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Advancing Breast Cancer Treatment: The Role of PLA-based Scaffolds in Tumor Microenvironment and Drug Delivery

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This review highlights the crucial role of polylactic acid (PLA)-based scaffolds in developing novel breast cancer treatment strategies. Despite advances in early detection and therapy, breast cancer remains a complex challenge with frequent resistance and relapse. Conventional treatments, while effective, have limitations such as restricted drug distribution and radiation toxicity. PLA scaffolds offer a promising alternative due to their biocompatibility and biodegradability, making them suitable for tissue engineering applications in oncology. The article examines the design and fabrication of PLA scaffolds that are not merely passive structures but play an active role in the therapeutic process. By tailoring their mechanical properties, these scaffolds can mimic the characteristics of actual breast tissue, creating a lifelike environment for studying cancer cell behavior. Furthermore, PLA scaffolds can mimic the tumor microenvironment, offering a three-dimensional representation that allows for a more accurate examination of tumor biology and treatment response. These scaffolds also function as advanced drug delivery systems, releasing therapeutic agents at the tumor site in a controlled manner, reducing systemic side effects, and enhancing drug efficacy. This review connects fundamental research with clinical practice, highlighting the revolutionary potential of PLA-based scaffolds in breast cancer management by mimicking the tumor microenvironment, delivering drugs locally, and enabling personalized treatment strategies.

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INTRODUCTION

Breast cancer is one of the most common cancers, affecting millions of women worldwide and having a significant impact on both societal and individual health care systems (Figure 1) [1, 2]. Although there have been breakthroughs in early detection and therapy, the complexity of breast cancer biology frequently leads to therapeutic resistance and recurrence. This is the case even though there have been advancements in both of these areas. The removal of tumor tissue is the most common method of treating tumors. This is followed by postoperative chemotherapy or radiation therapy, depending on the specific treatment being administered. Despite the enormous breakthroughs that have been made in the treatment of tumors, it is impossible to avoid encountering a variety of adverse postoperative side effects. This is the case even though there have been significant advances. Limited dispersion of chemotherapeutic agents at the target site and significant toxicity following radiation are two examples of these adverse consequences [3, 4]. As a result of this shift in focus, the development of drug delivery systems capable of overcoming these limitations has become the primary focus of cancer research.

In recent years, tissue engineering has emerged as a leading area of medical research, particularly in the field of oncology. The pursuit of reproducing the intricate biological activities and structures of human tissues has led to the investigation of several biomaterials, each possessing distinct features and potential applications. Among these options, PLA has become prominent because of its outstanding biocompatibility, i.e., it causes the least negative reactions in the body and its ability to biodegrade naturally over time [5-7].

PLA is a multifaceted substance with unique characteristics that can be divided into mechanical, physical, and chemical components. Mechanically, PLA demonstrates a high level of tensile strength, yet it is prone to brittleness. Its flexural strength can reach up to 140 MPa, and its Young's modulus ranges from 5 to 10 GPa. Nevertheless, it is not advisable for applications that entail abrupt impact stresses [8-10]. PLA is a physically transparent plastic that can be highly polished. It possesses a reasonably high level of difficulty and can undergo many processing methods, such as extrusion and injection molding. The material has a glass transition temperature of 60 to 65 degrees Celsius [11, 12]. PLA is a thermoplastic polyester with the chemical formula of $(C_3H_4O_2)_n$. The compound is derived from the condensation of lactic acid $C(CH_3)(OH)HCOOH$ with the removal of water. Another method of preparation involves the ring-opening polymerization of lactide $[–C(CH_3)HC(=O)O–]_2$, which is the cyclic dimer of the basic repeating unit. Poly (lactic acid) exhibits resistance to both

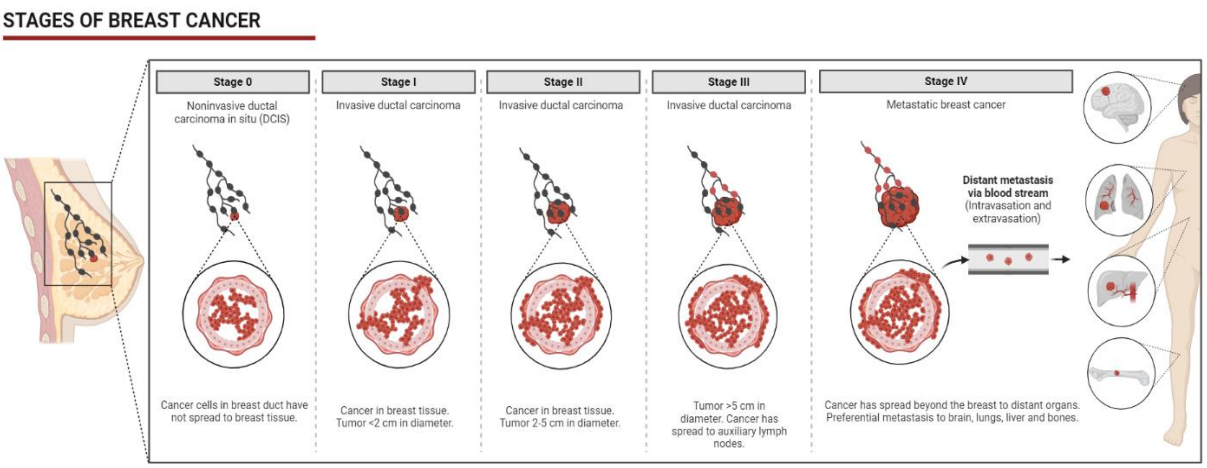

Figure 1. Schematic stages of breast cancer.

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moisture and ultraviolet (UV) radiation [9, 13]. The various properties of PLA contribute to its widespread use in numerous applications, while its appropriateness hinges on the precise requirements of the particular application.

PLA-based scaffolds have received considerable attention in cancer research, particularly for their contribution to breast cancer treatment. These scaffolds are not simply inert constructs; they are designed to engage with their environment actively. Their mechanical properties can be precisely adjusted to closely resemble those of actual breast tissue, creating a more biologically significant setting for investigating cancer cells. Understanding the behavior and spread of breast cancer cells is essential to developing more effective treatments [14].

Furthermore, PLA scaffolds function as a cutting-edge platform for drug delivery. Their permeable characteristics enable the inclusion of medicinal substances, which can subsequently be discharged in a regulated manner directly at the tumor location. This focused strategy reduces the occurrence of general side effects and enhances the effectiveness of anticancer medications. PLA-based scaffolds have the potential to significantly enhance the delivery and efficacy of these drugs, leading to significant improvements in outcomes for breast cancer patients [15]. PLA scaffolds possess a range of capabilities that go beyond their physical properties. They may be manipulated to replicate the tumor microenvironment, creating a three-dimensional structure that accurately imitates the extracellular conditions of tumors [16]. This enables a more precise examination of tumor biology and the evaluation of anticancer drugs, opening up possibilities for personalized medicine strategies in the treatment of breast cancer [15].

This review aims to highlight the significance of PLA-based scaffolds in breast cancer therapy. We will explore the intricacies of the design and production of these scaffolds, their capacity to replicate the tumor microenvironment, and their potential as vehicles for drug delivery. PLA-based scaffolds have the potential to advance breast cancer treatment by connecting basic research with clinical application, opening up new possibilities.

1. Scaffold Design and Fabrication

1.1 Electrospinning Technique:

The electrospinning process, developed in 1934, is a

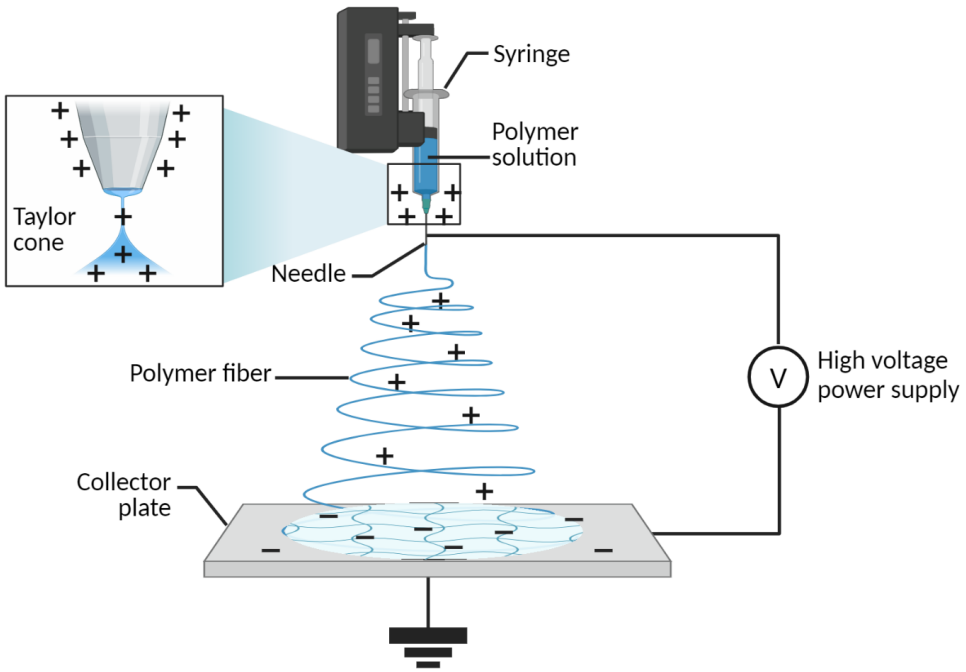

Figure 2. Schematic of electrospinning principals.

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highly adaptable technique for producingpolymeric fibers on the micro- to nanometer scale (Figure 2) [17, 18]. This research issue is currently a prominent area of study in the field of PLA research, with significant and rapid growth since 2001. The primary difference between conventional mechanical spinning and electrospinning is the driving force. In electrospinning, volumetric electrical forces are used to propel the charged jet. The electrospinning process can generate fibers with sizes ranging from 3 nanometers to several microns [19].

PLA electrospun fibers have great potential for diverse applications, such as drug delivery [20]. The diameter and shape of these fibers are greatly affected by several aspects, such as solvent quality, diffusion coefficient, flow rate, solvent evaporation, temperature, and environmental conditions. The polymer's molecular weight and its concentration in the solution are critical factors that impact the viscosity and spinnability of the polymer solution. Electrospun nanofibers can be produced by incorporating surfactants or salts into the polymer solution, using intermediate concentrations and molecular weight values. The surface texture and porosity of the nanofibers play an important role in biomedical applications by influencing cell adhesion and proliferation [21].

Electrospun ultrafine polymer fibers are commonly used for drug delivery because of their extensive surface area per unit mass and minute pore size. The fibers have several advantages, including extremely thin diameters, limited porosity, and appropriate surface shape, which enhance mass transfer and facilitate efficient drug release [22]. Additionally, they demonstrate improved therapeutic efficacy, resulting in decreased medication toxicity and/or reduced frequency of administration [22, 23].

Electrospun fibers have potential applications in the delivery of anticancer drugs, particularly in post-surgery procedures and localized chemotherapy [24]. BCNU (bis-chloroethyl nitrosourea) was effectively integrated and evenly distributed within biodegradable PEG-PLLA electrospun fibers. These fibers are utilized in the therapy of different forms of brain cancer, multiple myeloma, and lymphoma. The sustained release of BCNU at high concentrations enabled the creation of novel implanted polymeric devices for prolonged treatment of malignant glioma [24].

There are two different methods of electrospinning: compounding and coaxial electrospinning [25, 26]. Compounding is the process of combining bioactive substances with polymers. Coaxial electrospinning, on the other hand, produces composite fibers with a core layer surrounded by a shell. This shell contains drugs or mixtures, which are trapped within the polymer shell to create a drug delivery device that acts as a reservoir. PLA is a commonly used material in biomedical applications since it is both biocompatible and biodegradable.

However, its hydrophobic properties require the encapsulation of water-soluble substances to prevent the polymer from degrading and failing as a platform

Table 1. Overview of PLA Electrospun Fibers.

Key Aspect	Description
Material	PLA electrospun fibers
Applications	Medication administration, particularly in delivering anticancer medications
Factors affecting fiber properties	Solvent quality, diffusion coefficient, flow rate, solvent evaporation, temperature, environmental conditions, polymer's molecular weight and concentration
Benefits of ultrafine polymer fibers	Extensive surface area per unit mass, minute pore size, extremely thin diameters, limited porosity, appropriate surface shape
Methods of electrospinning	Compounding (combining bioactive substances with polymers) and coaxial electrospinning (creating composite fibers with a core layer surrounded by a shell)
Example of application	BCNU was effectively integrated and evenly distributed within biodegradable PEG-PLLA electrospun fibers for the therapy of different forms of brain cancer, multiple myeloma, and lymphoma
Common material in biomedical applications	PLA (biocompatible and biodegradable)

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for drug delivery (Table 1).

1.2. 3D Printing Technology

Additive manufacturing (AM) procedures refer to a method of combining materials to produce objects based on 3D model data, typically by adding layers one after another [27, 28]. These technologies allow for the creation of parts with more intricate shapes than traditional methods, such as injection molding, without requiring expensive mold tooling. This enables the creation of small quantities and even goods that are completely tailored to individual specifications (Figure 3) [29].

Additive manufacturing technologies are categorized into seven divisions, with material extrusion being the most widely used. Materials such as ABS and PLA are used, as well as engineering and high-performance plastics including nylon, polyetherimide (PEI), and polyphenylsulfone (PPSF). Other technologies include binder jetting and material jetting techniques, in which droplets forms of adhesive binder material are deposited to bind powder material [30]. Powder bed fusion is an important category of AM technologies. In this process, a layer of solid powder is deposited and exposed to a heat source, such as a laser or electron beam. These technologies are widely used in part manufacturing because they can sinter many materials and eliminate the requirement for support structures [31, 32].

Sheet lamination is the last category of additive AM technologies. It involves the use of a sheet of feedstock material that acts as a layer in the construction process. Different sheets are precisely cut into specific shapes and then either stacked and glued to existing layers or bonded to them for assembly. The resulting layers are subsequently cut and shaped to create the desired final product [33]. After undergoing extensive research and development for over thirty years, AM has evolved from a rapid prototyping method to a widely acknowledged manufacturing technology utilized in the production of finished components. PLA is an important substance used in 3D printing; however, it is not utilized in every technology that involves printing with PLA (Table 2) [33].

2. Physical Properties of PLA Scaffolds

The functional and integrative properties of PLA scaffolds are critical to their effectiveness and incorporation into the breast tissue environment. These properties include mechanical strength, degradation rate, and porosity, all of which can be customized to

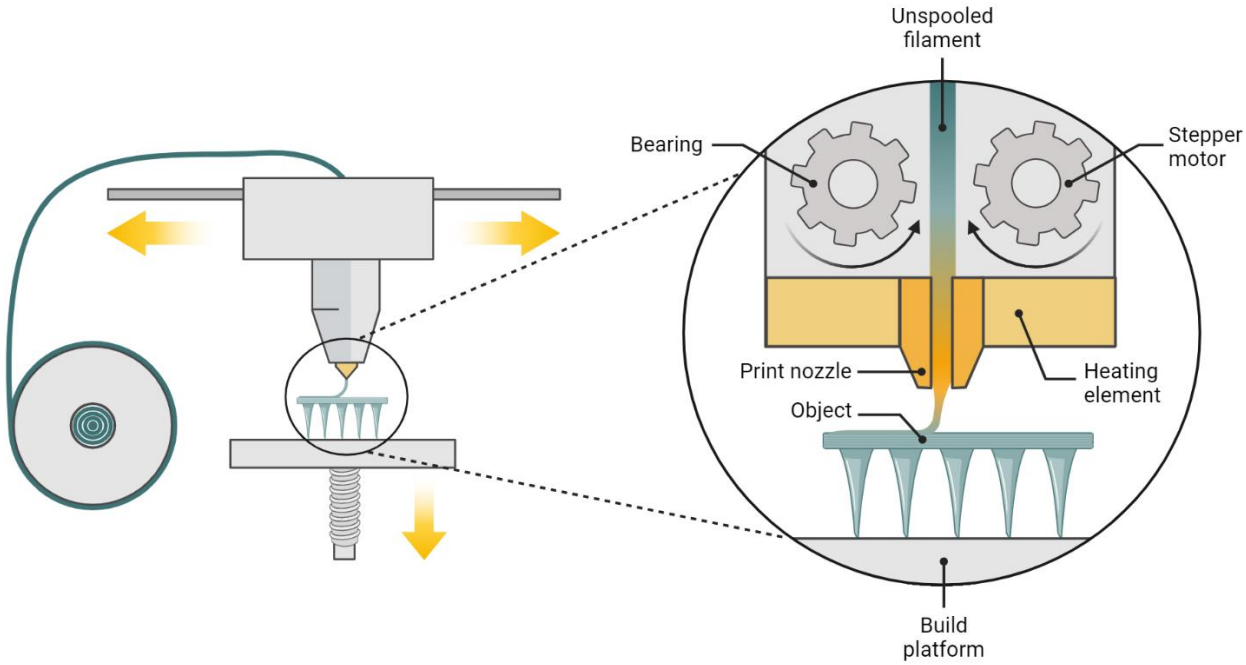

Figure 3. 3D printing, fused deposition modeling.

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Table 2. Detailed Overview of Additive Manufacturing (AM) Categories.

Additive Manufacturing (AM) Category	Description	Materials Used	Advantages
Material Extrusion	Most often used AM technology.	ABS, PLA, Nylon, Polyetherimide (PEI), Polyphenylsulfone (PPSF)	Allows for the creation of parts with more intricate shapes than traditional methods such as injection molding, without requiring expensive mold tooling.
Binder Jetting and Material Jetting	Techniques wherein droplet form of adhesive binder material is deposited to bind powder material.	Various, depending on the specific application	Enables the creation of small quantities and even goods that are completely tailored to individual specifications.
Powder-Bed Fusion	A layer of solid powder is placed and subjected to a heat source, such as a laser or electron beam.	Various, depending on the specific application	Widely used in part manufacture because they can sinter many materials and eliminate the requirement for support structures.
Sheet Lamination	Uses a sheet of feedstock material that acts as a layer in the construction process. Various sheets are precisely cut into certain shapes and then either stacked and glued to existing layers or bonded to them.	Various, depending on the specific application	The resulting layers are subsequently cut and shaped to create the desired final product.

fulfill precise clinical requirements.

2.1. Mechanical Strength

The mechanical strength of PLA scaffolds must be adequate to endure the physiological strains experienced within the breast tissue [34]. This is particularly important for scaffolds that could potentially be utilized to provide support for tissue regeneration following mastectomy or lumpectomy surgeries [35]. Scientists can modify the mechanical characteristics of PLA by adjusting the molecular weight of the polymer or by adding reinforcing substances, such as biocompatible fibers or nanoparticles, to improve the weight-bearing capacity of the scaffold [36].

2.2. Degradation rate

The degradation rate of the scaffold is a crucial characteristic that affects its lifetime and the time it needs to be replaced by natural tissue. PLA degrades to form lactic acid, a material found naturally in the body. This process helps to reduce inflammation and facilitates tissue repair. By manipulating the polymer's crystallinity and molecular weight or by incorporating certain additives, the rate of breakdown can be modified to match with the rate of tissue regeneration [37]. This ensures that the scaffold supports to the tissue for the required duration and no longer.

2.3. Porosity

Porosity is a crucial factor in the transport of nutrients and removal of waste, which are essential for the survival and growth of cells within the scaffold. Optimal pore size and interconnectivity are necessary to enhance cell infiltration and promote the creation of new tissue. Method s such as salt leaching, gas foaming, or phase separation can be used to produce a structure with a high degree of porosity and linked pores, imitating the extracellular matrix and facilitate the formation of blood vessels.

2.4. Surface Characteristics

Surface characteristics play a crucial role in determining how cells interact with PLA scaffolds. Cell adhesion, proliferation, and differentiation can be influenced by surface roughness, hydrophilicity, and the presence of functional groups [38]. Surface modifications, such as plasma treatment or the

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application of cell-adhesive proteins to scaffolds, can improve these interactions and facilitate the development of a functional tissue structure.

3. Tumor Microenvironment Simulation

In breast cancer, the tumor microenvironment (TME) is a critical factor in both disease progression and treatment response. PLA scaffolds provide a unique opportunity to model the TME, which in turn provides insight into the intricate interactions that occur between cancer cells and their environment [39, 40].

3.1 Replicating the Extracellular Matrix

The extracellular matrix, often known as the ECM, is a complex network of proteins and polysaccharides that are responsible for providing functional support to cells. ECM is a three-dimensional network of proteins and glycosaminoglycans (GAGs) that give the body what it needs, including physical support and biomechanical and biochemical signals that cells can use to adhere, proliferate, and move around. Using PLA scaffolds, which can be created to imitate the composition and architecture of the ECM, researchers may examine cancer cell behavior on a more realistic platform. Through the manipulation of the scaffold's fiber alignment, stiffness, and biochemical cues, researchers can explore how these parameters influence the growth of tumors, invasion, and metastasis [41]. Sanjeeb et al. [42] have created and assessed biodegradable porous polymeric microparticles as a structure to support the proliferation of cells. The researchers have proposed that microparticles with a carefully designed composition and characteristics will exhibit improved cell adhesion, leading to enhanced cell proliferation and the formation of a tissue-like structure. There are several benefits associated with the utilization of PLA and other synthetic hydrogels as ECM mimics. These benefits include the capability to regulate the release of medicinal drugs, improve cell adhesion and migration, and offer a more realistic environment for studying cell behavior. Nevertheless, there is still a requirement to incorporate further complexity into these systems to better represent the original environment of the ECM [43]. This may include reproducing the fibrillar structure of collagen as well as the possibility of cellular remodeling of the ECM [43, 44].

3.2 Studying Cell-Cell and Cell-Matrix Interactions

Investigation of cell-to-cell and matrix-to-matrix interactions between cancer cells and the ECM is extremely important for tumorigenesis. These interactions can be studied in a controlled environment by using PLA scaffolds [45]. Researchers can monitor how cancer cells respond to different components of the ECM and how they communicate with stromal cells, both of which can lead to the discovery of new treatment targets [46]. In addition, a study found that 3D-printed PLA scaffolds stimulated different responses from endothelial progenitor cells and adipose-derived stromal cells compared to typical 2D cultures. The study demonstrated that porous PLA scaffolds effectively facilitated the progression of the cell cycle in adipose-derived stromal cells. However, they also caused G1 arrest and decreased proliferation of expanded CD133+ cells [47].

In addition, studies have shown that the surface topography of PLA films might influence tissue attachment, growth, and viability [48]. Scaffold-based and three-dimensional cell culture models, particularly those utilizing PLA, have a greater capacity to elicit in vivo chemosensitivity and pathophysiological events compared to two-dimensional monolayers [49]. PLA scaffolds provide the capacity to replicate the specific composition of the ECM found in a particular tissue. This allows them to provide the essential biochemical signals required for cell-ECM interactions. These interactions are crucial for cellular communication and can impact the absorption of anti-cancer drugs in specific patients [50].

3.3 Vascularization and Nutrient Supply

It is important to have adequate vascularization within the scaffolds to deliver nutrients and oxygen to the cells. This is done to simulate the conditions that exist within an in vivo tumor. By designing PLA scaffolds with specific features that promote vascularization, it is

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possible to increase the usefulness of these scaffolds for both in vitro and in vivo research and studies [51]. Currently, there is little or limited data on the effect of PLA scaffolds on breast cancer. However, previous research has shown that PLA scaffolds can be designed to mimic the structure of bone and provide a favorable environment for co-cultivation of endothelial cells and osteoblasts. The study was conducted using a scaffold design consisting of a hydroxyapatite ring surrounding a PLA core. This design facilitated cell movement throughout the scaffold. In addition, the initial placement of endothelial cells on a scaffold was found to enhance the penetration of osteoblasts into certain regions of the scaffold [52].

A separate study emphasized the stimulated movement of endothelial cells into three-dimensional scaffolds due to chemicals released by pro-inflammatory macrophages at their original location. This model was designed to replicate the angiogenesis process by facilitating the movement of endothelial cells onto porous scaffolds through the influence of inflammatory cells [53]. These findings indicate that PLA scaffolds can promote the movement and proliferation of endothelial cells, therefore aiding in the creation of new blood vessels. These findings could have substantial ramifications for the fields of cancer treatment, tissue engineering, and regenerative medicine (Table 3).

Table 3. Application of PLA in tumor microenvironment.

Application	Details
Replicating the Extracellular Matrix (ECM)	- PLA scaffolds can mimic the composition and architecture of the ECM - Allows studying how ECM parameters like fiber alignment, stiffness, and biochemical cues influence tumor growth, invasion, and metastasis - Synthetic hydrogels like PLA offer advantages like controlled drug release, improved cell adhesion/migration, and more realistic environment - Need to incorporate more complexity to better represent native ECM fibrillar structure and cellular remodeling
Studying Cell-Cell and Cell-Matrix Interactions	- Provides a controlled environment to study cancer cell interactions with ECM components and stromal cells - PLA scaffolds elicit different responses from cells compared to 2D cultures - Surface topography of PLA influences cell attachment, growth, viability - Better replicates in vivo chemosensitivity and pathophysiology than 2D monolayers - Can mimic tissue-specific ECM composition and provide crucial biochemical signals for cell-ECM interactions
Vascularization and Nutrient Supply	- Designing scaffolds to encourage blood vessel formation is vital for nutrient/oxygen supply like in vivo tumors - PLA scaffolds engineered to mimic bone structure and co-culture endothelial cells and osteoblasts - Chemicals from pro-inflammatory macrophages stimulated endothelial cell migration into 3D porous scaffolds, mimicking angiogenesis

4. Drug Delivery Systems

A revolutionary method for the treatment of breast cancer is represented by the incorporation of drug delivery systems into PLA scaffolds. By using these systems, it is possible to establish a regulated and localized release of therapeutic agents, which in turn maximizes the therapeutic index while simultaneously lowering systemic toxicity (Table 4) [54].

4.1. Targeted Drug Delivery

PLA scaffolds can be functionalized to target specific cells or tissues, ensuring that drugs are delivered precisely where they require the most. This is referred to as targeted drug delivery [54].

PLA possesses several notable advantages, including its

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biocompatibility, ensuring its safety for use within the body, and its biodegradability, which allows it to gradually degrade in the body [55, 56]. PLA exhibits prolonged drug retention periods, enabling precise modulation of drug release. Additionally, it is highly adaptable and can be found in several forms that can have their mechanical qualities adjusted [55]. In addition, PLA is cost-effective and has been approved by several regulatory agencies for its use in biomedical applications, such as drug delivery [55].

Nevertheless, PLA does possess certain drawbacks. It does not interact with biological systems, which limits its effectiveness in certain applications because it is biologically inert [55]. PLA exhibits limited cell adhesion, which may hinder its ability to promote cell proliferation. Additionally, it exhibits a gradual deterioration, which may be unfavorable in scenarios that require a more rapid rate of disintegration [55]. Modifying PLA is important to accept both hydrophobic and hydrophilic medicines, as PLA itself is hydrophobic [56]. Certain techniques used in the manufacture of PLA-based materials can result in toxicity and the occurrence of adverse reactions.

Despite these obstacles, scientists are persistently striving to improve the PLA-based materials and overcome these limitations. For instance, PLA can be altered or combined with other substances to enhance its properties and make it more suitable for certain applications [55, 57]. PLA is a slightly inflexible substance, resulting in restricted flexibility and the potential for fracture or failure when subjected to stress. This reduces its suitability for applications that require flexibility, such as hinges. PLA exhibits hygroscopic properties, indicating its ability to absorb moisture from the surrounding atmosphere. This can result in the filament becoming fragile and resulting in printing errors. PLA prints are not designed for long-term use, as they naturally decompose into their components over time, leading to a steady decrease in mechanical strength [57]. These advantages are particularly beneficial in the case of breast cancer when focused therapy has the potential to greatly lessen the likelihood of causing damage to good tissue. Increasing the effectiveness of treatment can be accomplished by conjugating antibodies or ligands that identify cancer-specific markers to the scaffold. This allows drugs to be targeted to the site of the tumor. Obayemi et al. [54] have designed new 3D drug-loaded porous scaffolds carrying solutions of prodigiosin with properties similar to normal breast tissue with new insights on drug release kinetics and thermodynamics resulting in significant breast cancer cell death and greatly support normal breast cell proliferation/growth. An in vivo study shows that drug-loaded scaffolds prevent locoregional tumor recurrence. Pandey et al. [58] conducted a study to determine the efficacy of using tamoxifen (TMX) loaded PLA nanoparticles (NPs); their study showed that TMX-NPs exhibit substantial therapeutic efficacy against breast cancer while minimizing hepatotoxicity, renal toxicity, and inflammatory/immunogenic side effects. Abouhasera et al. [59] produced and analyzed Docetaxel-Loaded Methoxy poly(ethylene glycol)-poly (L-lactic Acid) Nanoparticles (DTX-mPEG-PLA-NPs) and developed and validated a simple, accurate, and reproducible method for DTX measurement. Their results show that the robust RP-HPLC method can detect DTX and that DTX-mPEG-PLA-NPs are a noticeable and biocompatible delivery vehicle with enhanced cytotoxic and anti-clonogenic potential, improving BC outcomes. Another study used 3D printing to successfully create porous polylactic acid/methotrexate (PLA/MTX) scaffolds that could be controlled to reduce tumor growth. The incorporation of the MTX medication into the PLA filament was validated by scanning electron microscopy and energy-dispersive spectroscopy. Sustained release of therapeutic molecules for more than 30 days in vitro was achieved using 3D-printed PLA/MTX scaffolds. These findings provide strong evidence that 3D-printed PLA/MTX scaffolds have promise as a versatile drug delivery strategy for tumor suppression in various malignancies [34].

4.2. Controlled Release Mechanisms

One of the most important features of PLA scaffolds is their ability to control drug release. It is possible to customize the release rate of pharmaceuticals to the pharmacokinetics of the drug as well as the dynamics of tumor progression through the process of encapsulating

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the drug within the scaffold or binding them to the scaffold matrix during the process (Figure 4) [60, 61]. This allows for prolonged drug exposure at the tumor site for an extended time, which can improve patient compliance and treatment success [62]. Amani et al. [63] utilized multifunctional magnetic nanoparticles to provide controlled release of an anticancer drug, target breast cancer cells, perform MRI/fluorescence imaging, and administer the anticancer drug. They achieved this by employing a copolymer called PLA-PEG-PLA. Wang et al. [64] conducted a study in which they effectively synthesized polymeric micelles containing tocopherol to augment the anticancer activity of fisetin (FIS) against breast cancer cells. The fisetin-loaded TPGS-PLA polymeric micelles are a promising alternative and potential candidate for the effective treatment of breast cancer, according to all of the findings. Allu et al. [65] conducted and assessed an in vitro experiment using poly(lactic acid) films to study the controlled release of lapatinib, an anticancer drug.

4.3. Enhancing Penetration and Retention

Improving Penetration and Retention One of the difficulties associated with the treatment of solid tumors is making certain that drugs are able to penetrate deeply into the tumor mass. It is possible to construct PLA scaffolds to improve drug penetration and retention within the tumor. This can be accomplished by designing the porosity of the scaffold and using penetration enhancers. Penetration enhancers are substances that facilitate the passage of drugs through the tumor interstitium [66]. Modulation of the tumor microenvironment and taking advantage of both internal and external cues are the mechanisms by which they work [66, 67]. Reduction of tumor stroma and the regulated release of anti-tumor drugs are two examples of tactics that have been utilized to improve drug penetration [67]. In cancer therapy, nanoparticles greatly enhance drug penetration and retention. Because of their enormous surface area and small size, they can effectively penetrate and accumulate in tumor tissue [68]. Their ability to retain drugs is enhanced by engineering them to release their drug load in response to certain stimuli in the tumor microenvironment. In addition, targeted ligands can be applied to their surface to enhance their affinity for cancer cells, leading to improved penetration and retention [69].

Increasing the concentration of drugs at the tumor site improves treatment efficacy while reducing systemic side effects. Nanoparticles are a potential solution to the problems associated with drug delivery in cancer treatment [69]. Park et al. [70] conducted a study aimed

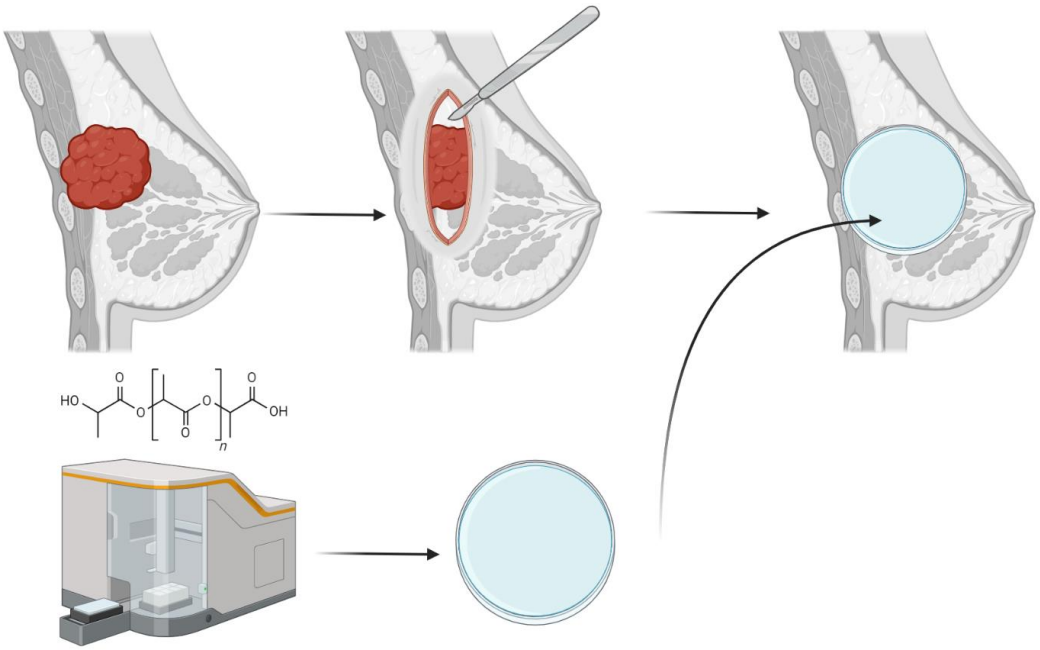

Figure 4. PLA as a drug delivery scaffold in breast cancer.

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to evaluate the practicality and benefits of utilizing a patient-specific breast bolus created by the utilization of 3D printing technology. The results indicated a strong correlation between the dosage distribution of a virtual bolus created by the Treatment Planning System (TPS) and the PLA bolus. Deng et al. [71] co-administered biocompatible nanoparticles made of self-assembled polylactic acid-hyaluronic acid block copolymers, along with a tumor-penetrating peptide called iRGD, for the treatment of metastatic breast cancer. Specifically, their research demonstrated a significant increase in drug distribution in the lungs, resulting in the successful suppression of the spread of breast cancer to the lungs. Therefore, the co-administration of iRGD with HA-PLA has great potential as a therapeutic strategy for the treatment of breast cancer (Table 4).

Table 4. PLA as a drug delivery scaffold in breast cancer.

PLA	Breast Cancer Drug Delivery
PLA-based materials have been thoroughly researched for biomedical applications.	Several drugs, including ibuprofen, amphotericin B, paclitaxel, 5-fluorouracil, doxorubicin, ketoprofen, rifampicin, salinomycin, ciprofloxacin, and ornidazole, have been successfully loaded into and released from PLA-based materials.
Due to the hydrophobic nature of PLA, its modification to accommodate both the hydrophobic and hydrophilic drugs are emphasized.	Biocompatibility, biodegradability, sustainable delivery, controlled release kinetics, increased patient compliance, and reduced fluctuation of drug concentrations in blood are among the benefits of using PLA in drug delivery.
Co-administration of biocompatible self-assembled polylactic acid–hyaluronic acid blocks copolymer nanoparticles with tumor-penetrating peptide-iRGD for metastatic breast cancer therapy.	The co-administration of iRGD with HA–PLA significantly increased drug distribution in the lung, which contributed to the effective inhibition of the lung metastasis of breast cancer.
PLA is a biodegradable and biocompatible polymer that has been widely used in the field of drug delivery.	PLA nanoparticles can be used to deliver chemotherapeutic drugs directly to the tumor site, reducing systemic toxicity.
The degradation rate of PLA can be controlled by adjusting its molecular weight and crystallinity, allowing for controlled release of the drug.	PLA-based drug delivery systems have shown promising results in preclinical and clinical studies for the treatment of breast cancer.

CONCLUSION

In conclusion, the investigation of PLA-based scaffolds presented in this study sheds light on the revolutionary potential of these scaffolds possess in the field of breast cancer treatment. These scaffolds represent a significant innovation that offers a dual benefit: they accurately mimic the physical properties of breast tissue, allowing for the accurate study of cancer cells, and they function as precise drug delivery systems, which minimize side effects while simultaneously maximizing therapeutic efficacy. The ability of PLA scaffolds to mimic the tumor microenvironment not only helps us develop a deeper understanding of cancer biology, but also brings us closer to developing personalized medical treatments. PLA-based scaffolds are at the forefront of innovation, ushering in a new age of breast cancer drugs that are both targeted and successful. This is because we continue to bridge the gap between fundamental research and clinical application.

ACKNOWLEDGMENTS

None declared.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICS APPROVAL

This study does not need an ethical approval number.

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