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Review Article

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PLGA Nanoparticles for Targeted Drug Delivery in Breast Cancer: A Comprehensive Review of Current Challenges and Future Directions

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ABSTRACT

Breast cancer remains a leading cause of cancer-related mortality universally, with its incidence rising, particularly among older women. Key risk factors include genetic predisposition, reproductive history, and lifestyle factors. Traditional treatment strategies encompass surgery, chemotherapy, radiation, endocrine therapy, and targeted therapies. However, these methods often lead to systemic toxicity and drug resistance, posing significant challenges in achieving effective and sustained treatment outcomes. Poly (lactic-co-glycolic acid) nanoparticles have emerged as a promising drug delivery system to address these challenges. PLGA is a biocompatible and biodegradable polymer approved by the FDA, offering several advantages for BC therapy. These nanoparticles can encapsulate a variety of chemotherapeutic agents, including doxorubicin, paclitaxel, and docetaxel, thereby protecting the drugs from premature degradation and ensuring controlled release. Despite promising preclinical results, translating PLGA-NPs into clinical applications presents several hurdles. These include accomplishing clinically relevant drug loading volumes, ensuring long-term safety profiles, and navigating complex regulatory landscapes. PLGA-NP development involves exploring combination therapies, utilising multi-omics approaches to identify molecular targets, and integrating personalised medicine strategies. Interdisciplinary association among material scientists, molecular biologists, oncologists, and clinicians is crucial to advancing PLGA-based nanomedicines and transforming BC treatment paradigms. Future research should focus on clinical translation, safety profiling, and scalable manufacturing to ensure the broader therapeutic application of this approach.

Key-words: PLGA Nanoparticles, Targeted Drug Delivery, Breast Cancer, Chemotherapeutic Agents, Cancer Stem Cells, Drug Resistance, Nanomedicines

INTRODUCTION

Carcinogenesis is a combination of genetic predispositions and environmental factors [1]. As cancer has been invading most countries in the world, the mortality rates have been attributed to it. Breast cancer (BC) is one of the most frequently diagnosed cancers among women and ranks fifth in global cancer-related mortality according to the Global Cancer Observatory. [1]. BC is the most diagnosed cancer in women, and presents challenges that may be addressed through nanotechnology.

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Nanoparticles (NPs), particularly those utilizing the enhanced permeability and retention (EPR) effect, show promise in targeted therapy. In 2020, an estimated 2.26 million new cases of BC occurred worldwide, making up 11.7% of all new cancer cases. BC incidence continues to increase with age, reaching a peak of 421.3 cases per 100,000 in women aged 75 to 79 years. The largest rise in BC rates occurred in the 70-74 years age group globally [2,3]. Between 2012 and 2021, localized-stage and hormone receptor-positive BC was rising by 1% annually. It was even rising more among women under 50 years of age, and specifically within Asian American/Pacific Islander populations [4]. Global Cancer Observatory (GLOBOCAN) estimated 1.3 million new cancer cases and about 850,000 cancer-related deaths in India. BC was the most common and contributed to 13.5% of new cases and 10.6% of cancer deaths [5]. According to epidemiological data, the burden of BC is expected to

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reach more than 2 million cases by 2030. In India, its incidence has increased by almost 50% over the last 26 years, with a 39.1% rise in age-standardized rates across all states [6] (Fig. 1).

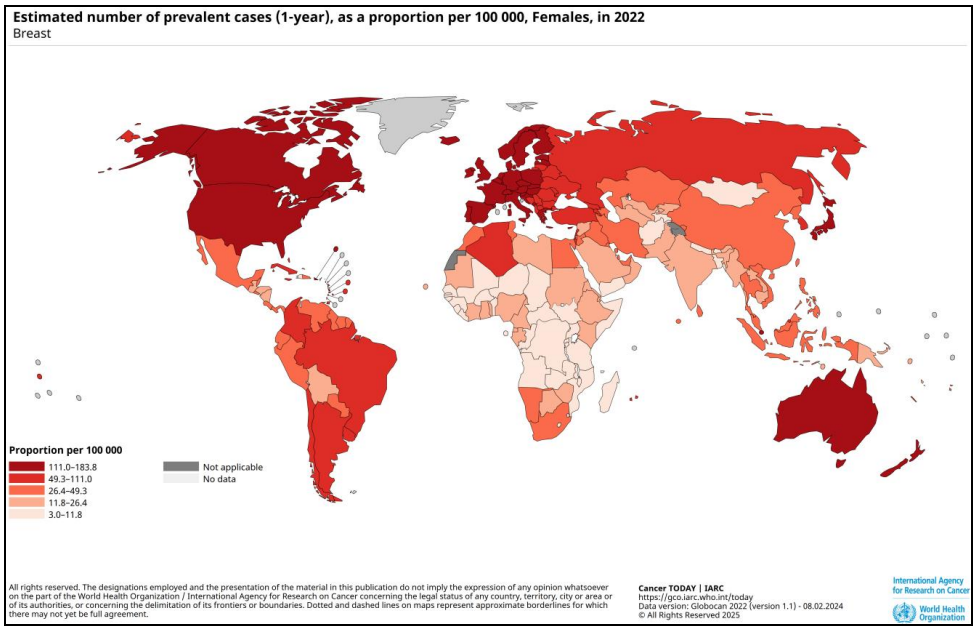

Fig. 1: Estimated one-year prevalence of breast cancer cases worldwide for 2022, indicating regional differences in disease burden. (Source: World Health Organization)

Significant factors that predispose people to non-modifiable risk are ~~the~~ female sex, older age, and genetic predisposition. Women are at a more significant risk because of hormonal influences in estrogen and progesterone levels, while age contributes to the accumulation of cell changes, which increases vulnerability; most cases occur at over 50 years. Risk is further increased due to a family history, particularly through mutations in BRCA1 and BRCA2 [1]. A case-control study was conducted by Liu *et al.* in Taiwan. The total number of cases collected for BC was 3,281, with matched controls totaling 19,686 subjects drawn from a cohort of 486,069 females. They found risk factors including obesity, hyperlipidemia, and prior thyroid, liver, and gastric cancers, which influence younger patients less than 55 years-old, and older patients above 55 years-old having increased chances of BC [6,7]. Similarly, Khoramdad *et al.* conducted a meta-analysis on 24 case-control studies involving 12,460 subjects, including 5,675 cases and 6,785 controls. Prevalent modifiable risks were obesity, late marriage (25–29 years vs <18 years), and second-hand exposure to tobacco smoke. Non-modifiable risks were history of radiation exposure, history of familial BC, and early menarche at 12–13 years vs ≥14 years [8].

Reproductive factors such as early menarche, late menopause, or limited breastfeeding raise risk, whereas early pregnancies and prolonged breastfeeding reduce the same. High breast tissue density and a history of benign or malignant breast conditions form additional risk factors. Exposures to radiation at any age, especially young age, are associated with the development of secondary BC [1]. Modifiable determinants of the risk for BC are drug intake, lifestyle exposures, and dietary factors. Obesity seems to be significantly associated with a more malignant disease, resulting in lower survival rates. It is believed that physical exercise is protective, possibly through less exposure to hormones. Excessive alcohol consumption and smoking further contribute to carcinogenesis in the breast tissue through hormonal imbalance and genetic mutations. Diets rich in processed foods and fats increase the risk, whereas nutrient-rich diets and vitamin D display protective potential [1].

Estrogen receptor (ER) is an essential biomarker for breast carcinoma, guiding most of the treatment decisions. High levels of ER positivity are beneficial because they are associated with a positive response to endocrine therapy. Co-expression of the progesterone receptor (PR) increases the accuracy of prognostication and is independently associated with increased survival. Her2 overexpression is typically associated with

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aggressive disease with poor prognosis; therefore, its assessment is a prerequisite in targeted therapies [1]. Caruana *et al.* conducted a study to evaluate the specialized role of ER expression in BC, characterized by low positivity (1-10%), and to assess the accuracy and implications for endocrine therapy [2,3]. Ki-67 is a proliferation marker that aids in estimating tumor growth and responsiveness to therapies, although its application has limitations. p53 mutations are a part of tumor progression and are associated with a poor prognosis. MicroRNAs are known to modulate key cancer pathways and could be used as potential diagnostic markers [1]. The study conducted by Healey *et al.* (2017) assessed Ki67 expression using Definiens digital image analysis (DIA) in 2653 cases of invasive BCs. Ki-67 scores yielded mean values of 8.9% for the luminal A subtype, 12.6% for the luminal B subtype, 17.9% for the HER2-enriched subtype, and 20.6% for the basal-like subtype. Luminal B tumors classified using the cut point of 14% showed more BC-specific mortality than luminal A (p=0.004). DIA was strongly correlated with manual scoring (ρ = 0.86) and demonstrated the clinical utility of Ki-67 for subtype classification and prognosis at the 14% threshold [9,10]. Treatment for BC ranges from different strategies depending on the individual's condition and the type of cancer. Surgery options include breast-conserving surgery (BCS) and mastectomy, where BCS is better in terms of cosmetic outcome and has a lesser psychological burden [1]. According to Pandey *et al.* reviews, current treatments for BC include chemotherapy, endocrine therapy, immunotherapy, radiotherapy, and surgery, with HER2 and ERs being primary therapeutic targets. Additional pathways implicated in breast cancer progression were identified, including PARP, BRD4, CDK4/6, EGFR, VEGFR, PLK1, PI3K/AKT/mTOR, HDAC, NF-κB, PD-L1, and aromatase [11]. Radiation therapy complements surgery by addressing residual cancer cells with the application of 3D-conformal radiotherapy and intensity-modulated radiotherapy (IMRT), among other techniques. Endocrine treatment is aimed at hormonal blockade; in hormone-positive BC, it happens to be effective, but through resistance development. Biologicals such as HER2 treatment and angiogenesis inhibitors turn out to be crucial drugs in HER2-positive, metastatic BC [12]. Choi *et al.* performed an RCT to compare the safety and efficacy of IMRT with that of 3-dimensional conformal radiotherapy (3DCRT) in patients with early BC. In the study by Oshi *et al.*, it was to investigate the predictive capacity for endocrine therapy response and survival of the estrogen-responsive early gene set score in BC. The analysis comprised 6,549 BC cases across multiple cohorts. The score was highest in ER-positive/HER2-negative BC subtypes, with lower AJCC stages and lower Nottingham pathological grades. Tumors with low scores showed enrichment for allograft rejection gene set, indicative of significant immune cell infiltration and high cytolytic activity. Low score tumors correlated with a worse response to endocrine therapy as well as worse survival, with a hazard ratio that was doubled for endogenous ESR1 expression [13].

Targeted drug delivery using nanotechnology enhances the therapeutic efficacy of breast cancer (BC) treatment by minimizing drug variability and toxicity. Biocompatible nanocarriers with specific ligands selectively deliver drugs to cancer cells, thereby avoiding damage to healthy tissues. Studies on fluorescent magnetic submicronic polymer nanoparticles (FMSP) and multifunctional nanocomposites like AS1411-DOX-AgNTs have shown dose-dependent effects in targeting BC cells, with enhanced inhibition and reduced side effects. Poly(lactic-co-glycolic acid) (PLGA) nanoparticles, known for their biodegradability, biocompatibility, and pH-sensitive drug release, are effective for BC treatment. Compared to other polymeric carriers, PLGA offers superior biodegradability, controlled degradation, and FDA approval, making it ideal for BC applications.

PLGA nanoparticles in chemotherapeutic delivery - PLGA is a promising form of NPs for cancer therapy, a synthetic thermoplastic aliphatic biocompatible polyester formed from lactic acid and glycolic acid [1,14] (Fig. 2); it enhances drug delivery and targeting efficacy while minimizing side effects. The drug pharmacokinetics and biodistribution by PLGA-NPs modify drugs to circulate for extended periods, targeting the site of action in cancerous tissues. When used in conjunction with iRGD, which can actively enhance tumor-penetrating peptides, they increase the antitumor effects. PLGA-NPs have demonstrated high accumulation in tumors and show promise for diagnostics and therapy, especially when combined with specific proteins like VEGF [15]. PLGA is a biocompatible copolymer formed from lactic acid and glycolic acid. It is available in a variety of copolymer ratios, with 50:50 being the most common, and in a variety of molecular

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weights. The FDA and the EMEA approved it for drug delivery, sustained drug release, and biocompatibility with tissues. Hydrolysis of PLGA results in the formation of lactic and glycolic acids, both of which are endogenous and non-immunogenic, and are metabolized easily through enzymatic pathways [16-19].

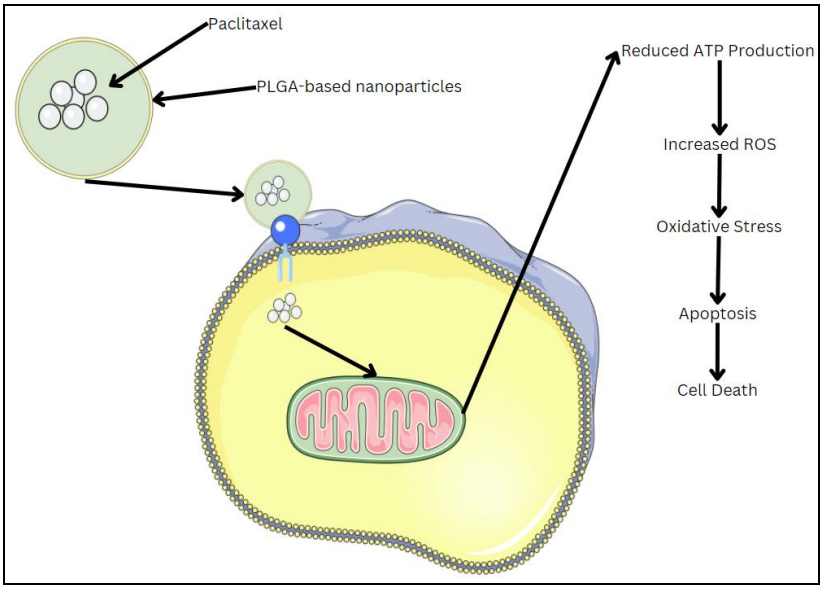

Fig. 2: Paclitaxel-loaded PLGA PLGA-based nanoparticle being delivered to the affected cells [20]

PLGA-NPs became a potential agent in BC because they are biodegradable NPs that could deliver drugs to the target site. For instance, ASC-J9 and curcumin drug delivery can be facilitated because these NPs act as targeted carriers for chemotherapeutic agents. The delivery of the drug is therefore controlled and sustained within the system, and systemic toxicity, which usually comes with the other drugs, is reduced so that therapeutic levels are maintained [21].

PLGA-NPs can also be functionalized with targeting ligands to increase specificity toward receptors overexpressed on the surface of BC cells, enhancing cellular uptake by mechanisms such as endocytosis. Their biodegradability is attributed to hydrolysis of ester bonds in bodily fluids, breaking down into lactic and glycolic acids, which are metabolized via the Krebs cycle and excreted as carbon dioxide and water. The ratio of lactic-to-glycolic acids is adjustable to alter the rate at which these NPs degrade, producing an optimum drug-release profile for BC treatments [22-24].

Doxorubicin-loaded PLGA-NPs enabled the efficacious incorporation of the drug while targeting it directly to BC cells and reducing the potential for cardiotoxicity [25]. Similarly, bio-CS-PLGA-NPs effectively encapsulated epirubicin with high efficiency, significantly enhancing its cytotoxic effects on BC cells. Palbociclib was delivered using redox-sensitive PLGA-NPs to increase drug uptake, augment cytotoxicity, and decrease tumor size. Additionally, PLGA-NPs successfully encapsulated chrysin, suggesting their potential for localized BC treatment. Such developments indicate the high versatility and therapeutic potential of PLGA-based NP systems [21,25-27]. Al-Saeedi *et al.* (2024) studied the action of DOX-PLGA NP on the pro-inflammatory genes in the MCF-7 BC cells. It showed an encapsulation efficiency of 60±1.5%, with loading capacity of 1.13±0.21%. It also had 18±0.550 mV zeta potential value. The mean size was observed at 172±55.6 nm. The 50% inhibitory concentration (IC50) of DOX-PLGA NP on MCF-7 cell viability was found to be 24.55 µg/mL at 72 hours of treatment. qRT-PCR studies revealed highly suppressed pro-inflammatory gene expression at a 20 µg/mL concentration, exhibiting dose-dependent effects. This study proves the superior ability of DOX-PLGA NP to inhibit the expression of pro-inflammatory genes more significantly than the free form of DOX alone [28]. Similarly, Kefayat and Vaezifar [29] successfully synthesized and characterized doxorubicin-loaded chitosan NPs that were loaded in the biodegradable implants called PLGA with CS-DOX for the subcutaneous implantation procedure. The effectiveness of these therapeutic implants was estimated on 4T1 breast tumor-bearing BALB/c mice using different groups, such as the no-treatment group, PLGA, PLGA/CS, PLGA/CS-

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DOX, and doxorubicin at 5 mg/kg/day. PLGA/CS-DOX implants demonstrated higher efficacy, as they significantly inhibited the growth and metastasis of the tumor, resulting in an overall reduction of 71% in tumor volume compared with the no-treatment group.

Gregorio *et al.* [21] designed a completely new drug delivery system on a nanometer scale for the treatment of BC based on PLGA-NPs to counteract the incompatibilities posed by systemic chemotherapy for cancer therapy, which are high toxicity and higher dosages. Docetaxel was loaded with fluorescent markers and MRI probes into these PLGA-NPs, while the surface was enriched with cyclic RGD tripeptides to target the αvβ3 integrins, which are commonly upregulated in BC cells. The therapeutic efficacy was tested through both in vitro studies using HER2+ and «triple-negative» BC cell lines and in vivo studies using mouse models. Enhanced therapeutic outcome and decreased cardiotoxicity were observed in targeted PLGA-NPs when compared to free docetaxel. The average hydrodynamic diameters of RGD-functionalized PLGA-NPs and untargeted control PLGA-NPs were found to be identical (150 nm), while ζ-potential values were the same as well (-3 mV). The encapsulation efficiency of Docetaxel was 18.2% for RGD-PLGA, compared to 27.3% for the control PLGA, indicating equal drug loading. This study supports the targeted and efficient treatment of BC using RGD-modified PLGA-NPs [21]. Tran *et al.* prepared docetaxel (DTX)- NPs and investigated their differential pharmacological effects on MCF-7 and MDA-MB-231 breast cancer cells. Characterization studies for the NPs revealed good physicochemical characteristics, with an average size of 160.5±3.0 nm and a zeta potential of -26.7±0.46 mV. There was sustained drug release at a neutral pH of 7.4 with 0.5% Tween 80. For cytotoxicity assays carried out, DTX-NPs reduced the viability of MDA-MB-231 and MCF-7 cells [30].

The efficacy of PLGA-NPs in enhancing the delivery of manganese (II)-based complexes to target cancer stem cells (CSCs) in BC. This study focused on the ROS-generating manganese (II) complex conjugated with diclofenac encapsulated in biodegradable PLGA copolymers. The encapsulated complex was selective towards breast CSCs, with toxicity lower than that of treated compounds such as salinomycin and cisplatin, compared to copper(II) counterparts. The effectiveness of PLGA-NPs encapsulating palmitic acid (PA) and doxorubicin for BC treatment. Given PA's hydrophobic nature and limited cellular permeability, PLGA-NPs were used for encapsulating either DOX alone or in combination with it. In vivo studies in mice with established mammary tumors indicated that PLGA-PA NPs were least effective. PLGA-PA NPs downregulated genes via caspase-3-independent pathways, and conferred immunomodulation by decreasing M2 macrophages and promoting leukocyte infiltration into the tumor microenvironment. These findings highlighted the potential of both PA, alone or in combination with DOX, as an innovative strategy in treating BC, relying on PLGA-NPs for delivery to improve therapeutic efficacy.

PLGA nanocapsules to develop the therapeutic potential of a magnolia plant extract, honokiol (HK), for cancer. Formulations and optimization of PLGA NCs were prepared by using different variables for obtaining the smallest particle size of 125 nm, a smooth spherical shape, a maximum drug loading of 94%, and superior cellular uptake in BC cells. In vitro studies conducted on MCF-7 and EAC cell lines have shown a significantly high inhibition of growth rates (80.2% and 58.1%, respectively), whereas free HK resulted in an inhibition of growth (35% and 31%). *In vivo*, the growth of a solid Ehrlich carcinoma BC model was significantly reduced 2.3-fold with HK-loaded NCs compared to free HK. In addition, the delivery system significantly decreased the levels of biomarkers for tumours and proved to be safe in animal models. Therefore, the present study revealed that PLGA NCs can be considered as an effective strategy to enhance the delivery and efficacy of HK in BC therapy. Doxorubicin curcumin modified PLGA-NPs for the treatment of BC with synergistic chemoradiotherapy. The NPs were produced using the double-emulsion technique and exhibited a high drug loading capacity, along with particle sizes below 250 nm. CD-340 antibody-conjugated PLGA-NPs for the targeted delivery of DOX to BC cells in mice, where the hydrophobic PLGA matrix, with poor drug loading, is optimized to incorporate a highly water-soluble drug through covalent conjugation with anti-human epidermal growth factor receptor-2 (HER2) antibody (CD-340). The NPs conjugated with CD-340 showed selective targeting to HER2-overexpressing BC cells such as SKBR-3, MCF-7, and MDA-MB-231; this was found to enhance accumulation at the tumor site when the *in vivo* studies were considered.

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PLGA-NPs have been promising in minimizing systemic toxicity and side effects associated with the treatment of BC. Studies have shown that NPs based on PLGA can increase the delivery of drugs to BC cells, thus reducing toxicity to normal cells. For example, PLGA-NPs loaded with anticancer agents such as palbociclib and acetyltanshinone IIA have demonstrated greater efficacy and reduced toxicity compared to free drugs. These NPs can target BC cells specifically, thus improving treatment outcomes while minimizing side effects [18,22]. In summary, PLGA nanoparticles have been successfully employed to deliver key therapeutic agents, including doxorubicin, paclitaxel, tamoxifen, and palbociclib. These agents address diverse subtypes of breast cancer, including triple-negative, HER2-positive, and hormone receptor-positive forms. The ability to encapsulate and target these drugs enhances efficacy while minimising toxicity.

Challenges in Clinical Translation- Despite promising pre-clinical results, significant challenges exist for the successful clinical translation of PLGA-NPs in BC treatment. The primary challenges include achieving clinical dose limits while maintaining therapeutically relevant outcomes [3]. The performance of NPs regarding their functions in vivo can be evaluated with very strict criteria, and it is necessary to reanalyze concerning NP-design problems based on failures in trials that span in vitro, in vivo, and clinical settings. The variability remains a significant obstacle, contributing to the moderate clinical translation of many nanomedicine formulations, including those based on PLGA [1].

There is a need to meet the clinical-grade standard through advanced manufacturing, with an emphasis on reproducible processes and retained therapeutic function. While regulatory frameworks are also an area of concern, existing standards often lack specific instructions that are applicable to the unique properties of NPs [28]. The current regulatory framework in India lacks specific guidelines for the use of PLGA nanoparticles in breast cancer treatment, thereby posing a challenge in terms of approval [28]. The current regulations do not effectively address the evaluation of the safety and efficacy of nanoparticle-based therapies, especially in terms of biodistribution and long-term effects. Lack of standardization in testing and quality control creates inconsistencies, which in turn prevent clinical development of these formulations. These gaps significantly hinder the development of nanoparticle-based drug delivery systems in cancer care [30]. The regulation of nanoparticles in cancer therapy in India is based on the Central Drugs Standard Control Organization (CDSCO), which is responsible for approving new drugs and conducting clinical trials. The greatest challenge in regulating nanoparticles is based on the lack of standardized testing protocols and safety assessment criteria [31].

Furthermore, the high cost of developing and deploying NPs for therapeutic uses, in conjunction with regulatory standards, hinders patient access. Economic analysis estimates can vary by up to an order of magnitude for NP-based formulations compared to conventional therapeutics, making them least accessible to poorer sections of society that remain underprivileged due to health inequality [32]. Incorporating findings from recent 2024 studies, such as those by Mehata *et al.* [15] and Kulothungan *et al.* [5] strengthens the translational significance of PLGA-NP research in modern breast cancer therapy.

CONCLUSIONS

PLGA is very rapidly becoming a versatile and promising drug delivery material in the treatment of BC. It can retain and release therapeutic agents, potentially leading to improved treatment efficacy with reduced systemic side effects and increased bioavailability of the drug at tumor sites. However, PLGA-based therapies still face several challenges, including the limitation of drug-load capacity and concerns about stability, as well as the need for multiple targeting sites to avoid off-target effects. In addition, safety and long-term effects remain important concerns, which necessitate optimized formulation and manufacturing processes. To overcome these limitations, interdisciplinary research, including material science, molecular biology, oncology, and clinical medicine, is required. The focus should be more on innovative solutions that include targeted drug delivery systems, synergistic therapies, and precision medicine.

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CONTRIBUTION OF AUTHORS

One author has only contributed to this article.

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