved an exceptionally low detection limit of 0.08 fM and a satisfactory dynamic range of

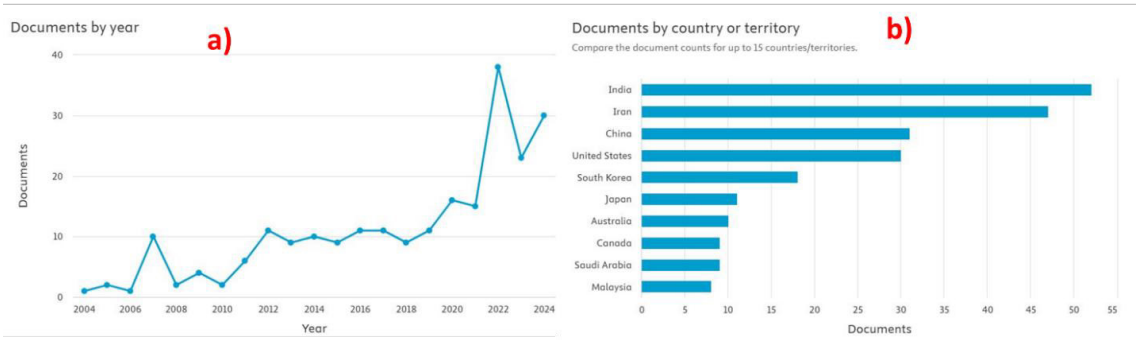


Fig. 1. a) Number of documents regarding the application of nanobiosensor in detection of diagnosis b) Top ten countries in this field

0.2 fM to 500 pM. The sensor demonstrated reproducibility and selectivity when evaluated against various mismatched target sequences. Furthermore, the efficacy of the nanobiosensor in detecting microRNA 155 was validated using real human serum samples, showing no significant interference from other molecular components. The effective operation of the biosensor in human serum samples demonstrates its appropriateness for application in clinical settings. Particularly in the context of breast cancer diagnosis, this biosensor is poised to be significantly impactful owing to its exceptionally low detection threshold.

In 2024, Poshteh et al. introduced a novel technology for the sensitive detection of exemestane, highlighting its applicability for precise monitoring of drug levels in clinical environments [44]. This research aimed to develop silver nanoparticles that were immobilized on a reduced-graphene-oxide modified glassy-carbon electrode (Ag-rGO/GCE) specifically for the sensitive detection of exemestane, a medication used in breast cancer treatment. Structural and morphological characterizations conducted through X-ray diffraction, scanning electron microscopy, and X-ray photoelectron spectroscopy confirmed the successful decoration of rGO nanosheets with Ag nanoparticles. Electrochemical assessments utilizing electrochemical impedance spectroscopy, cyclic voltammetry, and amperometric techniques demonstrated that the Ag-rGO/GCE exhibited enhanced electron transfer capabilities along with high sensitivity and selectivity for exemestane. The findings indicated a linear detection range of 10 to 750 µg/mL, a sensitivity of 0.5330 µA/µg·m$^{-1}$, and a limit of detection of 2.8 ng/mL. When evaluating the sensor's performance using blood serum, tap water, and agricultural wastewater samples, it achieved notable recovery rates exceeding 95.00% and maintained good precision, with a relative standard deviation below 4.75%. These results substantiate the reliability and accuracy of the Ag-rGO/GCE sensor for monitoring exemestane concentrations in both clinical and environmental contexts. The incorporation of silver and reduced graphene oxide nanoparticles in electrochemical sensors presents numerous benefits, such as enhanced sensitivity, selectivity, stability, and versatility. These nanoparticles significantly improve the performance of electrochemical sensing by facilitating the detection of analytes at extremely low concentrations while minimizing interference from complex sample matrices.

In 2024, Rajaei et al. reported the development of chitosan/agarose/graphene oxide/montmorillonite nanocomposites intended for use as drug delivery systems to facilitate the sustained release of curcumin, aimed at inhibiting MCF7 breast cancer cells [45]. These nanocomposites present several benefits, such as biocompatibility and sensitivity to pH changes, and were synthesized using a water-in-oil-in-water (W/O/W) emulsification method. Characterization of the nanocomposites was performed through Fourier-transform infrared spectroscopy (FTIR) and X-ray diffraction (XRD) analyses. The mean size of the resulting nanoscale emulsions was assessed using dynamic light scattering (DLS), while zeta potential measurements were conducted to evaluate the surface charge characteristics of the nanocomposites. Field emission scanning electron microscopy (FE-SEM) images revealed a uniform and smooth surface morphology of the synthesized materials. The results from the MTT assay indicated that these nanocomposites exhibited significant cytotoxicity towards MCF7 breast cancer cells. Additionally, flow cytometry analyses confirmed the induction of apoptosis in these cancer cells. A dialysis method demonstrated that curcumin was released more rapidly in acidic environments. Collectively, these findings suggest that the engineered CS/AG/GO/MMT@CUR nanocomposites hold promise as effective drug carriers for the treatment of breast cancer.

In 2024, Hosseine et al. introduced an innovative electrochemical biosensor designed for the detection of cancer [46]. This biosensor utilizes a glassy carbon electrode and features a nanocomposite comprising reduced graphene oxide, $Fe_3O_4$, Nafion, and polyaniline. The authors detailed the modification process through various characterization techniques, including scanning electron microscopy, transmission electron microscopy, Fourier-transform infrared spectroscopy, Raman spectroscopy, vibrating sample magnetometry, and electrochemical methods. To refine the experimental parameters and observe the immobilization processes, they employed electrochemical techniques such as cyclic voltammetry, electrochemical impedance spectroscopy, and square wave voltammetry. The calibration curve exhibited a linear range of 102 to 106 cells per mL, with a detection limit established

at 5 cells per mL.

In 2023, Panda and colleagues introduced a novel enzyme-free sensor that utilizes N-doped graphene quantum dots (N-GQDs) integrated with tin sulfide nanosheets ($SnS_2$) for the in situ detection of hydrogen peroxide ($H_2O_2$) produced by human breast cancer cells [47]. The N-GQDs, characterized by a size of less than 1 nm, were incorporated into $SnS_2$ nanosheets to create an N-GQDs@$SnS_2$ nanocomposite through a straightforward hydrothermal method. This hybrid material exhibited remarkable electrocatalytic properties for the reduction of $H_2O_2$, attributed to the synergistic effects of the highly conductive N-GQDs and the $SnS_2$ nanosheets. The sensing platform based on N-GQDs@$SnS_2$ demonstrated impressive detection capabilities, with a range spanning from 0.0125 to 1128 µM and a limit of detection of 0.009 µM (S/N = 3). Furthermore, the sensing performance of the N-GQDs@$SnS_2$ was noted for its stability, selectivity, and reproducibility. The practical utility of this sensor was validated through the quantification of $H_2O_2$ in various samples, including lens cleaner, human urine, and saliva. Additionally, the N-GQDs@$SnS_2$ electrode was effectively employed for real-time monitoring of $H_2O_2$ release from breast cancer cells and mouse fibroblasts. This research contributes significantly to the development of efficient non-enzymatic electrochemical sensors for the detection of diverse biomolecules using a simplified approach. The final conclusion drawn from their study indicates that the N-GQDs@$SnS_2$ platform is effective for detecting $H_2O_2$ in both MDA-MB-231 and L929 cell lines. The findings reveal that the release of $H_2O_2$ is significantly elevated in cancer cells compared to normal cells.

In 2023, Munoz et al. investigated the potential of graphene-based 3D-printed nanocomposite bioelectronics as advanced systems for the in situ monitoring and assessment of breast cancer cell adhesion and the chemosensitivity of anti-cancer agents [48]. To achieve this, they utilized 3D-printed nanocomposite graphene electrodes (3D-nGEs), which were fabricated from a commercially available graphene/polylactic acid filament. These electrodes were covalently biofunctionalized with an extracellular matrix protein, specifically fibronectin, by leveraging the carbon reactivity inherent in 3D-nGEs. The electrochemical system's specificity and selectivity for monitoring breast cancer cell adhesion were evaluated using electrochemical impedance spectroscopy (EIS). Notably, the developed 3D-printed bioelectronic system demonstrated remarkable accuracy in the rapid screening of anti-cancer drugs, yielding results that aligned closely with those obtained through conventional optical methods, while also benefiting from a label-free approach. This proof-of-concept represents a significant advancement in integrating electronics with biological systems through 3D printing technology, laying the groundwork for the sustainable and cost-effective production of graphene-based 3D-printed nanocomposite bioelectronics capable of simulating in vivo microenvironments with real-time electronic output signals. The electrochemical data obtained from the FN/3D-nGE was corroborated through comparison with the conventional optical method. This research lays the groundwork for integrating electronics with biological systems through 3D printing technology, facilitating rapid and label-free electrochemical assessments without the need for traditional bench-top equipment. Ultimately, the advantages of 3D printing may enable the miniaturization and incorporation of the device into portable electrochemical instruments, allowing for measurements at the point of use.

Nitric oxide is crucial for various physiological processes, including cardiovascular regulation, immune system activity, and intercellular communication. Nevertheless, its brief half-life presents significant challenges for real-time detection.

In 2023, Butler et al. introduced an electrochemical sensor designed for nitric oxide (NO) detection, utilizing fibronectin-modified, solution-processed graphene ink [49]. This sensor was fabricated through a straightforward method that included spin-coating and hot-plate annealing. Initial electrochemical characterization was performed using the NO donor spermine NONOate, revealing a dynamic detection range of 10–1000 µM. The fibronectin-modified graphene substrate facilitated the adhesion and proliferation of MDA-MB-231 breast cancer cells, as demonstrated through optical microscopy. The production of extracellular NO was induced by the amino acid L-arginine, leading to observable morphological alterations in the attached cells, which were reversible upon administration of the NO synthase inhibitor Nω-nitro-L-arginine methyl ester. Additionally, real-time amperometric

measurements confirmed NO production via the fibronectin-functionalized graphene sensors. Although the primary focus of this research is on NO detection, the scalable nature of this platform suggests potential applications in other cell types, including high-throughput screening of therapeutics and the development of biocompatible coatings. This study primarily concentrated on the detection of nitric oxide; however, the capacity of these graphene films to facilitate cell attachment suggests their potential utility as a platform for investigating various cellular systems.

In 2023, Yari and Shokri reported the development of a novel electrochemical sensor designed for the detection of human breast cancer cells (MCF-7) [50]. This sensor employs a folic acid (FA)-functionalized triazine-grafted reduced graphene oxide (RGOTrz) as a modifier for a glassy carbon electrode (GCE), serving as the sensing component. The structural and compositional characteristics of the FA-RGOTrz/GCE were analyzed through various techniques, including X-ray diffraction, Fourier-transform infrared spectroscopy, scanning electron microscopy, and UV-visible spectroscopy. Additionally, the electrochemical performance of the electrode was assessed using cyclic voltammetry and electrochemical impedance spectroscopy (EIS). MCF-7 cancer cells were tested in phosphate buffer solutions and $[Fe(CN)_6]^{3-/4-}$, which acted as an appropriate supporting electrolyte and a useful probe, respectively. The FA-RGOTrz/GCE demonstrated a conducive environment for reversible redox reactions, yielding significant electrochemical signals upon interaction with cancer cells. Differential pulse voltammetry (DPV) results revealed that the binding of the folate receptor (FR) on MCF-7 cells to the RGOTrz-modified electrode, in the presence of $[Fe(CN)_6]^{3-/4-}$, led to a reduction in folic acid, a decrease in electron transfer, and a collapse of the current signal. The sensor achieved a detection limit of 50 human breast cancer cells per milliliter during the measurement process. The unique structural design of the FA-RGOTrz/GCE markedly enhances electron transfer and electrochemical activity for the detection of MCF-7 cells. This sensor, characterized by its distinctive architecture, exhibits high sensitivity to FR in MCF-7 cells, demonstrating excellent, reliable performance and significant potential for applications in both industrial and medical fields.

In 2022, Tran et al. reported the development of an ultrasensitive electrochemical biosensor designed for the detection of breast cancer cells (MCF-7) in human serum [28]. This biosensor was constructed by depositing nitrogen-doped graphene quantum dots (NGQDs) and phytohemagglutinin-L (PHA-L) onto screen-printed electrodes (SE). The NGQDs, characterized by particle sizes ranging from 3 to 12 nm, were synthesized using a microwave-assisted hydrothermal technique that utilized passion fruit juice as a sustainable carbon source. Following their synthesis, the NGQDs were conjugated with PHA-L through an amide bond formed between the carboxyl (COOH) group of the NGQDs and the amino (NH2) group of PHA-L. This dual-functionalization not only improved the electrical conductivity of the electrochemical sensor but also allowed PHA-L, a highly specific receptor, to effectively anchor MCF-7 cells. Consequently, this led to the ultrasensitive and highly selective detection of MCF-7 cells. The resulting NGQDs/PHA-L sensor demonstrated a broad linear detection range of 5 to 106 cells $mL^{-1}$ in phosphate-buffered saline (PBS) and 20 to 106 cells $mL^{-1}$ in human serum, with remarkably low detection limits of 1 and 2 cells $mL^{-1}$, respectively. Furthermore, the sensor exhibited excellent selectivity against six different interferents and maintained long-term stability after 80 days of storage in human serum, establishing the NGQDs/PHA-L complex as a highly effective electrochemical probe for the early diagnosis and treatment of breast cancer and other malignant tumors. The findings distinctly support the assertion that electroactive NGQDs serve as highly effective sensing probes for the electrochemical identification of MCF-7 cancer cells in the presence of PHA-L. Furthermore, this study presents a methodology for the fabrication of environmentally friendly and sustainable NGQDs/PHA-L derived from natural sources, which can be utilized as sensing platforms for the ultrasensitive and selective detection of MCF-7 and other malignant cells.

In 2022, Isin and colleagues introduced a novel sensing platform utilizing Graphene-oxide and ionic liquid composite-modified pencil graphite electrodes (GO-ILPGEs) for the detection of the breast cancer 1 (BRCA1) gene [51]. The characterization of these GO-IL modified electrodes was performed using

scanning electron microscopy, cyclic voltammetry, and electrochemical impedance spectroscopy. The process of nucleic acid hybridization was assessed through differential pulse voltammetry, which involved the direct measurement of the guanine oxidation signal without the need for any indicators. Optimization of the biosensor response was achieved by adjusting the ionic liquid concentration, probe concentration, and hybridization duration. The limit of detection for the BRCA1 gene was determined to be 1.48 μg/mL within a concentration range of 2–10 μg/mL. The sensor's sensitivity was quantified at 1.49 μA mL/μg cm². This biosensor demonstrated a significant ability to differentiate between the complementary target sequence and both a three-base-mismatched sequence and a non-complementary sequence.

In 2022, Zare and Rhee introduced an innovative model that approximates the conductivity of nanocomposites based on the characteristics of graphene, tunneling effects, and interphase properties [52]. The influence of these factors on conductivity is thoroughly assessed and substantiated. Additionally, the predictions made by the model are compared with experimental data from various examples. It is observed that both the conduction and diameter of graphene significantly impact conductivity. The proposed model further indicates that a large interphase and narrow tunnels enhance conductivity, whereas a narrow interphase combined with large tunnels leads to an insulating behavior in the nanocomposite. The results from this new model align well with experimental findings, providing strong evidence for its validity, which may supersede traditional models in future research. This model holds potential for optimizing breast cancer sensors, as conductivity plays a crucial role in detection. Furthermore, a smaller contact diameter and higher tunneling resistivity markedly reduce tunneling conductivity, while a larger contact diameter and lower tunneling resistivity improve conductivity. The analysis also reveals that neglecting tunneling and interphase components tends to overestimate the percolation threshold. A satisfactory correlation is observed between experimental values and theoretical calculations, reinforcing the appropriateness of the proposed model. Among the various factors, the concentration and thickness of graphene nanosheets exert the most significant influence on conductivity. The developed model is particularly relevant for breast cancer cell sensors, given the critical importance of conductivity in detection.

In 2021, Shafiei and colleagues introduced a graphene-based aptasensor specifically engineered for the sensitive detection of human breast cancer cells [53]. This sensor utilized a composite of reduced graphene oxide, chitosan, and gold nanoparticles, which served as a biocompatible substrate to stabilize the receptor. The aptamer's significant role within this composite arises from the synergistic interactions among its components, which enhance various properties, such as electrical conductivity and effective surface area. Following the incubation of the aptasensor with MCF-7 cancer cells, specific interactions occurred between the cell membrane proteins and the three-dimensional structure of the AS1411 aptamer, facilitating the capture of cells on the sensor. The fabrication process of the aptasensor was analyzed using cyclic voltammetry and electrochemical impedance spectroscopy. An increase in cell concentration correlated with a greater number of captured cells on the aptasensor, which impeded the access of Ferro/Ferricyanide to the sensor, leading to an increase in charge transfer resistances. This aptasensor demonstrated a linear relationship with the logarithm of cell concentration, exhibiting high selectivity, a broad linear range from $1 \times 10^{1}$-1 to $1 \times 10^{6}$ cells/mL, and a low detection limit of 4 cells/mL. The aptasensor designed for the detection of MCF-7 cancer cells exhibits notable characteristics, including high selectivity, repeatability, reproducibility, sensitivity, and an extensive dynamic linear range.

In 2021, Pothipor et al. introduced a novel label-free multiplexed electrochemical biosensor utilizing a three-screen-printed carbon electrode (3SPCE) array modified with gold nanoparticles, graphene quantum dots, and graphene oxide (AuNPs/GQDs/GO) [54]. This innovative biosensor was successfully employed for the simultaneous detection of the biomarkers miRNA-21, miRNA-155, and miRNA-210 for the first time. The system incorporates redox species, specifically anthraquinone (AQ), methylene blue (MB), and polydopamine (PDA), which serve as redox indicators to anchor capture miRNA probes. These probes hybridize with their respective complementary targets: miRNA-21, miRNA-155, and miRNA-210. Upon the presence of these target

miRNAs, the square wave voltammetry (SWV) scan reveals three distinct peaks, each corresponding to one of the miRNAs, with peak intensity being quantitatively related to the concentration of the respective target analyte. This interaction leads to a significant reduction in the SWV peak current of the redox probes. The AuNPs/GQDs/GO-based biosensor demonstrates exceptional performance in simultaneous miRNA detection, exhibiting a broad linear dynamic range from 0.001 to 1000 pM and remarkably low detection limits of 0.04, 0.33, and 0.28 fM for miRNA-21, miRNA-155, and miRNA-210, respectively. Furthermore, it showcases high selectivity and applicability for detecting miRNAs in human serum samples, indicating its substantial potential for use in breast cancer diagnostics.

In 2021, Ghanbari and colleagues introduced an innovative drug delivery system characterized by its targeted, trackable, and pH-responsive properties [55]. This system was developed using glucosamine (GlcN) conjugated graphene quantum dots (GQDs) that were loaded with the hydrophobic anticancer agent curcumin (Cur). The primary aim was to assess the targeting efficacy and cytotoxic potential of this formulation against breast cancer cells that exhibit an overexpression of GlcN receptors. The GQDs, which are biocompatible and photoluminescent, were synthesized from graphene oxide utilizing a green and straightforward oxidizing technique. Comprehensive structural and spectral analyses of the synthesized GQDs and Cur/GlcN-GQDs were conducted. The dimensions of the GQDs ranged from 20 to 30 nm, and they were found to consist of fewer than ten layers. Notably, the Cur-loaded nanocarrier demonstrated pH-sensitive and sustained release characteristics, with a total release of 37% at pH 5.5 and 17% at pH 7.4 over a period of 150 hours. In vitro studies on cellular uptake, conducted through fluorescence microscopy and flow cytometry, revealed significantly enhanced fluorescence for the targeted nanocarrier in MCF-7 cells compared to the non-targeted variant, attributed to increased cellular internalization via GlcN receptor-mediated endocytosis. Additionally, results from the MTT assay indicated that the bare nanocarrier exhibited minimal toxicity, maintaining cell viability above 94% even at concentrations reaching 50 µg·ml−1. In contrast, the Cur/GlcN-GQDs demonstrated markedly greater cytotoxicity against MCF-7 cells when compared to Cur/GQDs. This advanced multifunctional nano-assembly thus presents a promising approach for targeted delivery in breast cancer treatment.

In 2021, Shakeri et al. introduced a sandwich-type electrochemical aptasensor designed for the concurrent detection of two significant breast cancer biomarkers: carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA 15-3) [56]. The biosensing substrate utilized was a nanocomposite of gold nanoparticles and three-dimensional graphene hydrogel (AuNPs/3DGH). For the biosensing probes, aptamers specific to CEA and CA 15-3 were conjugated with gold nanoparticles, a redox probe, and the graphene nanocomposite. In this system, hemin and ferrocene served as redox probes for CEA and CA 15-3, respectively, facilitating the generation of electrochemical signals necessary for the detection of both biomarkers. The aptamers for CEA and CA 15-3 were immobilized onto the surface of an electrode modified with AuNPs/3DGH. The differential pulse voltammograms exhibited peak currents and potentials that corresponded to the concentrations and characteristics of the biomarkers. The detection limits established for CEA and CA 15-3 using the duplexed aptasensor were determined to be 11.2 pg $mL^{-1}$ and $11.2 \times 10^{-2}$ U mL–1, respectively. Furthermore, the duplexed aptasensor was employed to evaluate clinical serum samples, with results aligning closely with those obtained from the ELISA method, thereby demonstrating the aptasensor's reliability. The outcomes obtained from utilizing the duplexed aptasensor for the assessment of CEA and CA 15–3 biomarkers in clinical serum samples demonstrated a high degree of concordance with the results derived from the ELISA method. Furthermore, the developed aptasensor was employed to create an "AND" logic gate for the simultaneous measurement of CEA and CA 15–3.

In 2021, Rezazadeh and Soheilifar introduced a multilayer configuration that incorporates graphene in both the upper and middle layers, with the middle layer designed in a ribbon shape [6]. The upper layer features a disk-shaped element, while a ring is integrated into the overall structure. This ring effectively surrounds the electromagnetic field, resulting in an enhancement of the Q-factor at a frequency of 6.7 THz. The researchers investigated the interactions between the layers and their influence on reflection, aiming

to optimize the proposed absorber by adjusting the chemical potential of the graphene layer within a range of 0.2 to 0.6 eV. Ultimately, the designed absorber is employed to differentiate between cancerous and healthy breast tissue. The study also explores the impact of tissue thickness and its distance from the absorber, focusing on how these factors affect sensitivity and the figure of merit (FOM), which are critical for cancer detection. The findings indicate that both the thickness of the tissue sample and its proximity to the absorber significantly influence sensitivity and FOM, thereby aiding in the differentiation of cancerous from healthy tissue. Notably, the proposed absorber demonstrates a high FOM of approximately 29,117 $RIU^{-1}$, in contrast to a FOM of 10,344 for healthy tissue.

In 2019, Hossain et al. presented a hybrid design and numerical analysis of a graphene-coated fiber-optic surface plasmon resonance (SPR) biosensor aimed at detecting BRCA-1 and BRCA-2 genetic mutations associated with breast cancer [57]. The study focused on two specific mutations: 916delTT in the BRCA-1 gene and 6174delT in the BRCA-2 gene, which were selected for numerical detection of breast cancer. This biosensor employs the attenuated total reflection (ATR) technique to identify individual point mutations within the BRCA-1 and BRCA-2 genes. The numerical results indicated a significant alteration in the SPR angle (at least 35% increase) and surface resonance frequency (SRF) (at least 36% increase) when probing DNA was exposed to varying concentrations of target DNA corresponding to the identified mutations. In contrast, the changes in SPR angle and SRF for mismatched DNA strands in the BRCA-1 and BRCA-2 genes were minimal, while those for complementary DNA strands were substantial. This notable variation is crucial for the accurate detection of genetic biomarkers (916delTT and 6174delT) for early breast cancer diagnosis. To the best of our knowledge, this represents the inaugural demonstration of such an effective biosensor for the detection of BRCA1 and BRCA2 genetic mutations related to breast cancer. The incorporation of graphene as a biomolecular recognition element significantly enhances the sensor's performance. The article concludes with an analysis of the sensor's sensitivity, highlighting its potential for early detection of BRCA-1 and BRCA-2 genetic breast cancers.

In 2019, Hossain et al. presented a straightforward hybrid design and numerical analysis of a graphene-coated fiber-optic surface plasmon resonance (SPR) biosensor aimed at the early detection of breast cancer genes BRCA1 and BRCA2 [58]. The study focused on two specific mutations, 916delTT in BRCA1 and 6174delT in BRCA2, for the numerical identification of breast cancer. This biosensor employs the attenuated total reflection (ATR) method to monitor deoxyribonucleic acid (DNA) hybridization, as well as to detect individual point mutations within the BRCA1 and BRCA2 genes. The numerical results indicated significant alterations in the SPR angle (with a minimum increase of 135%) and surface resonance frequency (SRF) (with a minimum increase of 136%) for probe DNA at varying concentrations of target DNA associated with the specified mutations. In contrast, the changes in SPR angle and SRF for mismatched DNA strands were minimal, while those for complementary DNA strands were substantial, which is critical for the accurate identification of genetic biomarkers (916delTT and 6174delT) related to early breast cancer. Additionally, the impact of electric field distribution due to the incorporation of a graphene layer was examined using the finite difference time domain (FDTD) technique, facilitated by Lumerical FDTD solution software. To our knowledge, this represents the inaugural demonstration of such an efficient biosensor for the detection of BRCA1 and BRCA2 mutations, thereby paving the way for advancements in breast cancer detection methodologies.

In 2018, Tagi et al. developed an innovative and highly sensitive label-free immunoassay utilizing gold nanospear (Au NSs) that were electrochemically assembled onto thiolated graphene quantum dots (CysA/GQDs) for the detection of CA 15-3 antibodies [59]. The hybrid interface of CysA/Au NSs/GQDs offers an extensive surface area conducive to the effective immobilization of CA 15-3 antigens, while also ensuring the bioactivity and stability of these immobilized antigens. The fabrication of the sensor was monitored using field emission scanning electron microscopy and energy-dispersive X-ray spectroscopy. Additionally, cyclic voltammetry was employed to assess the surface coverage of Au NSs by CA 15-3 antigens. Square wave voltammetry was utilized to examine the immunosensor's construction and to track the binding interactions between CA 15-3 antigens

and antibodies. Under optimized conditions, the immunosensor exhibited commendable sensitivity and specificity, detecting CA 15-3 at concentrations as low as 0.11 U/ml, with a linear detection range spanning from 0.16 to 125 U/ml. The enhanced sensitivity of the immunosensor is likely attributed to the substantial loading of CA 15-3 antibodies on the CysA/Au NSs/GQDs hybrid interface, which amplifies the number of binding interactions. This method was successfully applied to assay CA 15-3 in unprocessed human plasma samples, as well as in lysates from malignant cell lines, specifically the human breast adenocarcinoma cell line MCF-7.

In 2018, Dong et al. introduced a novel sensor for hydrogen peroxide ($H_2O_2$) that was developed using a trimetallic AuPtPd nanocomposite platform integrated with reduced graphene oxide (rGO) nanosheets [60]. The modification of the rGO and the trimetallic AuPtPd nanoparticles was achieved on a glassy carbon electrode (GCE) through physical adsorption techniques. Characterization and identification of these distinctive nanocomposites were performed using transmission electron microscopy and X-ray diffraction. Furthermore, the electrochemical characteristics of the sensor were assessed through cyclic voltammetry and chronoamperometry. The electrochemical analysis revealed that the AuPtPd/rGO-modified GCE exhibited remarkable electrocatalytic performance for the reduction of $H_2O_2$, demonstrating a broad linear detection range from 0.005 μM to 6.5 mM, a low detection limit of 2 nM, as well as good selectivity and satisfactory repeatability. Additionally, this sensor is capable of monitoring $H_2O_2$ release from live cancer cells. Consequently, this research not only enhances the simplicity and sensitivity of $H_2O_2$ detection at the nanomolar level but also lays the groundwork for potential biological and biomedical applications, including the early diagnosis of cancer.

In 2016, Tao and colleagues introduced a novel approach utilizing six luminescent nanodot-graphene oxide complexes as fluorescent nanoprobes within a sensing array designed to effectively differentiate between healthy, cancerous, and metastatic human breast cells [61]. This sensory system operates on the principle that the nanoprobe-graphene oxide sensor elements can be disrupted by the presence of breast cells, resulting in distinct fluorescent signals. Employing this multichannel sensor, the research successfully identified breast cancer cells and differentiated among various phenotypes, including estrogen receptor positive, human epidermal growth factor receptor-2 positive, and triple negative types. Furthermore, this method demonstrates high sensitivity, capable of detecting as few as 200 cells, while maintaining excellent reproducibility. Analysis of unknown cell samples revealed that the sensor accurately identified 49 out of 50 breast cell samples, achieving a detection accuracy of 98%. Collectively, this array-based luminescent nanoprobe-graphene oxide sensing platform offers a promising tool for cell screening, with significant potential for applications in biomedical diagnostics. The distinctive characteristics of these luminescent nanodots, including straightforward synthesis, affordability, remarkable brightness, minimal cytotoxicity, and high photostability along with aqueous solubility, enhance the advantages of the sensing platform. Furthermore, LDA has effectively been employed to classify 50 unidentified cell samples, encompassing ten distinct types of human breast cells, achieving an impressive accuracy rate of 98%. Collectively, this array-based fluorescent nanoprobe-GO sensing platform offers a promising approach for cell screening analysis, with significant implications for biomedical diagnostics.

In 2016, Ali et al. presented a label-free microfluidic immunosensor characterized by femtomolar sensitivity and exceptional selectivity for the early detection of epidermal growth factor receptor 2 (EGFR2 or ErbB2) proteins [62]. This innovative sensor employs a uniquely designed immunoelectrode constructed from porous hierarchical graphene foam (GF) that is enhanced with electrospun carbon-doped titanium dioxide nanofibers ($nTiO_2$), serving as the electrochemical working electrode. The anatase form of $nTiO_2$ is particularly suitable for electrochemical sensor applications due to its remarkable biocompatibility, inherent surface defects, rapid reaction kinetics, and robust stability in the presence of proteins. The three-dimensional, porous architecture of GF facilitates the physical adsorption of $nTiO_2$, allowing it to effectively infiltrate and adhere to the GF surface. The integration of GF with functional $nTiO_2$ results in increased charge transfer resistance, an expansive surface area, and enhanced accessibility of the sensing surface to the analyte, thereby opening new avenues for the advancement of electrochemical immunosensors. The application of EDC–NHS chemistry facilitated

the covalent immobilization of the ErbB2 antibody (anti-ErbB2) onto the GF–$nTiO_2$ composite. To achieve a compact sensor design, the composite working electrode was strategically positioned above the gold counter electrode within a microfluidic channel. The sensor was subjected to differential pulse voltammetry and electrochemical impedance spectroscopy for the quantification of breast cancer biomarkers. Both techniques demonstrated high sensitivities of 0.585 μA $\mu M^{-1}$ $cm^{-2}$ and 43.7 kΩ $\mu M^{-1}$ $cm^{-2}$ across a broad concentration range for the target ErbB2 antigen, spanning from 1 × 10–15 M (1.0 fM) to 0.1 × $10^{-6}$ M (0.1 μM), and from 1 × $10^{-13}$ M (0.1 pM) to 0.1 × $10^{-6}$ M (0.1 μM), respectively. The incorporation of the specific recognition element, namely anti-ErbB2, ensures a high degree of specificity, even in the presence of similar members of the EGFR family of receptor tyrosine kinases, such as ErbB3 and ErbB4. The integration of the porous GF–$nTiO_2$ composite into microfluidic devices is expected to yield numerous promising applications in the electrochemical detection of various chemical and biological entities.

In 2016, Rajesh and colleagues introduced biosensors utilizing graphene field effect transistors (GFETs) that were enhanced with antibody-functionalized platinum nanoparticles (PtNPs) for the precise quantification of the breast cancer biomarker HER3 [62]. The process involved the preparation and transfer of high-quality chemical vapor deposited graphene onto gold electrodes that were microfabricated on an SiO2/Si wafer, resulting in an array comprising 52 GFET devices. These GFETs were subsequently modified with PtNPs to create a hybrid nanostructure conducive to the attachment of HER3-specific, genetically engineered thiol-containing single-chain variable fragment antibodies (scFv), thereby facilitating the development of a biosensor for HER3 detection. The physical and electrical properties of the Bio-GFET devices were characterized using techniques such as electron microscopy, atomic force microscopy, Raman spectroscopy, and current–gate voltage measurements. The biosensor exhibited a concentration-dependent response to the HER3 antigen, ranging from 300 fg $mL^{-1}$ to 300 ng $mL^{-1}$, which aligned quantitatively with a model derived from the Hill–Langmuir equation of equilibrium thermodynamics. From the dose–response data, the dissociation constant was determined to be 800 pg $mL^{-1}$, suggesting that the high affinity of the scFv antibody is preserved post-immobilization. The limit of detection was established at 300 fg $mL^{-1}$, highlighting the potential application of PtNP/G-FETs in label-free biological sensing.

In 2014, Liu and colleagues developed a sensitive photoelectrochemical (PEC) detection strategy for SK-BR-3 cancer cells utilizing a ZnO/graphene (ZnO/G) composite in conjunction with the S6 aptamer, implemented through a portable indium tin oxide microdevice [63]. The ZnO/G composite was synthesized via a straightforward ultrasonic method, enhancing PEC performance due to the distinctive hollow structure of ZnO nanospheres and the advantageous properties of graphene. The S6 aptamer was subsequently employed for the specific identification of SK-BR-3 cancer cells. The detection of SK-BR-3 cells achieved a low limit of 58 cells $mL^{-1}$ and a broad linear range from 1 × $10^2$ to 1 × $10^6$ cells $mL^{-1}$, as indicated by a reduction in photocurrent intensity caused by increased steric hindrance during the specific binding with S6 aptamers. The system exhibited excellent discrimination between target and similar cells, underscoring the high selectivity of the proposed cell sensor. This research also highlighted a sensitive, stable, and low-cytotoxicity method for the early and precise detection of cancer cells.

## FUTURE DIRECTION

Functionalized graphene nanosheets are increasingly recognized as essential elements in the advancement of electrochemical nano-biosensors aimed at breast cancer detection. These biosensors utilize the distinctive characteristics of graphene, including its exceptional electrical conductivity and extensive surface area, to improve both sensitivity and specificity in identifying biomarkers such as CA 15-3 and HER2. Subsequent research should prioritize the optimization of nanomaterial integration and the investigation of innovative transducer components to enhance performance indicators, such as detection thresholds and operational reliability.

*Key Advantages of Graphene Nanosheets*

- *High Sensitivity*: Graphene-based sensors demonstrate exceptional sensitivity, with detection limits as low as 0.0001 U mL−1 for CA 15-3.
- *Cost-Effectiveness*: The low-cost nature

of graphene materials makes these biosensors accessible for widespread clinical use.

- *Non-Invasiveness*: Electrochemical biosensors provide a non-invasive alternative to traditional diagnostic methods, facilitating early detection.

*Future Research Directions*

- *Integration with AI*: Incorporating artificial intelligence could enhance data analysis and improve diagnostic accuracy.
- *Addressing Limitations*: Future studies should aim to overcome challenges related to the reproducibility and stability of graphene materials.

Although the progress made in graphene-based biosensors is encouraging, there are still obstacles to overcome in terms of standardizing manufacturing processes and achieving uniform performance across various applications. Ongoing research is crucial to fully harness their capabilities in clinical environments.

## CONCLUSION

The examination of functionalized graphene nanosheets as electrochemical nano-biosensors for the detection of breast cancer underscores their significant potential for early diagnosis and ongoing monitoring. These biosensors utilize the distinctive characteristics of graphene, including its exceptional conductivity and extensive surface area, to improve both sensitivity and specificity in identifying crucial biomarkers such as CA 15-3 and HER2. *Benefits of Electrochemical Biosensors A) Enhanced Sensitivity and Specificity*: Electrochemical biosensors exhibit greater sensitivity than traditional diagnostic methods, allowing for the identification of low levels of biomarkers. *B) Economic Viability*: These biosensors are typically more cost-effective and less invasive than standard diagnostic approaches, thereby increasing their accessibility for broader application. C) *Accelerated Results*: The incorporation of nanomaterials contributes to faster response times, which aids in making prompt clinical decisions. *Future Perspectives A) Ongoing Research and Development*: It is vital to pursue further advancements in nanocomposite materials and sensor architecture to address current limitations and improve overall performance. *B) Clinical Application*: Additional validation in clinical environments is necessary to confirm the dependability of these biosensors for routine diagnostic use. Despite the promising developments in electrochemical biosensors, challenges related to standardization and regulatory approval persist, potentially hindering their integration into clinical practice.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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