Tissue Engineering Scaffolds Loaded With a Variety of Plant Extracts: Novel Model in Breast Cancer Therapy

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Reyhaneh Azhari Rad[1*], Yasaman Naghdi[1*], Mobina Majidi Jamalabadi[2], Sima Masoumi[3], Leila Rezakhani[4,5] and Morteza Alizadeh[6]

[1]Student Research Committee, School of Paramedicine, Shahroud University of Medical Sciences, Shahroud, Iran. [2]Student Research Committee, School of Nursing and Midwifery, Shahroud University of Medical Sciences, Shahroud, Iran. [3]Graduate of Faculty of Veterinary Sciences, Sanandaj Branch, Islamic Azad University, Sanandaj, Iran. [4]Fertility and Infertility Research Center, Health Technology Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran. [5]Department of Tissue Engineering, School of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran. [6]Department of Tissue Engineering, School of Medicine, Shahroud University of Medical Sciences, Shahroud, Iran.

ABSTRACT: Despite recent improvements in detecting and managing breast cancer (BC), it continues to be a major worldwide health concern that annually affects millions of people. Exploring the anti-BC potentials of natural compounds has received a lot of scientific attention due to their multi-target mode of action and good safety profiles because of these unmet needs. Drugs made from herbs are secure and have a lot fewer negative effects than those made from synthetic materials. Early stage patients benefit from breast-conserving surgery, but the risk of local recurrence remains, necessitating implanted scaffolds. These scaffolds provide residual cancer cell killing and tailored drug delivery. This review looks at plant extract–infused tissue engineering scaffolds, which provide a novel approach to treating BC. By offering patient individualized, safer treatments, these scaffolds could completely change how BC is treated.

KEYWORDS: Tissue engineering, scaffolds, plant extracts, breast cancer, treatment

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CORRESPONDING AUTHOR: Morteza Alizadeh, Department of Tissue Engineering, School of Medicine, Shahroud University of Medical Sciences, Shahroud 3614773955, Iran. Email: mor1361@gmail.com

Introduction

Chemotherapy's efficacy is limited due to adverse effects, including congestive heart failure.[1] There is considerable debate over the precise causes of breast cancer (BC). Long-known markers for starting and advancing the difficult path to cancer include genomic and epigenetic changes.[2] However, concerns about the side effects associated with traditional BC treatments have sparked recent interest in the development of alternative approaches. Recent research has delved into the potential of creating targeted drug delivery methods for cancer, aiming to address some of the challenges associated with widespread chemotherapy.[3]

MicroRNAs (miRNAs) have lately been included in the definition of epigenetics, in addition to histone modification and DNA methylation. Because of their tumor suppressor properties, miRNAs are currently thought to be desirable targets for therapeutic intervention in cancer prevention and therapy.[2] Surgical procedures play a pivotal role in the comprehensive management of breast tumors, and choosing an appropriate surgical protocol has consistently posed a complex issue in the field of BC surgery.[4]

Recent research has indicated that early stage patients with BC may benefit from breast-conserving surgery, in which just the affected portion of the breast is removed.[5] Radiotherapy can significantly lower the likelihood of BC local recurrence, even though cases of BC treated with breast-conserving surgery had a higher rate of local recurrence than those treated with mastectomy. In addition, for long-term effective repair and reconstruction in most cancer treatments, restoring tissue abnormalities following cancer surgery is necessary.[6] As a result, there is a need to develop an implantable scaffold for the targeted administration of anticancer drugs, as well as for the efficient destruction of any remaining cancer cells and the prevention of local BC return. A promising alternative approach to reducing the likelihood of local cancer recurrence following resection has been suggested: local administration of chemotherapeutic drugs directly to the tumor sites[7] (Figure 1).

Breast Cancer

Metabolic shifts that facilitate the expansion of tumors are a defining feature of cancer. The triggers for these metabolic alterations can be found within the parenchymal cells of the tumor, where oncogenic mutations create an urgent need for rapid proliferation, thereby initiating and driving tumor growth. As the disease progresses, cancer cells undergo a significant reorganization of their metabolic processes, which are finely tuned to meet their energy demands and adapt to the fluctuating conditions of their environment.[8] Breast cancer is the most prevalent cancer in women worldwide and the second

*Both authors have contributed equally as the first author.

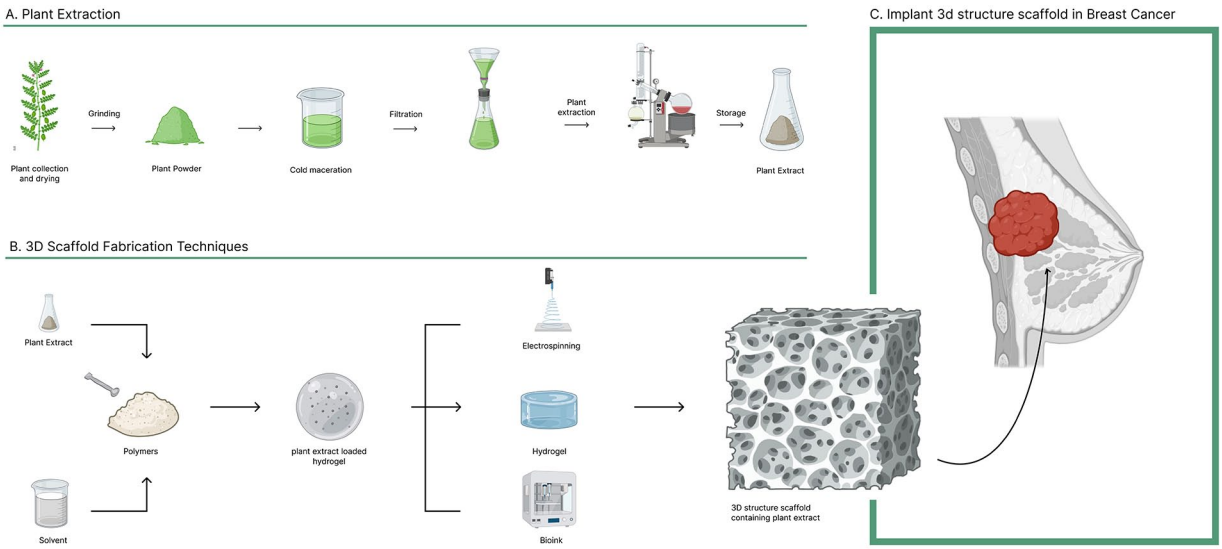

Figure 1. Treatment of BC with plant extract–loaded scaffold.

greatest cause of cancer death overall. It is frequently treated using a trimodal approach that combines surgery, chemo, and radiotherapy.[3,9]

According to molecular and histological evidence, BC can be classified into 3 distinct groups: BC that expresses hormone receptors, estrogen receptor-positive (ER+), or progesterone receptor-positive (PR+), and BC that expresses human epidermal growth factor receptor 2 (HER2+) and triple-negative breast cancer (TNBC) (which lacks expression of ER, PR, and HER2).[10] Breast cancer is the second-leading neoplastic cause of death in American women, after lung cancer, and a major contributor to cancer morbidity and mortality in underdeveloped nations.[2] Although BC was traditionally primarily thought to affect Western women, 62% of fatalities and 52% of new occurrences occur in underdeveloped nations.[11] About 300 000 women will be diagnosed with BC in the United States this year, and more than 40 000 of them will pass away from the illness.[12] In 2020, BC took the lead as the most prevalent cancer in women globally, with 2.6 million new cases, surpassing lung cancer. It constituted a significant portion, accounting for 7% to 10% of all malignant tumors.[13] According to statistics, 15% of female cancer deaths and 30% of newly diagnosed cancer cases in women are due to BC.[14,15] Every year, there are about 1 million confirmed instances of BC worldwide.[16,17] According to the reported statistics, BC has the highest prevalence in women compared with other cancers,[18] and its prevalence and mortality are different in different regions of the world. It is predicted that by 2040, the number of newly diagnosed cancers will grow by more than 40% and reach about 3 million cases per year, and the number of deaths due to it will increase by more than 50%, from 685 000 in 2020 to 1 million and reach in 2040[19] (Figure 2).

Plant Extracts in Breast Cancer Treatment

Recently, treatment options for BC include chemotherapy, radiotherapy, surgical procedures, immunotherapy, and hormonal treatment; however, BC is still not resolved. In addition, treatment-resistant tumor recurrence is induced by the currently available medications, which also result in toxicity and serve as a barrier to the treatment of BC.[20] To stop the growth of tumors or reverse the process, more potent medication formulations with fewer adverse effects are currently needed. Natural substances like plant extracts have recently been investigated for their potential to fight cancer. Because they are less harmful to the cellular or physiological environment than synthetic compounds, the benefits of natural compounds and phytochemicals outweigh those of synthetic compounds. They also have a high degree of selectivity.[21,22] When conditions are right, phytochemicals act as antioxidants and defend the body from free radical damage. However, several phytochemicals show prooxidant actions at high and low pH. These free radicals have the potential to harm crucial macromolecules and cause long-term illnesses like cancer. Free radicals can cause DNA mutations, raise the levels of mitogenic mediators, and aid in the development of new blood vessels in the case of cancer.[23] However, plant-based substances are a rich source of antioxidants that protect against free radicals and are employed in anticancer medications. These antioxidants, which are not enzymes, can interact with free radicals and control biological degradation. Other goals include lowering serious hazards, destroying cells, triggering programmed cell death, and trying to identify molecular components that are unusually expressed.[24,25] Plants produce phytoalexins, which are powerful pathogen activators. Pterocarpans, known as active flavonoids, possess antibacterial, anticancer, antiviral, and antimalarial effects. They exhibit effectiveness against enzymes like Protein tyrosine phosphatase 1B (PTP1B) and have been acknowledged for their anticancer actions in numerous cancer cell types.[26]

The secondary-class metabolite chemicals known as annonaceous acetogenins (ACG), found in abundance in *Annona muricata* leaves, have been shown to activate the mitochondrial

Figure 2. Distribution of cancer types and BC: (A) Distribution of cancer incidence and mortality among different types of cancer in 185 countries, BC is the important most commonly identified cancer with a total of 2.3 million new cases (11.7%),[18] (B) distribution of BC cases and deaths by world area (2020),[19] and (C) estimated number of BC cases and mortality from 2020 to 2040, by the level of Human Development Index (HDI).[19]

electron transport complex, mitochondrial adenosine triphosphate (ATP) production, and cell death in cancer cell lines. Researchers and medical professionals employ *annona muricata* leaf extracts (AME) to cure BC, obtain cytotoxic effects in experimental settings, and reduce body size and weight. *Nbutanolic* extracts of AME have been demonstrated to have antiproliferative effects on BC cells in vitro.[27]

Curcumin, derived from turmeric, possesses both anticancer and chemotherapy-like properties across various cancer types. Its effects are mediated through intricate molecular signaling pathways, including those involving proliferation, HER2, and ERs. *Chrysin*, a natural flavone presents in plant extracts, demonstrates chemotherapeutic effects by selectively modulating cellular mechanisms. Both *Curcumin* and *Chrysin* have been

observed to regulate epigenetic modifications such as histone modification, DNA methyltransferases, and miRNA expression. Nonetheless, these compounds suffer from drawbacks, including limited physicochemical stability, low water solubility, rapid metabolism, and poor bioabsorption.[28,29] In addition, *benzofuran*, a fundamental structural component found in various natural substances, has gained significant interest in recent times due to its similarity to both natural and synthetic materials. *Benzofuran* possesses several biological properties, including antimicrobial, antifungal, antiviral, antihyperglycemic, analgesic, antiparasitic, and antitumor activities, including efficacy against BC.[30]

Dicuma species are used to extract various substances. These naturally occurring substances derived from plants are not hazardous to normal or noncancerous cells and are used to treat a variety of malignancies, including breast, ovarian, prostate, and others. In particular, breast and lung cancer are treated with *D. anomala* extract's anticancer capabilities.[31] Secoisolariciresinol diglucoside, a kind of phytoestrogen lignan found in *Linum usitatissimum* (flaxseed), is fermented in the large intestine to produce enterolactone and enterodiol. This intellectual metamorphosis has a positive impact on flaxseed's anticancer properties. The ligand metabolites preferentially bind to ERs due to their structural resemblance to estrogen, which prevents estrogen-induced BC growth. According to the evidence currently available, flaxseed and its constituent parts are both safe and efficient in lowering the risk of and treating BC.[32]

Although numerous in vitro studies have demonstrated the potential of ginseng extract or its active components as effective anticancer agents in BC, it should be noted that the findings are limited to laboratory settings[31] These compounds have shown the ability to modulate signaling pathways associated with inflammation, oxidative stress, angiogenesis, metastasis, and the stem/progenitor-like properties of cancer cells. However, further research and clinical trials are necessary to establish the efficacy and safety of ginseng extract or its active components in the treatment of BC.[32] Consuming green tea may help prevent BC in Asian people due to its prevalence and potential health benefits. *Catechins*, which are present in green tea, have potent anticancer activities. In addition, it demonstrates how hormones and biomarkers may naturally alter BC through steroid activity.[33] Health-improving properties include anticancer, immune system stimulant, anti-blood sugar, neuroprotective, drug protecting, antifungal, antibiotic, prebiotic, and antiviral activity, in addition to those of herbal medicinal plants. Mycelium and fruiting bodies from fungi, as well as substances such as glucans and promoters, can all have anticancer properties. Several types of cancer, particularly big tumors, BC, and BC suppressors, are resistant to the anticancer effects of certain mushrooms.[34]

Three-Dimensional Scaffolds in BC Models

Hydrogel

Biomaterials which are called hydrogels are adaptable and are employed in a variety of processes, such as cancer research, tissue engineering, drug delivery, and wound healing. These 3-dimensional (3D) gels are made up of hydrophilic polymers that swell when exposed to water and interact with one another randomly or by being driven to crosslink[35] Collagen, a natural substance present in the extracellular matrix (ECM), is the main component of hydrogel-based scaffolds, which are less porous than their frozen counterparts. By altering production methods and characteristics, including degree of polymerization, mechanical properties, architecture, and biodegradability, hydrogel qualities can be changed. Due to its compatibility with the bodily environment, collagen is a frequently used component in the manufacture of hydrogels.[36,37] Researchers routinely use collagen-based hydrogels to analyze the behavior of various cell lines, making them a popular choice for examining BC cell proliferation. These tests have shown encouraging outcomes, showing strong cell multiplication and continued viability in the conditions. The positive results highlight the hydrogels' enormous potential as a useful and practical platform for furthering cancer research.[38]

Because of their hydrophilic nature and capacity to absorb water, these hydrogel scaffolds have great potential for use in drug testing in tissue engineering settings. Because of their potential biocompatibility and wide range of applications in biomedicine, especially in 3D cell cultures and targeted drug delivery systems, they have been investigated.[38,39]

The complex networks of hydrophilic polymers that make up hydrogels allow them to absorb a significant amount of water in relation to their dry weight. They can be found in a variety of forms, including membranes, microparticles, solid molded shapes, and even liquid forms.[35] Hydrogels can be made from natural or synthetic polymers,[40] or from mixes of both, as evidenced by their diverse physical compositions. It is important to emphasize, nevertheless, that the mechanical and porosity characteristics of hydrogels can be precisely adjusted during their synthesis by adjusting variables such as temperature, pH, and ionic strength.[38] Although collagen-based hydrogels, which are known for their biocompatibility, are widely used in hydrogel synthesis, changes in temperature and pH during the polymerization process can modify the architecture and mechanical strength of these hydrogels. In addition, because of their potential for 4-dimensional printing (4DP) and shape-morphing structures, smart hydrogels—which are recognized for their responsive behavior to external stimuli including temperature, pH fluctuations, and electric fields—have drawn interest.[41]

Electrospinning

Due to its distinctive characteristics, such as high surface-to-volume ratios, interconnected porosity, and manipulation of material properties throughout the electrospinning process, electrospinning has emerged as a possible alternative to cancer medication therapy.[42] Forced spinning is a newer method that pulls the fiber with centrifugal force rather than an electric field for the purposes of medication delivery.[43] To create nanofibers

(NFs) with various qualities, existing polymers such as poly (lactic acid), polyurethane, and poly (3-hydroxybutyrate-co-3-hydroxyvalerate) are employed.[44] Due to its great effectiveness, low cost, and high reproducibility, electrospinning stands out among NF manufacturing processes and is particularly well-suited for biomedical applications.[43]

By using electrical energy, charged filaments are drawn from polymer solutions or melts and spun into nanometer-sized fibers.[45] Biodegradable polymers are used in electrospinning research to create fast-dissolving drug delivery systems that permit regulated medication release without the need for a second surgery to remove implanted abutments.[46] These NFs interact in numerous ways with cells and tissues, simulating the ECM found in healthy tissues and assisting in the growth, proliferation, and regeneration of sick tissues.[47] As a result, electrospun NFs seem to be a good candidate for the delivery of anticancer drugs, providing several benefits over existing drug delivery mechanisms.[46] Electrospun collagen scaffolds have shown promise in BC research due to their high control over fiber architecture, rapid production process, and fibrous collagen network. These scaffolds have shown successful growth and proliferation of viable BC cells, unlike synthetic electrospun scaffolds.[48] The success of these scaffolds may be attributed to the completeness of tumor tissue resection during cancer surgery. Further exploration into electrospun collagen scaffolds could unlock their full potential in BC culture, providing a more accurate representation of the ECM and potentially leading to significant advancements in cancer research and treatment strategies.[49]

The process of electrospinning, which is praised for its ease of use, economy, and consistency, has aided in the creation of polymer composites reinforced with NFs, improving their chemical and physical characteristics while maintaining essential mechanical and biological characteristics like biocompatibility.[42] With the use of combinations, cross-linking, or polymer selection, this method enables precise control over the composition of the NFs, resulting in customized strength, elasticity, and porosity.[43] Among the various techniques, electrospun NFs stand out as affordable, expandable solutions, particularly effective in the biomedical fields.[44] They achieve targeted medication administration while preventing systemic exposure by enabling precise drug delivery through controlled spatial and temporal release. Smart systems that are sensitive to pH, temperature, and electromagnetic fields have been developed recently in electrospun NFs, improving medication release accuracy in line with predicted indicators.[45]

Three-dimensional printing

A cutting-edge technique called 3-dimensional printing (3DP) is used in BC treatment, manufacturing, and repair. It enables simple pharmaceutical product modification, individualized treatment programs, and dose form adjustments based on patient characteristics.[50] Making dynamic 3D-printed things capable of evolving their morphology and characteristics over time is the goal of 4DP. Through external stimuli such as pH, temperature, humidity, light, or magnetic field changes, these things can self-convert.[51,52] In comparison with conventional manufacturing methods, 3DP has benefits including rapid prototyping, structural control, accessibility, and cost.[53] It is seen as being environmentally beneficial because it uses less energy, reduces waste production, and eliminates the need for chemicals. Three-dimensional printing is constrained by issues such as size restrictions, post-processing requirements, and a lack of legal protections.[41]

Four-dimensional printing is interested in smart materials that can adapt to movement by changing their function and shape. Applications of 4DP involve advanced polymers, and numerous academic fields are working together to fully realize its promise in engineering and medicine.[54] In a study, primary mouse BC cells were grown in a 3D culture model for 8 weeks. The development of biomimetic 3D BC scaffolds made possible by improvements in bio-fabrication techniques allows for a more accurate portrayal of tumor situations.[55] These models enable more accurate drug testing platforms while providing greater insights into the development of cancer. These models support industry objectives by minimizing the use of animals in drug testing. New bioprinting methods enable the integration of cells into collagen solutions to produce "bio-inks" that aid cell distribution during printing.[38]

The fact that 3D implants are versatile and go beyond stimulating anticancer activity to include tissue regeneration indicates that they have the potential to be used in a variety of therapeutic contexts.[56] Conforming to the natural mechanical characteristics of breast tissue while promoting regrowth and preserving the breast's cosmetic integrity is a crucial requirement for these scaffolds.[50]

These scaffolds, which are produced using 3DP, have become more well-known because of their many benefits, which include strong mechanical qualities, outstanding processability, and biocompatibility,[55] and pioneered the development of soft scaffolds using 3DP with material extrusion, confirming the structural resemblances between printed devices and natural tissue. Furthermore, these 3D scaffolds have proven to be able to promote the differentiation of stem cells originating from adipose tissue, suggesting that they may be useful in promoting cellular differentiation. For the time being, the most common use of 3D scaffolds in BC research is to create scaffolds and implants that are loaded with drugs. These gadgets should help with tissue rebuilding, mimic natural tissue, and deliver drugs under controlled conditions[51] (Figure 3).

Plant Extract–Loaded Scaffolds in BC Treatment

Plant extract–loaded scaffolds hold promise as an innovative approach to BC treatment, building on standardized chemotherapy regimens. The synergy between phytochemicals and chemotherapeutic agents has the potential to enhance treatment

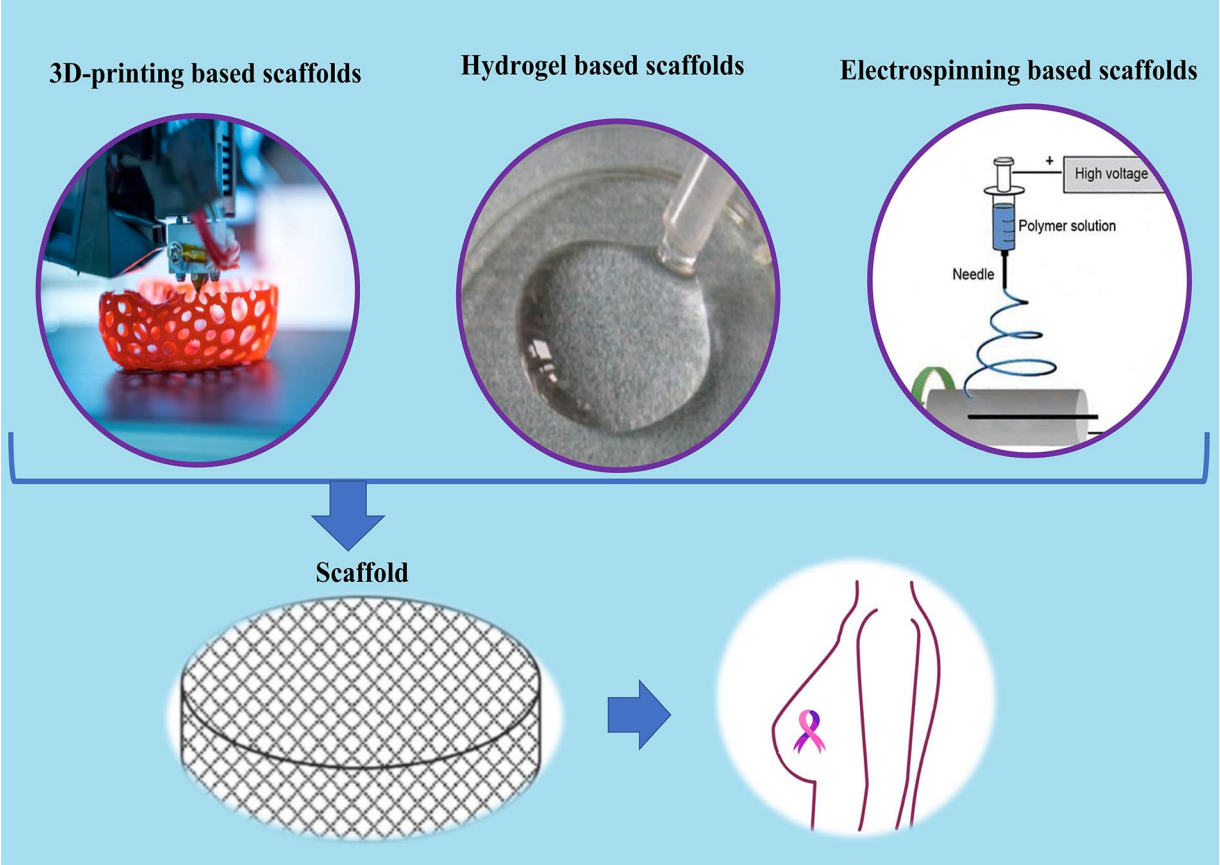

Figure 3. Different methods of fabrication scaffolds for BC studies.

effectiveness while mitigating the adverse effects commonly associated with conventional chemotherapy.[57] Researchers are working to create a natural extract recipe by combining specific ingredients with a synthetic biodegradable polymer called poly (caprolactone) (PCL). This composite could function as a natural drug-eluting stent or implant, specifically tailored for cancer treatment. Localized drug delivery offers advantages in efficacy enhancement and toxicity reduction.[58]

The introduction of synthetic biodegradable polymers, such as poly(lactic-co-glycolic) acid (PLGA) and poly(L-lactic) acid (PLLA), has paved the way for multifaceted approaches in cancer treatment. Electrospun nanofibrous scaffolds offer a promising avenue for drug delivery, but challenges such as burst release and sustained drug delivery hinder their application.[59] Innovations like mesoporous silica nanoparticles (MSNs) have demonstrated potential as controlled drug delivery vehicles, improved bioavailability, and targeting tumor sites. Recent research on BC treatment using plant extract–loaded scaffolds indicates cytotoxic effects on BC cells and reduced tumor size in vivo. Combining the strengths of phytochemicals and advanced drug delivery techniques, plant extract–loaded scaffolds hold the potential to revolutionize BC therapy.[60] In various concise studies outlined in the table, researchers have explored the potential of using plant extracts in combination with scaffolds to enhance BC treatment. By incorporating plant extracts into these scaffolds, a novel approach emerges to improve therapeutic outcomes while minimizing side effects. This strategy capitalizes on the natural properties of plant-derived compounds, enabling targeted and controlled delivery of therapeutic agents. This innovative method could significantly reshape BC therapy, offering a promising solution to the challenges faced by traditional treatments (Table 1).

In biomedical applications, nanofibrous scaffolds have become versatile instruments with promising possibilities in wound healing, tissue engineering, and controlled drug delivery.[47] These scaffolds have been investigated for their potential to encapsulate and release different medicinal substances in the field of medication delivery.[62] Research has demonstrated that extract-loaded NFs are effective at causing cytotoxicity to BC cells.[66] These NFs' controlled release method offers a possible means of lowering systemic toxicity and tumor recurrence after surgery.[39] In a similar vein, using piperine (PIP)-PCL75-Coll25 NFs in a 4T1 BC mouse model resulted in a tumor growth suppression that was effective and demonstrated the NFs' sustained-release capabilities and strong anticancer effectiveness. These results point to the possibility of tailored cancer therapy using NF-based drug delivery systems.[67] In addition, there have been encouraging outcomes with nanoparticles loaded with chemicals such as Chr and Cur. These nanoparticles demonstrated sustained and regulated release characteristics, working in concert to cause apoptosis in BC cells. The possibility of co-delivering Cur and Chr using nanoparticles in cancer treatment has also been investigated in the past.[2,7]

Table 1. Plant extract–loaded scaffolds in BC treatment.

PLANT EXTRACT	STRUCTURE	SCAFFOLD TYPE	MODEL STUDY	EXTRACT DOSE	BIOLOGICAL EFFECT	REF.
Curcumin	PLGA	Electrospinning	In vitro	11.8 ± 1.45 µg/mL	The cells moved less (lower migration) and had more cells dying (increased apoptosis).	61
Prodigiosin	PLGA-GE	Electrospinning	In vitro	0.005 g	Kill residual tumor tissues and promote the regrowth of normal breast tissues. These fibers also have the potential to improve wound healing.	62
Curcumin + aloe vera + neem	PCL	Electrospinning	In vitro	CUR 50 mg + aloe vera and neem ratio 1% with respect to PCL	In both the cell lines studied, curcumin in combination with neem or aloe vera reduced cell viability considerably.	63
Curcumin + Chrysin	PLGA-PEG—NPs	Electrospinning	In vitro	20-30 mg	Repressing several oncogenic attributes including the proliferation, survival, invasion, and metastasis of cancer cells	2
Garcinia mangostana + coconut water	Bacterial cellulose hydrogels	Hydrogel	In vitro	100 mL of the ethanolic mangosteen peel extract at concentrations of 0.01%, 0.10%, and 1.00%v/v	Herbivory effects on skin infective Gram-positive bacteria and BC cells	64
Annona muricata leaf extracts	PLGA/Ge	Electrospinning	In vitro	0.005 g	Kill the residual tumor cells and serve as substrates to promote the adhesion and proliferation of the native breast cells to regenerate	65
Cur + Chr	PLGA/PEG-NFs	Electrospinning	In vitro	Different weight ratios of Cur and Chr (5:0, 10:0, 0:5, 0:10, 5:10, 5:5, and 10:5 wt:wt%)	Raise the anticancer effects of the drugs and avoid local recurrence of BC after resection	7
Lentinula edodes	PVA/lentinan/ docetaxel	Electrospinning	In vitro	1000 µg/mL	Reduce the cell viability of human BC cells and significant effect on reducing the expression of the HER3 gene	66
Piperine	PCL	Electrospinning	Mice In vitro	PIP was added to each solution at 1:15 drug-to-polymer weight ratio	Reduction in cell proliferation and induction of apoptosis and necrosis	67
Amygdalin	PLA/PEG	Electrospinning	In vitro	20, 60, and 100 mg	Reduce the risk of local recurrence	68
A hamosus	Anticancer drug (cisplatin)	Hydrogel	In vitro	200 µL of different concentrations of the extract	Was used as a kind of herb as an antiproliferative agent in 3D fibrin gel against BC cell line	39

Table 2. Types of cell lines used in scaffold.

PLANT EXTRACT	CELL TYPES	SCAFFOLD TYPE	REF.
Curcumin	MCF-7	Electrospinning	61
Prodigiosin	MDA-MB-231 (TNBC) and MCF-7	Electrospinning	62
Curcumin + aloe vera + neem	MCF-7	Electrospinning	63
Curcumin + *Chrysin*	MDA-MB-231	Electrospinning	2
Garcinia mangostana + coconut water	B16F10 melanoma and MCF-7	Hydrogel	64
Annona muricata leaf extracts	MCF-7 and MDA-MB-231 and MCF10A	Electrospinning	65
Cur + Chr	T47D	Electrospinning	7
Lentinula edodes	MCF-7	Electrospinning	66
Piperine	MCF-7 and 4T1	Electrospinning	67
Amygdalin	MCF-7	Electrospinning	68
A hamosus	MCF-7	Hydrogel	39

Scaffolds made of nanofibrous materials are essential to tissue engineering. Although their stresses to failure are lower than those of human skin tissue, they have potential for covering wounds when immobilized at the site of the lesion, particularly in the absence of stress.[64] For soft tissue replacements to be successful, NFs and host skin/breast tissues must be mechanically compatible. Any discrepancy in mechanical characteristics could cause nutrient-deprivation problems, which would result in graft failure. Moreover, a crucial element is the way these scaffolds inflate. Elevated ratios of swelling, especially in specific cases, indicate the possibility of tissue fluid retention. Excessive swelling, however, could prevent nutrients from being transported or even displace implants, which would be problematic for practical use.[63] These scaffolds are intended for a wide range of uses. With an eye toward tissue regeneration, they are suggested to encourage the growth of normal breast tissues after regulated drug release. Furthermore, they have a promising ability to accelerate wound healing.[39]

All things considered, nanofibrous scaffolds exhibit exceptional adaptability in biological settings. Applications for these include possible use in tissue engineering and wound healing, as well as targeted drug delivery in cancer therapy. Even though there are obstacles to overcome, their ability to support wound healing and encourage tissue regeneration highlights how important they are to the advancement of biomedical research and applications.[62] On the contrary, not much is said about how patients receive these scaffolds inserted or how the body reacts to the procedure.[39,66] They emphasize how effective drug encapsulation and regulated release can reduce systemic toxicity and the chance of tumor recurrence.[65] However, a complete understanding of the practical implications of the medicines is hampered by the lack of data demonstrating clinical outcomes or patient reactions following therapy.[39] In a test on mice, all mice survived the procedure and both methods and treatments were well received as the mice showed minimal weight changes.[67]

Cell Types Used for Breast Cancer Treatment in 3D Models

In the realm of BC treatment, 3D models have proven invaluable, employing various cell types to advance our understanding. A roster of cell lines, including MCF-7, MDA-MB-231, MCF10A, T47D, MCF 10, MDAMB-468, HFF-1, 4T1, and MCF12A, are commonly harnessed to study treatment strategies.[26,65,69-71]

Diverse investigations have explored innovative approaches using these cell lines. One avenue involves electrospun scaffolds laden with *Annona muricata L* extract, tailoring for localized BC treatment using MCF-7 and MDA-MB-231 cell lines.[3] Similarly, NF films enriched with *Garcinia mangostana* peel extract have demonstrated efficacy against MCF-7 BC cells. Notably, the codelivery of curcumin and chrysin via electrospun NFs has showcased synergistic anticancer effects, targeting T47D BC cells.[64] Cell-based studies have delved into promising compounds, such as chromone-nitrogen mustard derivatives, revealing anti-BC potential against cell lines such as MCF-7, MDAMB-231, and MDA-MB-468. Meanwhile, innovative approaches employing tobacco mosaic virus-based protein nanoparticles and nanorods have probed chemotherapy delivery efficacy against MDA-MB-231 and MCF-7 cells.[12,72] Furthermore, the development of lentinan and docetaxel NFs has surfaced as a potential synergistic treatment for MCF-7 cells. These studies underscore the dynamic interplay between various cell types and treatment strategies within 3D models, contributing significantly to the advancement of BC research and potential therapeutic interventions[63] (Table 2).

Advantage of Plant Extract–Loaded Scaffolds in BC Models

In the field of biomedical research and therapeutics, the integration of natural compounds, particularly those derived from plants, into innovative medical applications has garnered significant attention. One prominent example of this integration is the utilization of plant extract–loaded scaffolds in BC models.[66] The inclusion of plant extracts, such as α-*mangostin*, in scaffolds designed for BC research offers several distinct advantages that contribute to their potential as a breakthrough in cancer therapy.[73]

Moreover, the utilization of lentinan, a natural compound, combined with conventional anticancer drugs within a nanodrug delivery system, emerges as a promising strategy for cancer treatment α-*mangostin*, renowned for its remarkable antibacterial properties, has demonstrated a higher potential for inhibiting the growth of Gram-positive bacteria than Gram-negative bacteria and yeast *Candida albicans*. It is noteworthy that the hydrophobic nature of drugs has been proven effective in treating Gram-positive bacterial infections.[64] Consequently, the exceptional antibacterial activity exhibited by the plant extract–loaded scaffolds against Gram-positive strains can be attributed to the high content of hydrophobic α-mangostin present in the ethanolic extract. This highlights the potential for these scaffolds to serve as a novel approach to combating bacterial infections in patients with BC.[74] Triple NFs loaded with polyvinyl alcohol (PVA)/lentinan/docetaxel significantly reduce the viability of human BC cells and down-regulate the expression of the HER3 gene, a member of the BC signaling pathway.[66]

While the effectiveness of conventional BC therapies such as Cur and Chr is well-established, their clinical utility is hampered by numerous challenges.[75] These challenges include poor water solubility, limited cellular uptake, low physicochemical stability, and rapid metabolism. To overcome these limitations, nanotechnological approaches have emerged as viable solutions. Plant extract–loaded NFs, characterized by their architecture and porosity, offer a means to enhance drug bioavailability and efficacy.[76] Moreover, the adaptability of drug-encapsulated NFs to conform to targeted regions holds promise for preventing local cancer recurrence post-resection. Notably, the choice of polymeric materials like poly (lactic-co-glycolic acid)/poly (ethylene glycol) (PLGA/PEG) further enhances the biocompatibility and biodegradability of the NFs, positioning them as a robust platform for drug delivery in BC therapy.[77]

An essential consideration in cancer treatment is the combination of drugs to enhance therapeutic outcomes while mitigating adverse effects. The heterogeneity of cancer cells and drug resistance necessitate combination therapies. This underscores the significance of using plant extract–loaded composite NFs for combination therapy, as they offer improved mechanical properties, thermal stability, and controlled release profiles. By mitigating initial burst release and enhancing antitumor effects, these composite NFs contribute to the advancement of BC treatment strategies.[78]

Limitations and Challenges

In the realm of developing plant extract–loaded scaffolds for BC research, several limitations and challenges warrant consideration. While collagen-based 3D in vitro models have propelled BC research, they fall short in replicating the intricate ECM of BC accurately.[79,80] Overcoming this limitation requires leveraging recent advances in bio-fabrication techniques to create biomimetic 3D BC scaffolds that more closely mimic the ECM's complexity and dynamics. Poor water solubility, rapid degradation, and low systemic stability hinder their clinical application.[38]

A notable challenge arises in the fabrication of electrospun fibers for drug delivery systems. Despite its advantages, routine blend electrospinning encounters hurdles such as burst release during initial drug delivery stages and difficulties in achieving sustained, long-term drug release.[81] This necessitates the development of implantable drug delivery systems based on electrospun NFs capable of sustained therapeutic molecule release over extended periods. In this regard, force spinning emerges as an alternative technique, harnessing centrifugal force to draw fibers and addressing limitations associated with traditional electrospinning, thereby improving production rates, material selection, and overall commercial viability.[7]

Furthermore, in vivo animal models, while informative, may not fully represent human responses due to size differences, genetic variations, and immune system disparities. Ethical concerns and limitations in replicating the tumor microenvironment also complicate animal trials.[82]

The incorporation of surfactants like pluronic F127 in scaffold fabrication presents a dual challenge. While surfactants enhance drug loading capacity and prolong the release profile, they also impact burst release dynamics.[62] Balancing the advantages and drawbacks of surfactant integration is crucial to achieving optimal sustained-release profiles. Moreover, the design of scaffolds should prioritize biocompatibility, mechanical properties, and the promotion of cell proliferation. Achieving a favorable combination of these characteristics remains a challenge.[38] Despite the strides made in plant extract–loaded scaffolds, challenges persist in clinical translation. Validating the efficacy and safety of these scaffolds in complex biological environments and diverse patient populations requires rigorous testing. Furthermore, achieving consistent and reproducible results across different plant extracts, scaffold designs, and cancer types poses a significant challenge.[44] In conclusion, while plant extract–loaded scaffolds hold immense promise for advancing BC research and therapy, addressing limitations and overcoming challenges will be instrumental in realizing their full potential. A multidisciplinary approach encompassing materials science, drug delivery, and cancer biology is essential to navigate these complexities and drive progress in the field.[83]

Conclusion

Plant extract–loaded scaffolds offer a promising alternative in BC therapy. They provide precise drug delivery, reducing side effects compared with conventional treatments. Recent research demonstrates their efficacy in reducing tumor size. This innovative approach has the potential to revolutionize BC treatment by combining phytochemicals and advanced drug delivery techniques, addressing longstanding challenges in traditional therapies, and preventing local cancer recurrence after surgery.

Author's Note

Morteza Alizadeh is now affiliated to Department of Tissue Engineering and Biomaterials, School of Advanced Medical Sciences and Technologies, Hamadan University of Medical Sciences, Hamadan, Iran.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Reyhaneh Azhari Rad: Investigation; Writing – original draft.
Yasaman Naghdi: Investigation; Writing – original draft.
Mobina Majidi Jamalabadi: Investigation; Writing – original draft.
Sima Masoumi: Investigation; Writing – original draft.
Leila Rezakhani: Investigation; Project administration; Writing – original draft; Writing – review & editing.
Morteza Alizadeh: Investigation; Project administration; Writing – original draft; Writing – review & editing.

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Availability of data and materials

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

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