



Contents lists available at SciOpen

Food Science and Human Wellness

journal homepage: <https://www.sciopen.com/journal/2097-0765>

Natural polysaccharides as promising biologics from traditional medicine: Next-generation therapeutic strategies for breast diseases

Song Wei ^a, Yi Li ^a, Xiujuan Li ^{b,*}, Fulei Liu ^{c,d,*}, Jingwei Xue ^{c,d,*}

^a School of Pharmacy, Qingdao University, Qingdao 266021, China.

^b Pharmaceutical Department, The Affiliated Taian City Central Hospital of Qingdao University, Taian, 271000, China.

^c Tumor Precise Intervention and Translational Medicine Laboratory, The Affiliated Taian City Central Hospital of Qingdao University, Taian, 271000, China.

^d Shandong Provincial Key Medical and Health Laboratory of Microenvironment Response Biomedical Materials, Taian City Central Hospital, Taian, 271000, China

ABSTRACT: Breast diseases (such as mastitis, mammary hyperplasia, and breast cancer) pose serious threats to women's health, necessitating the development of safe and effective treatment strategies. Natural polysaccharides have attracted considerable attention due to their unique biocompatibility, low toxicity, and multifaceted bioactivities, including antimicrobial, anti-inflammatory, immunomodulatory, and antitumor effects. This review systematically examines the therapeutic potential and mechanisms of natural polysaccharides and their derivatives in breast diseases. For mastitis, polysaccharides alleviate symptoms by modulating gut microbiota, exerting direct antibacterial effects, and providing antioxidative and anti-inflammatory protection. Polysaccharide-based nanomaterials further enhance diagnostic sensitivity, drug-targeting efficiency, and antibacterial performance. In mammary hyperplasia, polysaccharides intervene by regulating gut microbiota homeostasis, inhibiting abnormal cell proliferation, and exerting antioxidative and antifibrotic effects. In breast cancer treatment, polysaccharides not only directly suppress tumor cell proliferation, migration, apoptosis, and autophagy but also enhance antitumor immunity through immunomodulation. Moreover, polysaccharide-based biomaterials as drug carriers significantly improve the targeting ability and synergistic therapeutic efficacy of chemotherapeutic agents. Although natural polysaccharides demonstrate promising potential in breast disease management, their precise mechanisms of action, structural optimization, and clinical translation require further investigation. Future research integrating nanotechnology and multidisciplinary approaches may establish polysaccharides as a groundbreaking strategy for precision therapy in breast diseases.

Keywords: natural polysaccharides, breast diseases, nanomaterials, targeted therapy

1. Introduction

Breast diseases, as a major threat to women's health, present numerous challenges in clinical treatment. Mastitis, one of the most common breast disorders, can be classified into infectious and non-infectious types based on etiology. Infectious mastitis is primarily caused by pathogenic microorganisms such as *Staphylococcus aureus*, *Streptococcus spp.*, and *Escherichia coli*. While antibiotics remain the mainstay

*Corresponding author

lixujuan2@qdu.edu.cn (Xiujuan Li), liu_fulei@126.com (Fulei Liu)
xuejingwei1111@163.com (Jingwei Xue).

Received 7 November 2025

Received in revised form 19 December 2025

Accepted 23 January 2026

treatment, a growing body of evidence challenges the assumption that antibiotic efficacy can be sustained in the long term. The increasing problem of antimicrobial resistance has significantly compromised therapeutic efficacy. Studies have shown that the proportion of mastitis cases caused by methicillin-resistant *Staphylococcus aureus* (MRSA) increased markedly between 2000 and 2020 ^[1], substantially reducing the effectiveness of conventional antibiotics. Furthermore, antibiotic treatment leads to microbial dysbiosis and drug residue accumulation, particularly in livestock production where antibiotic overuse has become a global public health concern due to the spread of resistant strains ^[2]. Despite advances in diagnostics, a key unresolved debate centers on whether antibiotic treatment protocols should be tailored more precisely based on rapid pathogen identification versus relying on broad-spectrum empirical therapy in the absence of timely microbiological data. In China, the “Chinese Guidelines for the Diagnosis and Treatment of Lactational Mastitis” emphasize standardized early management (e.g., effective milk drainage and correction of breastfeeding techniques) and advocate rational antibiotic use according to clinical severity and, when possible, etiological evidence, to reduce unnecessary antibiotic exposure ^[3]. Non-infectious mastitis, associated with lactational duct obstruction, autoimmune responses, or hormonal imbalances, has more limited treatment options. Current management relies primarily on anti-inflammatory medications and symptomatic relief. However, long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) may cause gastrointestinal adverse effects and renal impairment ^[4]. Mammary hyperplasia and benign breast nodules, another common benign condition, are closely linked to imbalances in estrogen and progesterone levels, manifesting as excessive tissue proliferation and structural disorganization. Current therapies include hormonal modulators such as tamoxifen and danazol, but these drugs often induce side effects like hot flashes and menstrual irregularities, with recurrence rates reaching 40-60% after discontinuation ^[5]. Notably, atypical hyperplasia may progress to breast cancer in some cases ^[6], underscoring the critical need for safer and more effective prevention and treatment strategies. A Chinese expert consensus on breast hyperplasia further highlights the lack of unified concepts and classification in practice, and recommends standardized diagnosis, individualized management, and appropriate follow-up to improve outcomes and avoid overtreatment ^[7].

Breast cancer, the most prevalent malignant tumor among women worldwide, poses even more complex therapeutic challenges. According to the World Health Organization (WHO) 2022 Global Cancer Statistics Report, the number of new breast cancer cases has exceeded 2.3 million, accounting for 11.7% of all malignancies ^[8], with incidence rates showing a year-on-year increase. Current breast cancer treatment primarily follows a comprehensive model combining surgical resection with adjuvant therapies ^[9], where chemotherapy, radiotherapy, and targeted therapy serve as the three main approaches. However, there is ongoing debate regarding whether this traditional tri-modal approach adequately addresses tumor heterogeneity and the dynamic evolution of cancer clones during treatment. Chemotherapeutic agents such as paclitaxel and doxorubicin exert antitumor effects by interfering with tumor cell mitosis or DNA replication. However, their severe toxic side effects, such as myelosuppression, cardiotoxicity, and neurotoxicity, significantly limit their clinical application ^[10]. Although radiotherapy effectively controls local lesions, it

may cause complications such as radiation dermatitis and pulmonary fibrosis ^[11] and remains ineffective against distant metastases. Molecular targeted therapies, including trastuzumab for HER2-positive tumors and aromatase inhibitors (AIs) for hormone receptor-positive subtypes, have significantly improved outcomes for specific patient groups ^[12]. Nevertheless, primary or acquired drug resistance has become an increasingly prominent issue. An emerging critical discussion questions whether the current focus on monotherapy or dual-target approaches sufficiently tackles the complex signaling crosstalk and adaptive resistance mechanisms in advanced breast cancer, urging a paradigm shift toward more integrative and adaptable therapeutic strategies. These therapeutic dilemmas are driving researchers to explore novel strategies, particularly those involving natural bioactive compounds with multi-target mechanisms, low toxicity, and high safety profiles.

Against this backdrop, natural polysaccharides have emerged as a research hotspot due to their unique structural characteristics and extensive biological activities. These high-molecular-weight polymers, composed of more than ten monosaccharide units linked by glycosidic bonds, are widely distributed in plants (e.g., *Astragalus membranaceus*, *Ginseng*, *Ganoderma lucidum*), animals (e.g., chitosan from crustaceans), and microorganisms (e.g., β -glucans from yeast cell walls), with their bioactivities being closely associated with monosaccharide composition, glycosidic bond types, branching degrees, and functional modifications (e.g., sulfate, acetyl, and phosphate groups). Structural studies have demonstrated that β -glucans exhibit remarkable immunomodulatory properties ^[13], sulfated polysaccharides show excellent anticoagulant and antiviral capacities ^[14, 15], while acidic polysaccharides like hyaluronic acid display favorable moisturizing and anti-inflammatory characteristics ^[16]. Recent studies further illustrate how structural engineering can enhance polysaccharide functionality; for instance, ultrasonic complexation with *Lycium barbarum* polysaccharide significantly improves the aqueous solubility and bioavailability of curcumin, which may expand its utility in breast cancer therapy by enhancing drug delivery efficiency ^[17]. Recent comprehensive reviews have systematically summarized the hepatoprotective efficacy and underlying molecular mechanisms of polysaccharides extracted from traditional Chinese medicinal herbs, highlighting their significant anti-inflammatory capabilities with minimal adverse effects and their intricate regulatory functions in disease management ^[18, 19]. In breast disease treatment, natural polysaccharides demonstrate multifaceted therapeutic advantages: immunologically, they enhance innate and adaptive immune responses by activating Toll-like receptors (TLRs) and complement system, promoting macrophage polarization toward antitumor M1 phenotype ^[20] and boosting natural killer (NK) cell activity ^[21]; antioxidatively, they directly scavenge free radicals while activating the Nrf2/ARE pathway to upregulate antioxidant enzymes like superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) ^[22, 23]; anti-inflammatorily, they suppress NF- κ B and MAPK signaling pathways to reduce pro-inflammatory cytokines such as TNF- α and IL-6 ^[24]; and microbiologically, certain polysaccharides act as prebiotics to promote beneficial gut microbiota proliferation, thereby modulating the mammary microenvironment through the "gut-mammary axis" ^[25]. Additionally, systematic reviews on medicinal and edible fungi highlight the broad bioactivity spectrum of polysaccharides from

sources such as *Poria cocos* and *Ganoderma*, which encompass immunomodulation, anti-tumor, and gut-microbiota-regulating effects, further supporting their potential role in breast disease management [26].

Furthermore, polysaccharide-based biomaterials have demonstrated multifunctional clinical value in breast disease treatment, showing particular advantages for mastitis and breast cancer management. In mastitis diagnosis and treatment, polysaccharide nanomaterials such as chitosan/chondroitin sulfate or chitosan/sericin layer-by-layer (LbL) films have been applied in microfluidic gene sensors to identify *Staphylococcus aureus*-specific DNA with exceptional sensitivity and selectivity [27]. Meanwhile, chitosan nanocarriers have significantly enhanced antibiotic concentration at infection sites through targeted delivery [28]. Compared to natural chitosan, nano-formulated Ch-NPs exhibit superior penetration capacity and cell membrane disruption ability, effectively damaging bacterial cell structures, inhibiting proliferation, and interfering with biofilm formation and stability [29]. For breast cancer therapy, polysaccharide materials with surface modifications (e.g., hyaluronic acid targeting CD44 receptors) have markedly improved tumor targeting of chemotherapeutic drugs like paclitaxel while reducing systemic toxicity [30]. Systems like PEGylated PLGA nanoparticles co-loaded with *Astragalus* polysaccharides and gold nanorods have significantly enhanced tumor ablation efficiency and antitumor immune responses by augmenting focused ultrasound's thermal effects and immune activation [31]. Researchers have also developed a nano-photosensitizer (COI) through self-assembly of oleanolic acid-modified chitosan (CsO) and indocyanine green (ICG), which synergizes chemotherapy with photothermal therapy by improving tumor penetration and photothermal stability, thereby significantly enhancing treatment efficacy for deep-seated tumors [32]. These properties establish polysaccharide-based materials as ideal carriers for precision therapy in breast diseases, with their excellent biocompatibility and biodegradability further ensuring clinical safety. Beyond cancer-specific applications, the broader bioactivity profile of polysaccharides, which includes their documented hypoglycemic, antioxidative, and gut-modulatory effects, may also contribute to managing metabolic and inflammatory comorbidities in breast cancer patients. This supports the development of holistic therapeutic strategies [33].

In conclusion, natural polysaccharides have brought new hope for treating mastitis, mammary hyperplasia, breast nodules, and breast cancer through their unique bioactivities and low toxicity. With ongoing research advancements, they are expected to become an important complementary approach in breast disease management, offering patients safer and more effective therapeutic strategies.

2. Methodology

A systematic literature search was conducted to identify research and review articles pertaining to the therapeutic potential of natural polysaccharides in breast-related conditions, including mastitis, mammary hyperplasia, and breast cancer. Several online databases were comprehensively searched, including PubMed, Web of Science, ScienceDirect, and Google Scholar. Additionally, a manual search of the reference lists from identified relevant papers was performed to ensure thorough coverage. This process resulted in the documentation of approximately 150 related references, spanning from foundational studies to the latest research available until 2025.

The following keywords were queried individually and in combination to identify research pertinent to this review: “natural polysaccharides,” “mastitis,” “mammary hyperplasia,” “breast cancer,” “immunomodulation,” “targeted drug delivery,” “gut microbiota modulation,” “antioxidant,” “anti-inflammatory,” “antibacterial,” “polysaccharide-based nanomaterials,” “diagnosis,” and “anti-breast cancer.” We included primarily English-published articles and books that reported findings directly applicable to the subjects under review. We included only English-published articles and books that reported results applicable to this review subject.

3. Mechanisms and targeted therapy of natural polysaccharides in mastitis

3.1 Regulatory mechanisms of natural polysaccharides in mastitis

Natural polysaccharides demonstrate multi-pathway synergistic effects in mastitis treatment through their unique structural diversity: (1) Gut microbiota modulation: Acting as prebiotics to promote the proliferation of beneficial bacteria (e.g., *Lactobacillus*) and reduce mammary tissue inflammation via the "gut-mammary axis"; (2) Direct antibacterial action: Disrupting pathogen biofilms (e.g., *Staphylococcus aureus*) and inhibiting their adhesion and invasion; (3) Antioxidant activity: Scavenging ROS and upregulating the Nrf2/HO-1 pathway to alleviate oxidative stress damage; (4) Anti-inflammatory effects: Blocking NF- κ B signaling and downregulating pro-inflammatory factors such as TNF- α and IL-1 β . This trinity regulatory mode targeting "microecology-pathogen-host response" provides novel insights for developing green mastitis therapeutics without antibiotic residues, particularly suitable for bovine mastitis control and lactational mastitis management.

3.1.1 Gut microbiota modulation

Natural polysaccharides exert potential therapeutic effects in mastitis through modulation of the gut microbiota (gut-mammary axis). Their soluble fibers are fermented by intestinal microorganisms to produce short-chain fatty acids (e.g., butyrate), which enhance intestinal barrier function, reduce endotoxin translocation, and consequently mitigate systemic inflammation. Simultaneously, polysaccharide-regulated probiotics (e.g., *Lactobacillus*, *Bifidobacterium*) promote immune homeostasis by suppressing pro-inflammatory cytokines (e.g., IL-6, TNF- α) and migrate to mammary tissue via the gut-mammary axis, competitively inhibiting pathogenic bacterial colonization. This trans-organ immunomodulatory mechanism provides an eco-friendly therapeutic strategy for mastitis, highlighting the crucial role of "microbiota-host" interactions in mammary health.

Polysaccharides from *Angelica sinensis* (ASP) have been demonstrated to significantly alleviate *Staphylococcus aureus*-induced mastitis in murine models, primarily through gut microbiota modulation. Research reveals that oral ASP administration not only increases the abundance of beneficial bacteria (e.g., *Lachnospiraceae_NK4A136*) while reducing pathogenic *Erysipelatoclostridium*, but also elevates anti-inflammatory metabolites like tabersonine and riboflavin through metabolic pathway alterations, thereby mitigating mammary inflammation. Crucially, the anti-inflammatory effects of ASP were correspondingly

diminished or transferred when gut microbiota was disrupted by antibiotics or through fecal microbiota transplantation (FMT), further confirming the pivotal role of intestinal flora in its therapeutic mechanism [34]. Similar effects have been observed with Pomegranate flower polysaccharides (PFPS). PFPS not only inhibits the release of inflammatory factors (e.g., $\text{TNF-}\alpha$ and $\text{IL-1}\beta$) in vitro, but also significantly improves inflammatory and oxidative stress status in mammary tissue in vivo. These effects are equally dependent on gut microbiota regulation: PFPS effectively suppresses pathogenic bacteria (e.g., *Oscillospira* and *AF12*) while enhancing the proportion of beneficial bacteria like *Butyricimonas* and *Parabacteroides*, thereby maintaining intestinal microecological balance and indirectly improving blood-milk barrier (BMB) function to exert anti-mastitis effects [25]. Furthermore, *Astragalus* polysaccharides (APS) have been shown to promote the enrichment of *Ruminococcus bromii*, thereby increasing short-chain fatty acid (SCFA) levels (e.g., acetate and butyrate) - metabolites that play crucial roles in suppressing *S. aureus*-induced inflammatory responses and restoring BMB integrity. Through gut microbiota depletion and FMT experiments, the therapeutic effects of APS have been further attributed to its specific regulatory capacity on intestinal flora (Fig. 1) [35].

In summary, natural polysaccharides effectively alleviate mastitis and associated pathological changes by remodeling gut microbiota composition and function, activating beneficial metabolite production, and regulating inflammatory factor release and oxidative stress responses. This mechanism not only offers novel perspectives for mastitis treatment but also establishes a theoretical foundation and practical approach for intervening in other inflammatory diseases, demonstrating the broad prospects of natural polysaccharides as gut-targeted therapeutic agents.

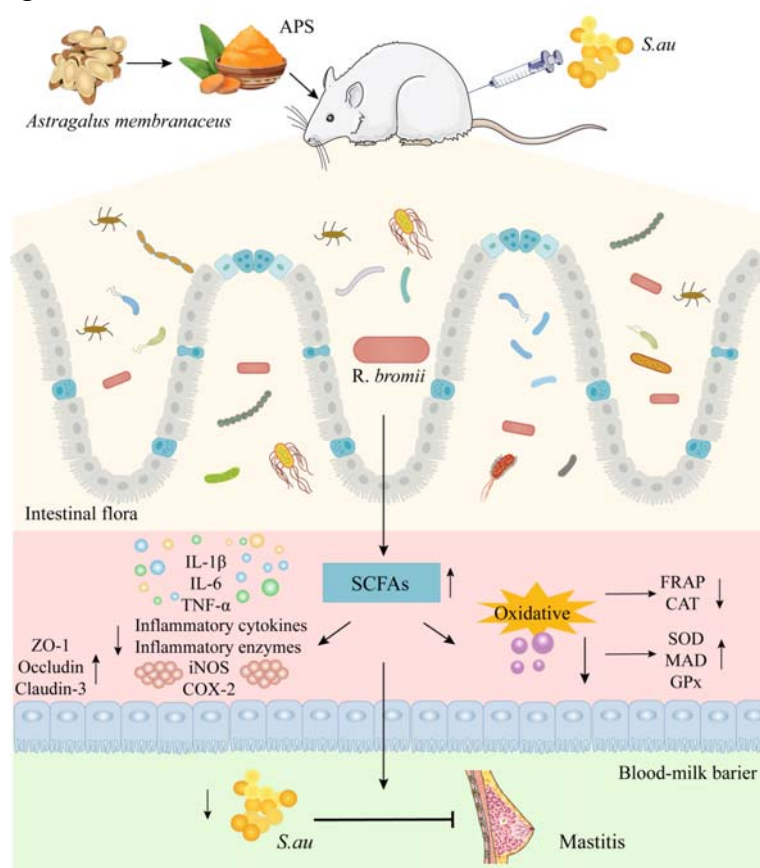


Fig. 1. APS alleviated mastitis disrupted by *Staphylococcus aureus* infection by regulating gut microbiota and SCFAs metabolism.

3.1.2 Antibacterial effects

Staphylococcus aureus has been identified as one of the primary pathogenic factors in mastitis, with its virulence manifested not only through infectivity but also via biofilm formation that enhances drug resistance and complicates treatment. In this context, natural polysaccharides are emerging as novel candidates for antibacterial mastitis therapy due to their broad-spectrum antimicrobial activity and excellent biocompatibility. Research has demonstrated that *Salvia miltiorrhiza* polysaccharides (SMP) exhibit significant anti-*S. aureus* activity. In rat models, SMP effectively reduces bacterial colonization in mammary tissue and inflammatory cell recruitment while markedly suppressing pro-inflammatory cytokines (e.g., IL-1 β , IL-6, TNF- α). By inhibiting NF- κ B and MAPK signaling pathway activation, SMP alleviates mammary tissue damage and inflammatory responses, highlighting its potential for mastitis prevention and treatment [36]. On the other hand, modified chitosan-oligosaccharides (OCHT), with improved water solubility and deacetylation degree, demonstrate enhanced antibacterial efficacy against *S. aureus*. Importantly, structural features such as low molecular weight and a high deacetylation degree are key factors contributing to OCHT's potent activity. These features increase positive charge density and enhance interaction with negatively charged bacterial cell membranes. Experimental evidence shows that OCHT rapidly inhibits bacterial growth, inducing destructive morphological changes such as cell swelling, deformation, and lysis under microscopic observation. Additionally, OCHT activates host immune responses by increasing monocyte ratios and pro-inflammatory cytokines (e.g., IL-6, IFN- γ), thereby improving survival rates in infected animal models. This dual mechanism, which combines direct bactericidal action with immunomodulation, positions OCHT as a highly promising natural antibacterial polysaccharide [37]. Notably, chronic recurrent mastitis is closely associated with bacterial biofilms formed by *S. aureus* and other pathogens. Low-molecular-weight chitosan (LMW-CS) exhibits distinctive advantages in this regard, which are largely attributed to its specific structural characteristics, such as lower molecular weight that enhances penetration into biofilm matrices. Studies confirm that LMW-CS not only inhibits *S. aureus* and *Streptococcus xylosus* growth in a dose-dependent manner but also suppresses biofilm formation, reduces viability, and disrupts pre-existing biofilm structures. These broad-spectrum anti-biofilm effects, observed at relatively low concentrations, highlight the structure-dependent efficacy of LMW chitosan against staphylococcal infections. This anti-biofilm capability offers a novel strategy for managing chronic mastitis [38].

In summary, natural polysaccharides—including *Salvia* polysaccharides, chitosan oligosaccharides, and their low-molecular derivatives—demonstrate compelling efficacy against *S. aureus* and other mastitis pathogens through multifaceted mechanisms: direct bactericidal effects, immunomodulation, and biofilm inhibition. These findings provide both scientific rationale and practical foundations for integrated mastitis control, underscoring the potential of polysaccharides as alternative antimicrobial therapeutics.

3.1.3 Antioxidant and anti-inflammatory activities

Natural polysaccharides demonstrate considerable therapeutic potential for mastitis treatment due to their anti-inflammatory and antioxidant properties, particularly in bovine mastitis induced by *Escherichia coli* (*E. coli*) or lipopolysaccharide (LPS). Their multifaceted bioactive mechanisms provide scientific rationale for developing natural antibiotic-alternative strategies. *Lycium barbarum* polysaccharides (LBP), as a potent plant-derived polysaccharide, exhibit remarkable immunomodulatory and anti-aging effects while significantly mitigating inflammation and oxidative stress. Research has revealed that LBP effectively suppresses inflammatory cascades and oxidative damage in primary bovine mammary epithelial cells (pbMECs) or bMECs challenged with *E. coli*/LPS by upregulating SOCS3 expression, activating peroxisome proliferator-activated receptor γ (PPAR γ) signaling, while concurrently inhibiting MAPK and NF- κ B pathways. Specifically, LBP significantly reduces pro-inflammatory mediators (IL-1 β , TNF- α , COX-2), decreases ROS and MDA production, and enhances antioxidant enzyme activities (SOD, T-AOC), thereby preserving mammary tissue integrity at cellular level. Moreover, LBP demonstrates restorative potential by rescuing proliferation capacity in LPS-injured mammary cells [22]. Complementing LBP, chitosan oligosaccharides (COS) serve as natural antioxidants and anti-inflammatory agents, exhibiting exceptional efficacy against LPS-induced mammary epithelial cell inflammation. COS not only downregulates TLR4 and downstream inflammatory factors but also activates the Nrf2 pathway to bolster cellular antioxidant defenses and reduce ROS accumulation, ultimately alleviating cellular stress. Through dual modulation of TLR4/NF- κ B and Nrf2 pathways, COS provides comprehensive mammary cell protection, with its natural origin and safety profile making it an ideal adjuvant for mastitis therapy [23]. Lentinan, another bioactive polysaccharide, has been experimentally validated to inhibit LPS-induced inflammatory responses both *in vitro* and *in vivo*. By modulating the Wnt/ β -catenin pathway, it effectively reduces inflammatory factor expression and mammary tissue pathology, suggesting therapeutic value not only for acute mastitis but also potential prophylactic benefits against chronic conditions. This mechanism, distinct from conventional NF- κ B or MAPK pathway modulation, offers novel anti-inflammatory targeting strategies [24].

In summary, natural polysaccharides exert synergistic effects in alleviating inflammatory responses and oxidative stress in mastitis through their multi-pathway regulatory capabilities—simultaneously reducing the synthesis and secretion of pro-inflammatory factors while restoring antioxidant system functionality. Particularly in the current context where mastitis treatment faces increasing challenges of antibiotic resistance, representative polysaccharides such as LBP, COS, and lentinan demonstrate unparalleled advantages: they are safe, non-toxic, widely available, and exhibit multi-target, multi-mechanism therapeutic properties. These characteristics position them as innovative solutions for the eco-friendly prevention and control of bovine mastitis. With further validation through clinical and field trials, these polysaccharides are expected to emerge as promising candidate therapeutics for mastitis, thereby advancing the naturalization and sustainable development of animal health management practices.

3.2 The applications of polysaccharide-based nanomaterials in mastitis

Polysaccharide-based nanomaterials have emerged as a groundbreaking solution for precision diagnosis and treatment of mastitis, leveraging their exceptional biocompatibility and tunable functionality. In diagnostic applications, chitosan-carbon nanotube composite immunosensors enable specific identification and imaging of mastitis pathogens (e.g., *Staphylococcus aureus*). For targeted therapy, chitosan/alginate nanocarriers achieve precise antibiotic (e.g., cephalosporins) delivery to infection sites through pH-responsive or enzyme-triggered release mechanisms, significantly enhancing local drug concentrations. More remarkably, these polysaccharide nanomaterials possess intrinsic antimicrobial enhancement properties - cationic chitosan nanoparticles disrupt bacterial membrane integrity while selenized dextran amplifies bactericidal effects through reactive oxygen species (ROS) generation. This integrated "diagnosis-treatment-antimicrobial" smart nano-platform represents a novel approach for effective mastitis management, particularly valuable for combating drug-resistant clinical mastitis cases.

3.2.1 Mastitis diagnosis

In recent years, the rapid development of nanotechnology and biosensing has demonstrated the tremendous potential of polysaccharide-based nanomaterials for early mastitis diagnosis. Mastitis, a disease severely affecting dairy cow lactation performance, is frequently caused by pathogens such as *Staphylococcus aureus* (*S. aureus*), making highly sensitive and specific rapid detection crucial for accurate diagnosis. Polysaccharides including chitosan, chondroitin sulfate, and sericin have been extensively employed in constructing nanostructured sensor platforms due to their excellent biocompatibility, film-forming properties, and functionalization capacity. For instance, layer-by-layer (LbL) films fabricated from chitosan/chondroitin sulfate or chitosan/sericin combinations have been incorporated into microfluidic genetic sensors for *S. aureus*-specific DNA detection, achieving an exceptional detection limit of 5.90×10^{-19} mol/L with outstanding sensitivity and selectivity [27].

Beyond genetic sensors, researchers have developed electronic tongue technology utilizing impedance spectroscopy to analyze *S. aureus* DNA. This system employs sensing units composed of multilayer films from diverse polysaccharide combinations, with machine learning algorithms enabling data interpretation and bacterial concentration differentiation. Although slightly less specific than genetic sensors, the electronic tongue attains 66% accuracy through multidimensional calibration space (MCS) construction, offering a simpler and more cost-effective screening alternative for resource-limited settings [27].

Further research has revealed that immunosensors combining chitosan with carbon nanotubes can achieve an ultra-low detection limit of 2.6 CFU/mL in complex milk matrices. This exceptional sensitivity originates from the specific binding between antibodies and *Staphylococcus aureus*, coupled with electrochemical impedance spectroscopy and PM-IRRAS techniques, enabling reliable identification of trace pathogens even in the presence of interfering substances like lactose and milk fat. Through decision tree modeling for impedance data learning and classification, this sensor system demonstrates not only outstanding sensitivity but also remarkable interference resistance and interpretability [39]. Notably, integrating electronic tongue technology with machine learning methods can further enhance the discriminative capability of

polysaccharide nanosensors. For instance, by establishing 6-dimensional or 7-dimensional multivariate calibration spaces, these systems achieve 94%-100% accuracy in classifying *S. aureus* contamination from different sources in raw milk, maintaining excellent recognition performance even with diluted samples or drug-treated specimens [40].

In conclusion, polysaccharide-based nanomaterials have revolutionized mastitis diagnostics by creating functionalized sensing interfaces that significantly improve detection sensitivity and selectivity. These advancements provide essential material and technical support for developing portable, low-cost, on-site rapid detection devices. As these technologies undergo further optimization and integration, polysaccharide nanosensors are expected to enable early and precise mastitis diagnosis directly on dairy farms, substantially enhancing the efficiency and accuracy of herd health management.

3.2.2 Targeted drug delivery

Polysaccharide-based nanomaterials are emerging as promising drug delivery systems for mastitis treatment due to their excellent biocompatibility, biodegradability, and drug-loading capacity. Conventional antibiotic therapy faces challenges including short half-life in mammary tissue and difficulty maintaining effective drug concentrations, particularly exacerbated by frequent milking during lactation. To address these limitations, researchers have developed polysaccharide-based nanodrug delivery systems. For instance, chitosan nanoparticles encapsulating ciprofloxacin achieve sustained release, enhancing drug stability and bioavailability at infection sites. Experimental studies have demonstrated that these nanoparticles exhibit potent antibacterial activity against clinically isolated *Escherichia coli* and *Staphylococcus aureus* strains with low toxicity, showing dose-dependent antimicrobial efficacy [28].

Particularly in controlling *S. aureus* biofilms, polysaccharide-based nanodrug systems demonstrate unique advantages. Chloroxillin-loaded chitosan nanoparticles (CLX-CS NPs) have shown remarkable performance *in vitro*, significantly reducing minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) while effectively penetrating and inhibiting biofilms formed by clinical mastitis isolates. This enhanced targeted drug delivery approach not only improves therapeutic efficacy but also helps delay the development of antibiotic resistance [41].

Recent studies have further demonstrated that polysaccharide-based nanomaterials can serve not only as antibiotic carriers but also as delivery vehicles for natural antimicrobial compounds. For instance, berberine hydrochloride (BH), a plant-derived antibacterial agent, has been successfully incorporated into carboxymethyl chitosan hydrogels (BH-CMCH). This formulation not only prolongs drug retention at infection sites but also significantly reduces *S. aureus* bacterial load in mammary tissue during *in vivo* experiments. The system simultaneously activates lysosomal pathways and enhances host innate immune responses. These thermosensitive, injectable hydrogel materials exhibit substantial clinical potential [42].

Additionally, to minimize antibiotic usage, researchers have developed novel drug delivery systems combining chitosan nanoparticles with thermosensitive hydrogels (e.g., BLfcin-NPs@CS/ β -GP) for encapsulating bovine lactoferrin nanoparticles. The system demonstrates excellent antibacterial activity,

temperature responsiveness, and biodegradability in vitro, along with low cytotoxicity, offering a safe and effective alternative to conventional antibiotics [43].

In summary, polysaccharide-based nanomaterials significantly enhance therapeutic efficacy at infection sites by improving drug stability, targeting capability, and sustained-release properties. They provide ideal solutions for controlling biofilm infections and reducing antibiotic dependence. With ongoing advancements in intelligent drug-loading systems and targeted delivery strategies, polysaccharide nano-platforms are expected to play an increasingly pivotal role in preventing and treating major livestock diseases such as mastitis.

3.2.3 Enhanced antibacterial performance

Chitosan, a natural polysaccharide, has been extensively investigated in mastitis treatment in recent years due to its excellent biocompatibility, biodegradability, and inherent antimicrobial properties. These advantages are particularly pronounced when chitosan is formulated into polysaccharide-based nanomaterials. Staphylococci, especially *Staphylococcus aureus* (*S. aureus*), represent primary mastitis pathogens capable of forming biofilms within mammary tissue, thereby evading both host immune defenses and antibiotic attacks, resulting in chronic, refractory persistent infections. In this context, chitosan nanoparticles (Ch-NPs or NQo) have emerged as novel natural antimicrobial materials offering innovative solutions to overcome the limitations of conventional antibiotic therapy [44].

Research has demonstrated that chitosan nanoparticles prepared via reverse micelle or ionotropic gelation methods exhibit ultra-small particle sizes (typically 20-30 nm) and strong positive surface charges (e.g., +55.4 mV). These physicochemical characteristics endow them with superior bacterial targeting capability and cell membrane affinity. Ch-NPs display dose-dependent antimicrobial activity against mastitis-associated pathogens including *S. aureus* and *Pseudomonas spp.* Compared to native chitosan, nano-formulated Ch-NPs possess enhanced penetration capacity and membrane disruption ability, effectively damaging bacterial cellular structures, inhibiting proliferation, and interfering with biofilm formation and stability. Experimental evidence confirms that while maintaining bovine mammary cell viability, Ch-NPs significantly inhibit biofilms of clinical *S. aureus* isolates and can even eradicate established mature biofilms [29].

Moreover, Ch-NPs have demonstrated remarkable efficacy against highly drug-resistant environmental pathogens like *Pseudomonas spp.* While conventional antibiotics often fail to treat such infections effectively, Ch-NPs successfully inhibit and eradicate *Pseudomonas* biofilms through their unique anti-biofilm mechanisms, significantly improving therapeutic outcomes. Their antibacterial performance has shown outstanding results across multiple evaluation methods, including disk diffusion assays, minimum inhibitory concentration (MIC), and minimum bactericidal concentration (MBC) tests [45].

In summary, chitosan represents not only an abundant and naturally safe polysaccharide but also, in its nano-formulated state, exhibits broad application potential for antimicrobial mastitis therapy. It effectively inhibits and destroys pathogenic bacteria, particularly stubborn biofilm-forming strains, while potentially

reducing antibiotic dependence and associated resistance development. Looking ahead, integrating chitosan nanoparticle delivery systems with localized controlled-release technologies and hydrogel platforms promises to develop more efficient, safer, and sustainable mastitis treatment strategies, thereby advancing the dairy industry toward greener and healthier practices.

4. Therapeutic mechanisms of natural polysaccharides in mammary hyperplasia

In recent years, the incidence of mammary gland hyperplasia (MGH) has been steadily increasing, making it one of the most significant diseases affecting women's health. MGH primarily results from estrogen-progesterone imbalance, with a complex pathogenesis involving multiple pathological processes including endocrine dysfunction, abnormal cell proliferation, inflammatory responses, and fibrosis. With the ongoing development of the "gut-mammary axis" theory, the role of gut microbiota in regulating mammary function and disease development has gained increasing attention. Natural polysaccharides, as widely available, highly safe, and biologically active substances, have demonstrated remarkable intervention effects in multiple MGH-related studies, primarily manifesting through multiple mechanisms including gut microbiota modulation, inhibition of abnormal cell proliferation, and antioxidant/anti-fibrotic effects.

Firstly, polysaccharides indirectly alleviate MGH symptoms by regulating gut microbiota and improving hormonal balance. For instance, *Atractylodes Macrocephala* Rhizoma polysaccharides (AMP) significantly reduce estradiol (E₂) and prolactin (PRL) levels while increasing progesterone (P) levels in MGH rat models, demonstrating notable hormonal regulation. Gut microbiota analysis via 16S rRNA high-throughput sequencing reveals that AMP restores MGH-induced gut dysbiosis, enhances microbial community diversity, increases beneficial bacteria (e.g., *Lactobacillus*, *Bifidobacterium*), and reduces pathogenic bacterial abundance, thereby reconstructing intestinal microecology and alleviating hormone disorder-induced abnormal mammary tissue responses [46]. Similarly, *Prunella vulgaris* L. polysaccharides (PVP) exhibit multi-target advantages in MGH intervention. Beyond gut microbiota regulation, PVP downregulates AKT-FOXO3a pathway phosphorylation, activates antioxidant enzymes (MnSOD, CAT), significantly reduces malondialdehyde (MDA) levels, inhibits oxidative stress, and indirectly improves mammary hormone levels and microenvironment (Fig. 2) [47].

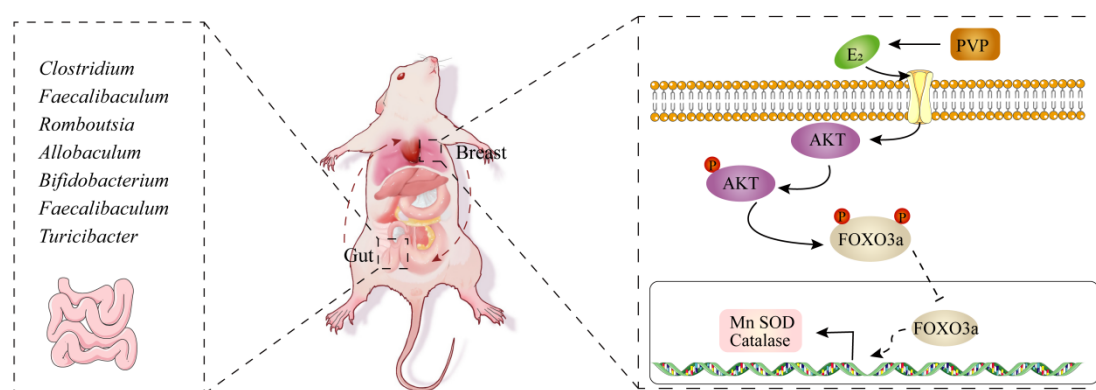


Fig. 2. The anti-hyperplasia effect of polysaccharide from *Prunella vulgaris* L. on mammary gland hyperplasia in rats through regulation of the AKT-FOXO3a signaling pathway and intestinal flora.

Secondly, natural polysaccharides have demonstrated remarkable efficacy in suppressing abnormal cell proliferation. *Porphyra haitanensis* polysaccharides (PH) effectively inhibit intestinal epithelial cell proliferation by activating the Hippo/YAP pathway and modulating its crosstalk with the mTOR signaling axis, suggesting their potential application in regulating pathological hyperplasia in MGH. This discovery not only reveals the regulatory capacity of natural polysaccharides at the signaling pathway level but also provides novel molecular targets for treating hyperplastic disorders [48]. Meanwhile, the Qi-tonifying and Yin-nourishing composite polysaccharide (YYC) targets hormone receptor expression, significantly downregulating estrogen receptor (ER α) and progesterone receptor (PR) levels. By suppressing the anti-apoptotic protein BCL-2 and upregulating the pro-apoptotic protein Bax, YYC induces programmed apoptosis in mammary tissue cells, restoring the dynamic balance between proliferation and apoptosis to prevent MGH progression [49].

Finally, fibrosis—a critical pathological outcome of long-term MGH—can also be effectively mitigated by polysaccharide therapy. *Astragalus* polysaccharides (APS) exhibit potent anti-inflammatory and anti-fibrotic effects in both in vitro and in vivo studies. In LPS-induced mammary tissue injury models, APS significantly reduces ROS levels, restores antioxidant enzyme activities (e.g., SOD, CAT), and alleviates oxidative stress. Moreover, by modulating the expression of phenotypic markers such as E-cadherin, α -SMA, and N-cadherin, APS inhibits epithelial-mesenchymal transition (EMT) and attenuates mammary tissue fibrosis. Additionally, APS regulates the NLRP3 inflammasome pathway, reducing the expression of inflammatory factors (e.g., IL-1 β , Caspase-1), thereby providing dual protection against fibrosis and chronic inflammation in MGH treatment [50].

In summary, natural polysaccharides demonstrate broad therapeutic potential for MGH through multiple mechanisms, including gut microbiota modulation, hormonal regulation, suppression of abnormal cell proliferation, and attenuation of tissue fibrosis. These findings not only provide novel insights for MGH prevention and treatment but also establish a solid theoretical foundation for applying polysaccharide-based functional compounds in chronic disease management. With further research elucidating structure-activity relationships and multicenter clinical validation, natural polysaccharides are expected to transition from laboratory research to clinical practice, emerging as safe, effective, and sustainable therapeutic strategies for MGH.

5. Therapeutic mechanisms and targeted therapy of natural polysaccharides in breast cancer

5.1 Regulatory mechanisms of natural polysaccharides in breast cancer

Natural polysaccharides, as bioactive macromolecules, demonstrate dual therapeutic efficacy in breast cancer treatment through both direct antitumor effects and indirect immunomodulatory mechanisms. In terms of direct action, polysaccharides can target tumor cells by inhibiting proliferation, inducing apoptosis and autophagy, as well as suppressing metastasis. Regarding indirect mechanisms, they remodel the tumor microenvironment by activating macrophages, enhancing NK cell cytotoxicity, and promoting T cell

infiltration. This "dual-pronged" characteristic positions natural polysaccharides as a potential strategy for combination therapy against breast cancer.

5.1.1 Direct tumor suppression

Inhibition of tumor cell growth and proliferation

Natural polysaccharides, as a class of highly bioactive natural products, demonstrate significant potential for directly inhibiting tumor cell growth and proliferation in breast cancer treatment. In recent years, multiple studies have confirmed that specific polysaccharide molecules can exert distinct anti-breast cancer effects by directly interfering with tumor cell proliferation mechanisms, cell cycle progression, and apoptosis signaling pathways, independent of immune cell regulation. For instance, *Astragalus* polysaccharides (APS), widely used as chemoadjuvants to enhance efficacy and reduce toxicity, have increasingly been shown to possess direct mechanisms targeting breast cancer cells. In a recent study analyzing seven gene expression datasets, researchers identified 116 downregulated genes and 73 upregulated genes, with these differentially expressed genes broadly involved in critical biological processes such as cell cycle regulation, cell proliferation, and apoptosis. Notably, EGFR and ANXA1 were identified as hub genes strongly associated with breast cancer progression. Under APS treatment, EGFR was significantly downregulated, while ANXA1 was markedly upregulated. This regulatory pattern indicates that APS can effectively suppress the proliferative potential of tumor cells by modulating key intracellular pathways, thereby offering potential molecular targets for breast cancer therapy [51].

In addition to *Astragalus*, the sulfur polysaccharides (SPS) derived from the edible-medicinal fungus *Laetiporus sulfureus* have also demonstrated significant anti-breast cancer activity. Comparative analysis of its three components (F1, F2, and F3) revealed that the medium-molecular-weight F2 fraction, with its relatively higher sulfate and protein content, exhibited the strongest inhibitory effect on MDA-MB-231 cells. This superior activity of F2 underscores a clear structure–activity relationship, where factors such as molecular weight, degree of sulfation, protein conjugation, and monosaccharide composition collectively govern its anti-proliferative potency. F2 effectively arrested breast cancer cells in the G0/G1 phase by interfering with cell cycle-related protein expression, thereby preventing cellular proliferation. Notably, F2 demonstrated selective cytotoxicity against breast cancer cells without inducing significant apoptosis, suggesting its primary anticancer mechanism operates through cell cycle regulation [52]. This selectivity provides a strong foundation for its potential development as a low-toxicity therapeutic candidate for targeted therapy.

In summary, natural polysaccharides have emerged as a crucial research focus in cancer biotherapy due to their multifaceted mechanisms for directly inhibiting breast cancer cell growth and proliferation. Whether through modulating key gene expression, blocking cell cycle progression, or inducing apoptosis, these natural compounds exhibit remarkable and precise targeting effects against breast cancer cells. Their plant- or fungus-derived nature not only ensures low toxicity but also promises broad application prospects in future personalized and comprehensive cancer treatment regimens. Further integration with modern

pharmacological approaches and nanodelivery technologies could enhance polysaccharide bioavailability and targeting efficiency, accelerating their translation into clinical breast cancer therapies.

Induction of tumor cell apoptosis

Natural polysaccharides are increasingly demonstrating tremendous potential in breast cancer therapeutic research due to their high efficacy, low toxicity, and wide availability. Particularly in inducing breast cancer cell apoptosis, numerous natural polysaccharides have been shown to effectively inhibit breast cancer cell growth and metastasis by activating mitochondrial apoptotic pathways, modulating estrogen receptor expression, or interfering with key signaling pathways. Among these, *Psidium guajava* L. seeds fraction 3 (GSF3), a natural polysaccharide derived from guava seeds, has been proven to induce apoptosis in MCF-7 breast cancer cells through both direct and indirect mechanisms. Experimental data reveal that GSF3 not only downregulates the expression of the anti-apoptotic gene Bcl-2 but also significantly upregulates the pro-apoptotic gene Bax, increasing the Bax/Bcl-2 ratio and thereby driving cells toward programmed cell death. Furthermore, GSF3 enhances Fas-mediated apoptotic signaling by culturing immune cell-conditioned medium, indirectly suppressing cancer cell survival and demonstrating its ability to synergize with the immune system to inhibit tumors [53].

Similarly, *Grifola frondosa* polysaccharides (GFP) exhibit potent antitumor effects. GFP demonstrates significant cytotoxicity against both MCF-7 and MDA-MB-231 breast cancer cells by inducing reactive oxygen species (ROS) accumulation and mitochondrial membrane potential loss, thereby activating the mitochondrial apoptotic pathway. After GFP treatment, breast cancer cells show downregulated Bcl-2 and Bcl-xL expression alongside upregulated Bax, cleaved caspase-3, and caspase-8, ultimately triggering apoptosis. Additionally, GFP suppresses AKT/GSK3 β and ERK pathway phosphorylation in a time-dependent manner, an effect further validated in mouse tumor xenograft models, confirming its anti-breast cancer efficacy [54].

Polysaccharides derived from traditional Chinese medicine Yulangsang (YLSPS) have also demonstrated potent breast cancer growth inhibition through apoptosis induction. In vitro studies show that YLSPS significantly suppresses the proliferation of 4T1 murine breast cancer cells by upregulating Bax while downregulating Bcl-2 and caspase-3 expression to trigger apoptosis. In mouse models, YLSPS treatment markedly reduces tumor volume and weight, with these antitumor effects being closely associated with angiogenesis inhibition, reduced pulmonary metastasis, and alleviated oxidative stress [55].

Similarly, the SP1 polysaccharide isolated from Huaier (*Vanderbylia robinophila*) fruiting bodies exhibits strong pro-apoptotic activity. SP1 effectively downregulates the oncogene MTDH expression and increases the Bax/Bcl-2 ratio, thereby promoting apoptosis in MCF-7 cells. Likewise, the aluminum/nitrogen-modified polysaccharide SpaTA from *Sparganii* Rhizoma demonstrates selective estrogen receptor modulator (SERM)-like activity by regulating ER α expression and nuclear translocation, while activating key apoptotic executors including caspase-3/-8/-9 and PARP through estrogen receptor-dependent pathways, revealing its potential as a novel SERM for breast cancer therapy [56, 57].

Fucoidan, a marine-derived sulfated polysaccharide, has attracted significant attention for its pro-apoptotic mechanisms in breast cancer. Studies reveal that fucoidan not only activates caspase-3 and caspase-9, triggering the release of cytochrome c (cyt C) and Smac, but also upregulates the expression of apoptosis-inducing factor (AIF) and endonuclease G (EndoG), demonstrating dual apoptotic pathways involving both caspase-dependent and -independent mechanisms. Furthermore, this polysaccharide effectively suppresses breast cancer cells in both in vitro and in vivo models by downregulating the PI3K/AKT/GSK3 β pathway and inhibiting β -catenin expression [58].

In summary, natural polysaccharides have emerged as a crucial breakthrough in anti-breast cancer research through their apoptosis-inducing capabilities. These polysaccharides can directly target cancer cells via intrinsic mitochondrial pathways, Fas-mediated pathways, and cytokine-regulated pathways, while also synergizing with immune mechanisms to exert anticancer effects. Their mechanisms involve multiple key signaling pathways including Bcl-2 family regulation, caspase cascades, estrogen receptor signaling, and PI3K/AKT, offering unique advantages such as multi-target effects, low toxicity, and dual regulatory functions. Consequently, polysaccharide-based strategies not only provide novel approaches for natural drug development but also offer safer and more effective treatment options for breast cancer patients. Future research should focus on further mechanistic elucidation and clinical translation of these promising compounds.

Induction of tumor cell autophagy

A growing body of research has demonstrated that natural polysaccharides can inhibit breast cancer growth and metastasis by inducing tumor cell autophagy. Autophagy, a cellular self-degradation process, eliminates damaged cellular components and maintains homeostasis. When autophagy is impaired, tumor cells often develop drug resistance and exhibit enhanced proliferation and metastasis. Therefore, inducing tumor cell autophagy has emerged as an important anticancer strategy, with natural polysaccharides offering novel therapeutic approaches through autophagy pathway activation.

Mushroom polysaccharides have garnered considerable attention due to the significant biological activity and pharmacological effects exhibited by many edible and medicinal fungi. A growing body of evidence supports their potential in the management of breast diseases [59–62]. Recent reviews emphasize that the bioactivity of mushroom polysaccharides is strongly influenced by controllable structural features, such as glycosidic linkage types, branching degree, and molecular-weight distribution. These structure–activity relationships are closely associated with mechanisms including antitumor, immunomodulatory, and antioxidant effects [59]. For example, Lentinan, a polysaccharide from shiitake mushrooms, has been found to induce autophagy in MCF-7 breast cancer cells through direct action or indirect immunomodulation, accompanied by significant cell death. Studies show that Lentinan stimulates autophagosome formation and increases intracellular autophagic flux, subsequently triggering apoptosis. Pretreatment with autophagy inhibitors reduces Lentinan-induced cell death, confirming the crucial role of autophagy in this process. Furthermore, Lentinan enhances tumor cell apoptosis by regulating the expression of caspase-7, cytochrome

C, and the Bax/Bcl-2 ratio. These findings indicate that Lentinan exerts anticancer effects by simultaneously modulating both autophagy and apoptosis pathways in breast cancer cells [63].

Similarly, *Ganoderma applanatum* polysaccharides (GAP) effectively suppress the proliferation and migration of MCF-7 breast cancer cells through autophagy induction. Research reveals that GAP treatment significantly upregulates the expression of autophagy markers LC3 and Beclin-1 in MCF-7 cells, demonstrating its ability to activate the autophagy pathway. Further experiments indicate that GAP-induced autophagy is mediated through the MAPK signaling pathway, particularly via upregulation of p-p38 and p-JNK, which promotes autophagic processes. These results suggest that GAP exerts antitumor effects by inducing early-stage autophagy in breast cancer cells through the MAPK/ERK signaling pathway. Additionally, GAP treatment markedly enhances apoptotic responses, providing new insights for breast cancer therapy [64].

Fucoidan, a marine-derived sulfated polysaccharide, has recently been confirmed to inhibit breast cancer progression through autophagy regulation. This natural compound demonstrates antitumor activity not only against MCF-7 and MDA-MB-231 breast cancer cells but also enhances their sensitivity to chemotherapeutic agents such as doxorubicin and cisplatin. Research has revealed that fucoidan activates autophagy by downregulating the mTOR/p70S6K/TFEB signaling pathway. The induced autophagy renders breast cancer cells more vulnerable to chemotherapy, thereby potentiating the anticancer effects of these drugs. These findings provide new evidence for fucoidan's potential as a chemosensitizer and establish important theoretical foundations for combination therapy strategies in breast cancer treatment [65].

In summary, natural polysaccharides inhibit breast cancer growth and proliferation directly through autophagy induction while synergistically enhancing the efficacy of chemotherapeutic drugs. Studies on lentinan, *Ganoderma* polysaccharides, and fucoidan have demonstrated that autophagy plays a crucial role in the antitumor effects of these natural compounds. Looking ahead, the application of natural polysaccharides in breast cancer treatment may emerge as an effective complementary therapy, particularly when combined with conventional chemotherapy, offering improved therapeutic outcomes with reduced side effects. These investigations provide novel perspectives and theoretical support for developing natural polysaccharides in cancer therapeutics.

Suppression of tumor cell migration and invasion

Natural polysaccharides demonstrate significant therapeutic potential by inhibiting tumor migration and invasion through multiple mechanisms. Research has shown that *Aconitum coreanum* polysaccharide (ACP1) and its sulfated derivative ACP1-s exhibit remarkable inhibitory effects on the migration of human breast cancer MDA-MB-435s cells. Notably, the sulfated derivative ACP1-s, which possesses additional negatively charged sulfate groups, demonstrates a more potent anti-migratory activity compared to the native ACP1. This highlights how specific chemical modifications, such as sulfation, can critically enhance bioactivity by altering charge distribution and molecular interactions. Transwell assay results indicate that both ACP1 and ACP1-s treatments significantly suppress the migratory behavior of MDA-MB-435s cells, with notable

reductions in cumulative migration distance and average velocity. Further analysis suggests this inhibition may be associated with ACP1's interference with actin cytoskeleton dynamic remodeling and suppression of signaling molecule phosphorylation and activation. These structural modifications not only improve solubility and stability but also facilitate stronger engagement with cellular targets involved in migration pathways. These findings reveal new therapeutic potential for *A. coreanum* polysaccharides and their derivatives in combating breast cancer metastasis [66].

In studies on triple-negative breast cancer (TNBC), Huaier polysaccharide (PS-T) has also demonstrated potential in inhibiting cancer cell migration and invasion. Investigations reveal that PS-T suppresses epithelial-mesenchymal transition (EMT) by inducing autophagy, thereby significantly weakening breast cancer cells' invasive and migratory capabilities. Particularly, PS-T controls EMT progression through Snail protein degradation, potentially improving TNBC prognosis. This mechanism not only provides novel insights for breast cancer treatment but also offers a potential therapeutic option for clinical management of TNBC patients [67].

Furthermore, polysaccharides derived from *Korean Citrus* hallabong peels have been identified as possessing anti-metastatic properties against breast cancer. Research demonstrates that the HBE polysaccharide fraction from hallabong peel extract significantly inhibits tube formation in human umbilical vein endothelial cells (HUVECs), with the HBE-II component exhibiting the most pronounced inhibitory effect. Additionally, HBE-II suppresses the migration of MDA-MB-231 breast cancer cells by downregulating matrix metalloproteinase-9 (MMP-9) expression, thereby reducing their invasive potential. These findings further validate the therapeutic potential of polysaccharides in breast cancer treatment, particularly offering novel approaches and molecular targets for combating triple-negative breast cancer metastasis [68].

In summary, natural polysaccharides exhibit remarkable anti-metastatic effects in breast cancer, especially against triple-negative subtypes, through multiple mechanisms including inhibition of cytoskeletal remodeling, regulation of epithelial-mesenchymal transition (EMT), and suppression of MMP-9 activity. Consequently, these natural compounds not only provide innovative biotherapeutic strategies for breast cancer treatment but also open new avenues for cancer prevention and management.

Prevention of tumor metastasis or recurrence

In addition to their direct therapeutic effects on existing breast lesions, natural polysaccharides have also demonstrated notable potential at the secondary prevention level by “inhibiting metastasis/reducing the risk of recurrence.” The underlying rationale lies in the fact that metastasis and recurrence often originate from the migratory and invasive capabilities of residual tumor cells and their prolonged “dormancy” within an immunosuppressive microenvironment. Polysaccharides can intervene simultaneously through two pathways: “inhibiting the metastatic cascade” and “remodeling the tumor microenvironment/enhancing immune surveillance.”

In terms of directly suppressing the metastatic cascade, polysaccharides can block key processes such as epithelial-mesenchymal transition (EMT) and extracellular matrix degradation. For example, fucoidan derived from seaweed has been shown in multiple studies to significantly upregulate the expression of the epithelial marker E-cadherin while downregulating the activity of matrix metalloproteinase MMP-9, thereby effectively inhibiting the migration and invasion of breast cancer cells and reversing EMT-related phenotypes. Systematic reviews further indicate that fucoidan exerts multi-target regulatory effects on several metastasis- and drug-resistance-related pathways, including MAPK/ERK and PI3K/Akt, providing a mechanistic basis for its anti-metastatic potential observed in preclinical models ^[69]. Similarly, astragalus polysaccharide has been confirmed to effectively reverse the EMT process by inhibiting the classical Wnt/ β -catenin signaling pathway, thereby significantly reducing the migratory and invasive abilities of both MCF-7 (ER⁺) and MDA-MB-231 (TNBC) cells. This suggests its potential value in early intervention against “aggressive evolution” during tumor progression, thereby lowering the risk of recurrence ^[70].

In remodeling the tumor microenvironment and enhancing immune surveillance, polysaccharides exhibit a unique bidirectional regulatory advantage. Modified citrus pectin (MCP), under hypoxic conditions, can inhibit the survival of tumor-associated macrophages (TAMs) and block their polarization toward the M2-like pro-tumor phenotype, effectively reducing the formation of lung metastases in the 4T1 triple-negative breast cancer model. This key mechanism is partly attributed to the antagonistic effect of MCP on galectin-3, which has been shown to disrupt the malignant crosstalk among tumor cells, stroma, and immune cells, thereby interfering with multiple rate-limiting steps in the metastatic process, including adhesion, survival, and angiogenesis ^[71]. On the other hand, β -glucans represented by lentinan primarily establish an anti-metastatic defense by positively regulating the host immune system. Studies have shown that lentinan effectively promotes the repolarization of macrophages toward the M1-type anti-tumor phenotype and enhances the tumor-killing functions of effector cells such as natural killer cells. In the Luc-4T1 mouse model, this immunomodulatory effect ultimately translates into significant inhibition of lung metastasis, indicating promising prospects for its exploration as an “immune consolidation therapy” during the maintenance phase after surgery or adjuvant treatment to reduce the risk of distant metastasis and local recurrence ^[72].

Despite accumulating preclinical evidence, clinical studies on polysaccharides for preventing breast cancer recurrence/metastasis remain limited. Future progress requires: 1) establishing quality control based on structural characterization; 2) conducting well-designed studies to define optimal dosing and timing; and 3) exploring rational combinations with standard therapies. Systematic translational research is essential to validate clinical benefits and identify suitable patient populations.

Multiple pathways

In recent years, with the deepening understanding of breast cancer pathogenesis, natural polysaccharides have demonstrated significant therapeutic potential due to their multi-target effects, low toxicity, and excellent biocompatibility. Extensive research has confirmed that natural polysaccharides can not only effectively inhibit the proliferation, migration, and invasion of breast cancer cells but also induce apoptosis and regulate

the cell cycle, thereby intervening in tumor progression at multiple levels. Studies on sulfated polysaccharides represented by SPUP have revealed that these compounds can significantly suppress the proliferation of MCF-7 breast cancer cells in a time- and dose-dependent manner. Through MTT assays, colony formation tests, and PCNA immunofluorescence labeling, SPUP has been shown to comprehensively inhibit cell cycle progression and proliferative activity. Furthermore, Transwell and wound healing assays have verified its remarkable suppression of tumor cell migration, while flow cytometry and Hoechst staining results confirm its ability to induce apoptosis and cell cycle arrest. These findings suggest that SPUP possesses the potential to synergistically combat tumor progression through multiple mechanisms [73].

Another natural polysaccharide, SVP, derived from *Sanghuangporus vaninii*, also exhibits broad-spectrum antitumor activity. SVP demonstrates moderate antiproliferative effects against various cancer cell lines, including MCF-7, while effectively inducing apoptosis, regulating the cell cycle, and suppressing cell migration and invasion to weaken tumor dissemination. Mechanistic studies indicate that SVP activates p53-related pathways and downregulates the expression of matrix metalloproteinases (MMPs), which are closely associated with extracellular matrix degradation, thereby inhibiting the metastatic behavior of breast cancer cells (**Fig. 3**) [74].

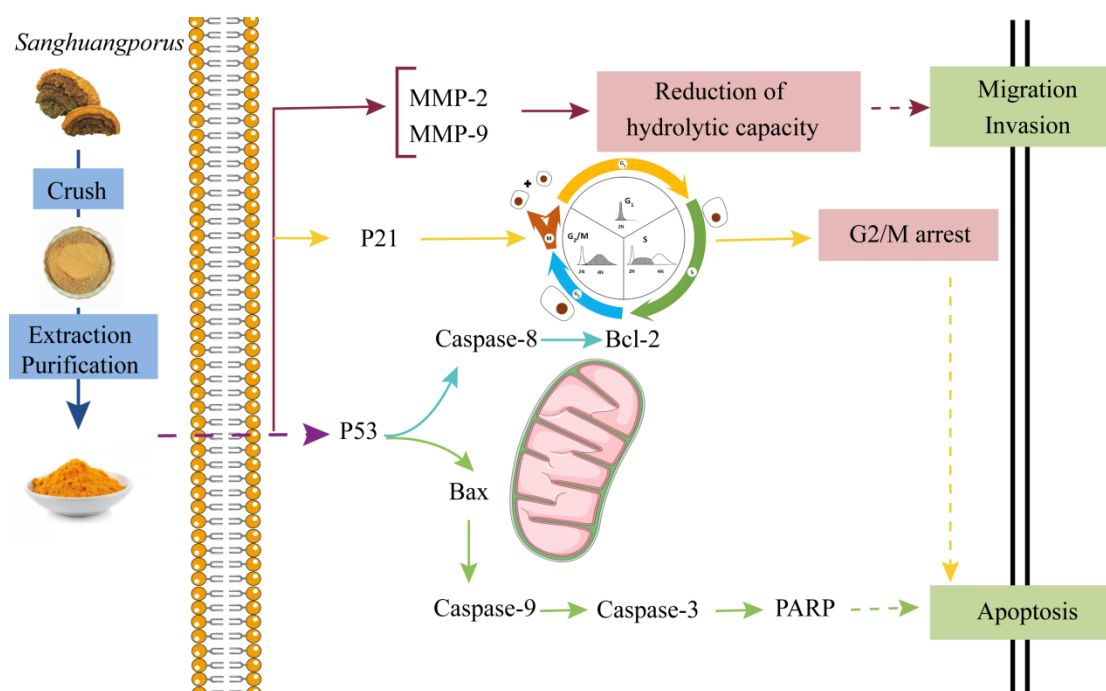


Fig. 3. PVP effectively regulated cell cycle, promoted apoptosis, and reduced the migratory and invasive capacities of MCF-7 cells.

The sulfated polysaccharide F2 isolated from *Laetiporus sulphureus* has further elucidated the molecular mechanisms of natural polysaccharides. Characterized by a medium molecular weight (approximately 23.8 kDa), moderate sulfate content (2.1%), and a significant protein moiety (15.6%), its structural profile is closely associated with its biological functions. Notably, the absence of a triple helix conformation contributes to this relationship. This compound effectively arrests MDA-MB-231 breast cancer cells in the G0/G1 phase by downregulating cyclin-dependent kinase CDK4 and Cyclin D1 while upregulating the tumor suppressor p21, demonstrating significant cell cycle regulatory effects. These effects can be attributed, in part, to its

sulfate groups and protein conjugation, which facilitate enhanced interaction with cell surface receptors and signaling proteins. Concurrently, F2 inhibits the EGFR signaling pathway and phosphorylation of downstream key molecules (ERK1/2, Akt, GSK-3 β), thereby suppressing NF- κ B and β -catenin activation. Additionally, F2 significantly reduces MMP-2 and MMP-9 expression, further blocking cancer cell migration and invasion pathways [75].

Angelica sinensis polysaccharide (ASP) also exhibits unique advantages in breast cancer treatment. Research reveals that ASP modulates the non-coding RNA miR-3187-3p and its target gene PDCD10 to interfere with the Wnt/ β -catenin pathway, thereby inhibiting malignant biological behaviors of breast cancer cells. ASP not only suppresses cell proliferation, migration, and invasion but also demonstrates precise regulation of molecular signaling networks by downregulating key proteins including p-GSK-3 β and β -catenin through miRNA axis modulation [7].

In summary, natural polysaccharides exert combined anti-breast cancer effects through multiple mechanisms: (1) regulating cell cycle and related protein expression to prevent excessive proliferation; (2) inducing apoptosis to compromise tumor cell viability; and (3) inhibiting cell migration and invasion to block metastasis. This synergistic action not only enhances therapeutic efficacy but also provides a solid theoretical foundation for developing novel multi-target, low-toxicity breast cancer treatment strategies. With advances in modern drug delivery systems and structural modification techniques, natural polysaccharides are poised to become important biotherapeutic candidates for breast cancer treatment.

5.1.2 Immunomodulation

In recent years, with deepening research on the tumor immune microenvironment (TME), immunomodulation has emerged as a crucial strategy in breast cancer treatment. Compared to the toxic side effects caused by conventional chemotherapy and radiotherapy, natural polysaccharides have garnered significant attention due to their low toxicity, high biocompatibility, and multi-target immunomodulatory capabilities. Numerous studies have demonstrated that polysaccharides can activate immune effector cells such as macrophages, dendritic cells (DCs), and natural killer (NK) cells, thereby reshaping the tumor immune environment and enhancing anti-tumor responses to suppress breast cancer progression. These findings highlight their tremendous potential as either immunotherapeutic adjuvants or core therapeutic agents. Notably, beyond “immune activation” per se, accumulating evidence suggests that polysaccharides can improve the efficacy of cellular immunotherapies by mechanistically facilitating (i) immune-cell trafficking and homing into tumors, (ii) functional persistence in an immunosuppressive milieu, and (iii) TME remodeling (e.g., TAM repolarization, metabolic reprogramming, and suppression of hypoxia-driven inhibitory signaling). It is important to note, however, that while these immunomodulatory effects are generally considered beneficial in the context of cancer, excessive or non-specific immune activation carries a theoretical risk of triggering autoimmune-like responses or cytokine release syndromes. Current safety data from preclinical and limited clinical studies suggest that well-characterized polysaccharides, when

administered at appropriate doses, exhibit favorable safety profiles with no serious adverse events reported in breast cancer models.

Recent studies further refine our understanding of polysaccharide-immune interactions. For example, a structurally defined arabinogalactan (NLBPE1) isolated from *Lycium barbarum* has been shown to activate dendritic cells through the TLR4–IKK–NF- κ B axis, promoting antigen cross-presentation and CD8⁺ T-cell priming. This activity synergizes with anti-PD-1 therapy to enhance tumor control ^[76]. Comparative analyses also reveal that neutral *Lycium barbarum* polysaccharides (NLBP), which are characterized by low galacturonic acid content and a porous structure, exhibit superior immunoregulatory activity. This activity includes dendritic cell activation and macrophage repolarization, leading to significant tumor growth inhibition in melanoma models ^[77]. Together, these findings underscore the importance of precise structural characterization in linking polysaccharide features to specific immune-modulating functions. *Astragalus* polysaccharide (APS) represents one of the most extensively studied natural polysaccharides, with its anti-breast cancer mechanisms clearly linked to macrophage activation. In breast cancer models, while APS shows no direct cytotoxicity against MCF-7 cells, it significantly enhances anti-cancer activity by activating RAW264.7 macrophages. APS promotes the production of NO and TNF- α , which are recognized as critical mediators of tumor cell apoptosis. Furthermore, APS-treated macrophages exhibit G1 phase cell cycle arrest and a remarkable 13.26-fold increase in the pro-apoptotic Bax/Bcl-2 expression ratio, suggesting its ability to indirectly inhibit tumor growth by enhancing macrophage function (**Fig. 4**) ^[78]. Similarly, *Saposhnikovia divaricata* polysaccharides (SDPs) demonstrate indirect anti-breast cancer effects through immune cell modulation. Although SDPs exhibit no direct cytotoxic effects on MCF-7 and MDA-MB-231 cells, they promote the proliferation and functional activation of U937 monocytes, leading to indirect tumor suppression. In mouse breast cancer xenograft models, SDPs significantly reduce tumor volume without observable toxicity, establishing an innovative treatment paradigm centered on enhancing host immune responses ^[79]. Importantly, macrophage-centered immunomodulation may also “prepare” the chemokine landscape for lymphocyte homing: M1-skewed macrophages typically increase pro-inflammatory cytokines and antigen-presentation capacity while reducing immunosuppressive mediators, collectively supporting T-cell recruitment and functional maintenance within tumors.

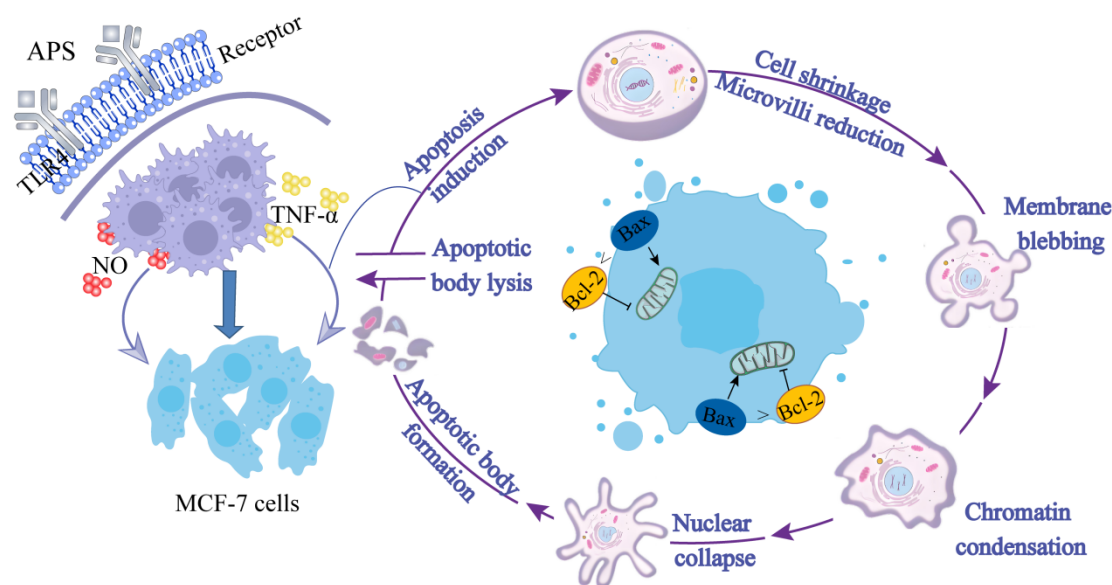


Fig. 4. APS combated breast cancer indirectly by activating macrophages to enhance tumoricidal effects—inducing G1 cell cycle arrest, upregulating pro-apoptotic Bax/Bcl-2 ratio (13.26-fold), and stimulating NO/TNF- α secretion—rather than directly inhibiting cancer cell growth, offering a potential immunomodulatory strategy to mitigate chemotherapy/radiotherapy toxicity.

In recent years, tumor-associated macrophages (TAMs) have garnered significant attention due to their tumor-promoting role in the tumor microenvironment (TME). Natural polysaccharides have demonstrated the ability to reprogram TAMs from pro-tumor M2 phenotype to anti-tumor M1 phenotype. For instance, the fraction of *Lycium barbarum* polysaccharides (LBP) within the 50–100 kDa molecular weight range exhibits the most potent M2-to-M1 repolarization capacity. This clear molecular weight dependence underscores an important structure–activity relationship, where intermediate chain length and corresponding spatial conformation may optimize receptor recognition and downstream signaling activation. The activated M1 macrophages display enhanced phagocytic activity against breast cancer cells and induce tumor regression in vivo. RNA sequencing analysis further confirms that LBP modulates innate immune pathways, providing a novel TAM-targeting strategy for breast cancer immunotherapy [20]. From a mechanistic standpoint, TAM repolarization is closely linked to improved effector-cell homing and persistence: shifting TAMs toward an M1-like state can reduce M2-associated immunosuppressive signals (e.g., IL-10-like programs and pro-tumor metabolic support) while favoring Th1-type inflammatory cues and chemokine gradients that facilitate the infiltration of cytotoxic lymphocytes. Such remodeling is particularly relevant for adoptive cell therapies (e.g., CAR-T), whose efficacy in solid tumors is often limited by immune exclusion and suppressive myeloid niches. Modified citrus pectin (MCP), an edible natural polysaccharide, also exerts anti-breast cancer effects partially through TAM modulation. Under hypoxic conditions, MCP more strongly inhibits TAM survival, reduces glucose uptake, and suppresses M2 polarization by downregulating galectin-3 expression and STAT3 signaling. In both orthotopic and metastatic 4T1 breast cancer models, MCP treatment significantly decreases TAM infiltration and blocks their tumor-promoting activity, highlighting natural polysaccharides as effective tools for remodeling key TME components to enhance immunotherapy efficacy [71]. This MCP–galectin-3/STAT3 axis provides a concrete mechanistic rationale for synergy with cellular

immunotherapy: galectin-3 and STAT3 signaling are widely implicated in myeloid-driven immunosuppression, immune-cell exclusion, and hypoxia-adapted metabolism; thus, MCP-mediated attenuation of these pathways may alleviate barriers to T-cell (including CAR-T) tumor entry and mitigate exhaustion-promoting cues, thereby potentially improving intratumoral retention and effector durability.

Regarding dendritic cells (DCs), polysaccharides show remarkable potential as immune adjuvants. When combined with DC vaccines, *Portulaca oleracea* L. polysaccharide (POL-P3b) significantly enhances anti-breast cancer immune responses. POL-P3b promotes DC maturation via the TLR4/MyD88/NF- κ B pathway, improving antigen presentation and cytokine secretion to induce potent T-cell immunity. In mouse models, it effectively suppresses tumor growth and pulmonary metastasis without observable toxicity, underscoring its role as a vaccine adjuvant for tumor-specific immunity^[80]. Mechanistically, DC maturation driven by TLR4/MyD88/NF- κ B signaling is also expected to enhance T-cell priming quality and trafficking efficiency: mature DCs typically upregulate co-stimulatory molecules and functional cytokines, and can promote chemokine programs that support effector T-cell recruitment toward tumor sites. Thus, polysaccharide-adjuvanted DC vaccines may strengthen both the magnitude of tumor-specific T cells and their tumor-homing competence. Similarly, *Plantago asiatica* L. polysaccharide (PLP) stimulates DC maturation and function, activating and recruiting CD4⁺ and CD8⁺ T cells to markedly inhibit mammary tumor growth. In vivo, PLP not only enhances immune cell infiltration but also induces cytotoxic effects in breast cancer cell-immune cell cocultures, validating its practical utility in immunotherapy^[81]. The observed increase in immune-cell infiltration is consistent with a “DC–T cell axis” in which polysaccharide-conditioned DCs amplify effector differentiation and reinforce chemotactic recruitment, offering a mechanistic basis for improved cellular immunotherapy responses when combined in rational regimens. Beyond traditional immunomodulation, emerging strategies highlight the interplay between metabolic reprogramming and immune activation. For example, targeted degradation of pyruvate dehydrogenase kinase 1 (PDK1) via proteolysis-targeting chimeras (PROTACs) not only reverses the Warburg effect but also induces immunogenic cell death and reverses immunosuppression in the TME, thereby enhancing antitumor immunoreactivity in breast cancer models. When combined with α PD-L1, such metabolic-immune modulators further promote immune cell infiltration and improve therapeutic efficacy^[82]. This underscores a broader paradigm wherein polysaccharides and other bioactive compounds may complement metabolic interventions to achieve synergistic immune remodeling.

Natural killer (NK) cells, as the first line of innate immune defense, have emerged as crucial targets for polysaccharide-mediated immunomodulation. For instance, *Solanum nigrum* polysaccharide SN-ppF3 effectively suppresses tumor growth in murine breast cancer models (65% reduction in volume, 40% decrease in weight) by enhancing host immune responses through NK cell activation, macrophage stimulation, and increased tumor-infiltrating T cell populations. Concurrent elevation of TNF- α , IFN- γ , and IL-4 alongside significant IL-6 downregulation further confirms its cancer-inhibiting mechanism rooted in broad immune system activation^[21]. In mechanistic terms, boosting NK-derived IFN- γ may further “license” antigen

presentation and promote CXCR3-ligand–associated trafficking of effector lymphocytes, thereby contributing to a positive feedback loop for immune-cell homing and sustained intratumoral immunity. Preclinical studies also demonstrate that oral administration of *Grifola frondosa* polysaccharide extracts induces measurable immunomodulatory effects in post-operative breast cancer patients, revealing potential clinical applicability. Immunological endpoints including enhanced NK cell activity and altered T cell ratios indicate that even dietary-derived polysaccharides can produce tangible immune-boosting effects in humans at appropriate doses [83]. Such systemic reinforcement of innate immunity may be particularly valuable for maintaining effector-cell fitness and persistence during long treatment courses, serving as an immunological “support layer” for combination strategies. Notably, the same mechanisms that enhance anti-tumor immunity could, in principle, predispose to immune-related adverse events. Available clinical observations from adjuvant use of polysaccharides like lentinan in cancer patients generally report mild and transient side effects, such as fever or fatigue, with severe toxicity being rare. These data support the relative safety of polysaccharide immunomodulators but emphasize that individualized monitoring remains essential, especially in combination with other immunotherapies.

In summary, natural polysaccharides exhibit tremendous potential in breast cancer prevention and treatment by modulating multiple immune cell populations (macrophages, dendritic cells, and NK cells). Their multifaceted mechanisms include: macrophage-mediated apoptosis induction, DC vaccine adjuvant effects for T cell response amplification, and TAM polarization reprogramming to reshape the tumor immune microenvironment. While the immunomodulatory properties of polysaccharides are largely advantageous, a balanced perspective requires acknowledging the theoretical risk of excessive immune activation. Current evidence indicates a favorable safety profile for well-defined polysaccharides at therapeutic doses, but further clinical studies are needed to systematically assess long-term tolerability and optimize their integration into combination immunotherapy regimens. As research further elucidates structure-function relationships, polysaccharides are poised to become integral components of breast cancer immunotherapy strategies, synergizing with existing immunotherapies to advance diversified and precision clinical approaches.

5.2 The applications of polysaccharide-based biomaterials in breast cancer

Polysaccharide-based biomaterials (e.g., chitosan, hyaluronic acid, sodium alginate) demonstrate tremendous potential in breast cancer treatment due to their exceptional biocompatibility, biodegradability, and targeting capabilities. For targeted drug delivery, these polysaccharides enable pH/enzyme-responsive release and specifically recognize tumor cells overexpressing CD44/MMP-2, thereby reducing systemic toxicity. In combination therapies, polysaccharide materials serve as effective carriers for photothermal agents (e.g., selenized chitosan combined with NIR phototherapy) or immune adjuvants (e.g., β -glucan-activated dendritic cells), significantly enhancing chemo-/immuno-therapeutic efficacy. This integrated "delivery-therapy" design highlights the unique advantages of polysaccharide-based materials in precision breast cancer treatment.

5.2.1 Targeted delivery of chemotherapeutic drugs

In the field of breast cancer treatment, systemic toxicity, severe side effects, limited efficacy, and multidrug resistance (MDR) of chemotherapeutic agents have remained persistent clinical challenges. Conventional chemotherapy drugs often cause extensive damage to healthy tissues due to their lack of targeting specificity. In recent years, polysaccharide-based biomaterials have emerged as a research focus for constructing targeted drug delivery systems, owing to their unique biocompatibility, biodegradability, structural diversity, and modifiability, offering innovative solutions for efficient, targeted, and low-toxicity drug delivery. This review summarizes recent advances in polysaccharide-based nanodelivery systems for breast cancer treatment, with emphasis on their construction strategies, delivery mechanisms, and therapeutic outcomes.

A representative rigid polysaccharide self-assembly system is the novel nanotube (LNT-NT) constructed from triple-helical β -glucan (LNT). Driven by the "minimum surface energy" principle, this system forms hollow nanotube structures through "side-by-side" and "head-to-head" self-assembly via hydrogen bonding and hydrophobic interactions, leveraging its rigid backbone and amphiphilic properties. Hydrophobic drugs like doxorubicin (DOX) can be stably encapsulated within its hydrophobic cavity. Experimental results demonstrate that the LNT-NT system significantly enhances DOX accumulation in breast cancer cells, inducing tumor cell apoptosis and inhibiting proliferation. The system exhibits remarkable antitumor efficacy both *in vitro* and *in vivo*, achieving a tumor suppression rate of 74.5% - substantially higher than free DOX - while significantly reducing side effects. This achievement establishes a paradigm for constructing efficient hydrophobic drug carriers using rigid polysaccharides ^[84].

To address the common clinical challenges of paclitaxel (PTX), including high toxicity and efficacy variability, researchers have developed an injectable hydrogel carrier using *Pinus koraiensis* polysaccharide (PKP). This hydrogel exhibits excellent rheological properties—including shear-thinning, rapid recovery, and thixotropy—ensuring smooth *in vivo* injection. *In vitro* experiments demonstrate potent inhibitory effects of the PKP-based hydrogel against both 4T1 and MCF-7 breast cancer cell lines, while *in vivo* models confirm significant tumor suppression alongside markedly reduced PTX-induced systemic toxicity. These findings establish PKP hydrogel as an ideal localized drug delivery platform capable of achieving high local drug concentrations with sustained release ^[85].

Furthermore, a polyelectrolyte complex composed of chitosan (Ch) and Tamarind Gum (TGP) has been utilized to stabilize simvastatin nanoparticles, demonstrating strong inhibitory effects against MCF-7 breast cancer cells. Prepared via antisolvent precipitation, these nanoparticles exhibit optimal size, high encapsulation efficiency, and sustained-release characteristics—validated through biological barrier-mimicking experiments using egg and tomato membranes. This study systematically evaluates the delivery platform's potential through stability, encapsulation efficiency, and release kinetics analyses, particularly highlighting its enhanced anticancer efficacy. The results provide experimental evidence for repurposing statins in oncology therapeutics ^[86].

For hormone receptor-positive (ER+) breast cancer treatment, hyaluronic acid (HA)-based targeted delivery platforms demonstrate enhanced specificity. By conjugating HA with estradiol (ES) to form amphiphilic derivatives (HA-ES), the system self-assembles into nanogels (NHs) in aqueous solutions, enabling efficient loading of hydrophobic drugs like curcumin (CUR) and docetaxel (DTX). Through ER receptor recognition, this platform achieves active targeting of ER+ breast cancer. Experimental results reveal that ES-NHs/DTX combinations exhibit significantly superior antitumor efficacy against MCF-7 cells compared to free drugs, with negligible toxicity, demonstrating excellent biosafety and selectivity for high clinical translation potential [87].

To enhance therapeutic efficacy while mitigating chemotherapy toxicity, another study incorporated *Lycium barbarum* polysaccharide (LBP) and photothermal polypyrrole nanoparticles (PPY NPs) into a thermosensitive hydrogel composed of poloxamers 407 and 188, enabling doxorubicin (DOX) combination therapy. Under near-infrared irradiation, PPY-generated heat synergized with DOX to achieve 80% tumor cell killing efficiency—substantially higher than DOX alone. *In vivo* studies confirmed outstanding anticancer performance (75% tumor suppression) with minimal toxicity. This pioneering work represents the first integration of photothermal therapy with anticancer polysaccharide hydrogels, establishing a technical foundation for multimodal combination therapy [88].

To address multidrug resistance (MDR) in breast cancer treatment, researchers have developed an acid-sensitive polysaccharide-DOX conjugate combined with high-dose lapatinib (HPP-Dox/Lap). This system employs HA modification to target CD44 receptors on MCF-7/ADR cells, significantly enhancing cellular uptake (reversal fold up to 29.83) and cytotoxicity while successfully suppressing P-gp expression. Animal studies demonstrate that even at low doses, the system achieves 93% tumor suppression with concurrent lung metastasis inhibition and minimal side effects, fully demonstrating its advantages in MDR reversal and high-efficacy treatment [89].

In summary, polysaccharide-based biomaterials are emerging as ideal carriers for chemotherapeutic drug delivery in breast cancer due to their superior biocompatibility and multifunctionality. Whether through rigid structures for efficient encapsulation or targeted recognition for specific delivery, polysaccharide nano-platforms exhibit remarkable advantages in toxicity reduction, therapeutic efficacy enhancement, and drug resistance reversal. Future development should focus on: (1) advanced functionalization of polysaccharide structures, (2) intelligent responsive system design, (3) optimization of multidrug combination strategies, and (4) systematic clinical translation pathways. Leveraging the sustainability and modifiable flexibility of polysaccharide materials will enable more precise, safe, and effective therapeutic solutions for breast cancer patients.

5.2.2 Targeted delivery of natural products

In the field of breast cancer research and treatment, overcoming the limitations of conventional chemotherapy and multidrug resistance (MDR) has become a critical challenge. In recent years, polysaccharide-based nanodelivery systems have attracted widespread attention due to their excellent

biocompatibility, modifiability, and targeting capabilities. By integrating natural products with polysaccharide-based nanomaterials, researchers can not only improve drug stability and bioavailability but also achieve tumor microenvironment-responsive release, thereby enhancing therapeutic efficacy.

For instance, a study co-loaded the BET inhibitor JQ1 and the bioactive diterpenoid oridonin (ORI), derived from traditional Chinese medicine, into propylene glycol alginate sodium sulfate (PSS) nanoparticles modified with the iRGD peptide. This approach achieved superior tumor targeting and intracellular internalization. The results demonstrated that iRGD-PSS@PBAE@JQ1/ORI NPs not only significantly enhanced the synergistic antitumor activity of JQ1 and ORI but also reversed immune tolerance by downregulating PD-L1 expression. Additionally, ORI exerted multiple effects, including anti-proliferation, antioxidant stress, and inhibition of lactate secretion, collectively improving breast cancer treatment outcomes (Fig. 5) [90].

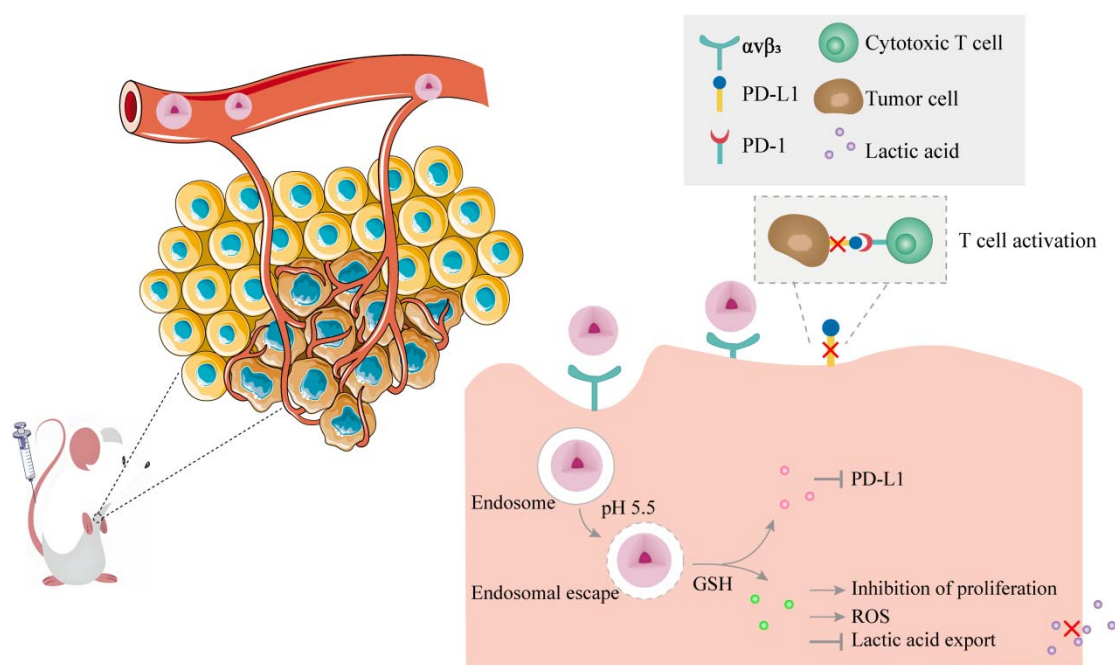


Fig. 5. Schematic illustration of the iRGD-modified marine sulfated polysaccharide nano-delivery system for enhanced breast cancer therapy.

On the other hand, another innovative polysaccharide-based delivery platform, termed "nano-pomegranate" (QDAF), has also demonstrated potential in breast cancer therapy. Composed of quercetin derivatives, astragalus polysaccharides, and folic acid, this system enables efficient drug release in the reductive tumor intracellular environment. It significantly suppresses drug resistance in estrogen receptor α -positive breast cancer cells while enhancing cellular uptake, inducing necrosis, and promoting apoptosis. In vivo studies further confirmed its superior antitumor efficacy and reduced systemic toxicity compared to free drugs [91].

In summary, polysaccharide-based nanomaterials exhibit unique advantages in delivering natural products for breast cancer treatment. They not only help overcome drug resistance and side effects but also provide new insights for developing combination therapies. With further research, these systems hold great promise as a key direction for precision medicine in breast cancer.

5.2.3 Combination therapy

Polysaccharide-based nanomaterials are increasingly demonstrating significant potential in breast cancer treatment through synergistic therapeutic mechanisms. Focused ultrasound (FUS), as a non-invasive tumor treatment modality, possesses excellent thermal and mechanical ablation properties along with certain immunostimulatory effects, yet its standalone application often suffers from insufficient antitumor immune responses. To enhance FUS therapeutic efficiency, researchers have developed a PEGylated PLGA-based nanosystem co-loaded with *Astragalus* polysaccharides (APS) and gold nanorods (AuNRs). This innovative platform not only achieves photoacoustic imaging and thermal enhancement but also significantly amplifies FUS-induced immune responses. The nanoplatform's thermal synergy expands tumor necrotic areas while reducing the energy efficiency factor (EEF), and simultaneously promotes dendritic cell maturation and stimulates production of key inflammatory cytokines (IL-12 and IFN- γ), thereby enhancing systemic antitumor immunity^[31].

Furthermore, polysaccharides as natural bioactive compounds exhibit remarkable advantages in green nanosynthesis. For instance, carbon dot@silver nanoparticles (CD@AgNPs) synthesized via a one-pot method using natural polysaccharides from sweet lemon peels demonstrate exceptional antibacterial activity at ultralow concentrations while showing selective toxicity against MCF-7 breast cancer cells. This anticancer effect primarily stems from intracellular reactive oxygen species (ROS) upregulation. Such polysaccharide-metal hybrid nanomaterials present promising applications through their synergistic anticancer effects (**Fig. 6**)^[92].

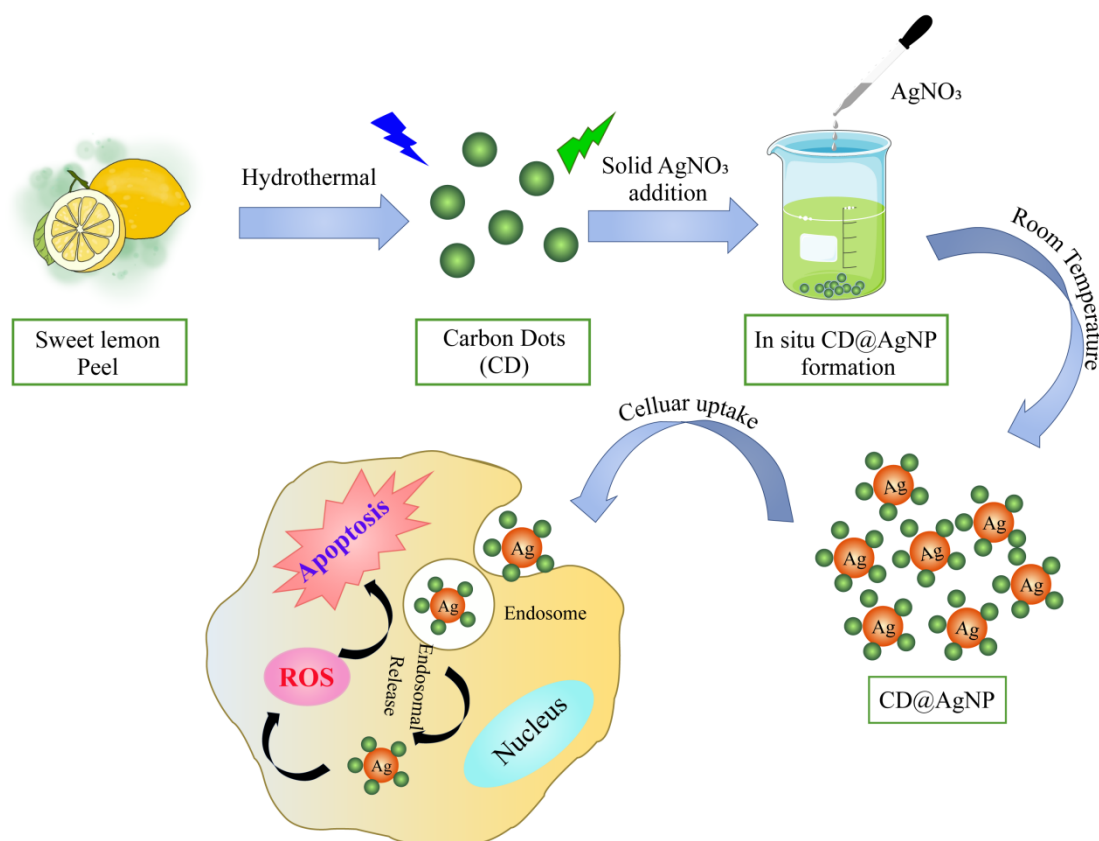


Fig. 6. Green synthesis of silver nanoparticles using natural polysaccharide-derived carbon dots for synergistic breast cancer therapy.

In another study, bovine serum albumin (BSA)-modified molybdenum disulfide nanosheets were incorporated into a self-healing polysaccharide hydrogel. Formed through the reaction of oxidized sodium alginate with hydroxypropyl chitosan, this injectable hydrogel demonstrates stable retention at tumor sites and, when combined with near-infrared laser irradiation, enables photothermal-photodynamic synergistic therapy to significantly expand tumor ablation areas [93].

Notably, the combination of *Lycium barbarum* polysaccharides (LBPs) with low-dose doxorubicin (DOX) and photosensitive polypyrrole nanoparticles (PPY NPs) has been shown to enhance DOX uptake efficiency in breast cancer cells while achieving over 80% tumor suppression in vivo with markedly reduced cardiotoxicity and hepatotoxicity. Within this chemo-photothermal synergistic system, polysaccharides play a pivotal role in improving drug delivery, enhancing immune responses, and minimizing adverse effects [94].

In summary, polysaccharide-based nanomaterials exhibit multiple synergistic mechanisms in breast cancer treatment, including: (1) enhanced thermal ablation and phototherapy efficacy, (2) activated antitumor immunity, (3) improved drug targeting and biocompatibility, and (4) reduced systemic toxicity. These capabilities establish an integrated therapeutic platform combining diagnosis, imaging, and immunomodulation, demonstrating promising potential for precision oncology applications.

6. Conclusion and prospect

Breast diseases (mastitis, mammary hyperplasia, and breast cancer), as significant threats to women's health, urgently require the development of safe and effective treatment strategies. Natural polysaccharides have demonstrated considerable therapeutic potential due to their unique biocompatibility, low toxicity, and multifaceted bioactivities, including antimicrobial, anti-inflammatory, immunomodulatory, and antitumor effects. In mastitis treatment, natural polysaccharides exert therapeutic effects through multidimensional mechanisms: modulating gut microbiota homeostasis to indirectly improve the mammary immune microenvironment; directly inhibiting pathogenic microorganism proliferation; and alleviating tissue oxidative damage and inflammatory responses by scavenging free radicals and regulating inflammatory factors. It is noteworthy, however, that the current evidence base heavily relies on rodent models, which may not fully recapitulate the pathophysiological complexity and microbial ecology of clinical mastitis, particularly in dairy cows or humans. While these animal studies provide invaluable mechanistic insights, their translational validity requires cautious interpretation. Meanwhile, polysaccharide-based nanomaterials have significantly enhanced mastitis diagnosis sensitivity (e.g., photoacoustic imaging improvement) through functional modifications, achieved targeted drug delivery to mammary tissue, and synergistically improved antibacterial performance (e.g., combined with photothermal therapy). For mammary hyperplasia, polysaccharides intervene in disease progression by regulating estrogen metabolic pathways, suppressing abnormal proliferation of mammary ductal epithelial cells, and exerting antioxidant and antifibrotic effects. In the more challenging area of breast cancer, natural polysaccharides not only inhibit malignant tumor behaviors through direct mechanisms (e.g., cell cycle arrest, apoptosis activation, autophagy induction, and metastasis suppression) but also remodel the tumor microenvironment via immunomodulatory pathways such as

macrophage polarization and T-cell infiltration. However, some inconsistencies exist in the literature regarding the primary mechanisms of action for certain polysaccharides, which may stem from variations in polysaccharide source, purity, structural characteristics, and the specific cell lines or animal models used. Furthermore, polysaccharide-based nanobiomaterials (e.g., hyaluronic acid-doxorubicin conjugates) enable tumor-targeted delivery of chemotherapeutic drugs through the EPR effect or receptor-mediated endocytosis, forming synergistic combination strategies with other therapies (e.g., photodynamic therapy, immunotherapy).

Natural polysaccharides, as a class of bioactive macromolecules with broad application prospects, have demonstrated unique therapeutic advantages in the prevention and treatment of breast diseases. However, their clinical translation still faces several critical scientific and technological challenges that need to be addressed. At the fundamental research level, the structure-activity relationship between the complex structural features of polysaccharides and their biological functions has not yet been fully elucidated. Although chemical modifications such as sulfation and carboxymethylation are known to significantly alter the biological activities of polysaccharides, the precise regulatory mechanisms of specific modification sites and degrees on disease targets require systematic investigation. More importantly, the inherent structural heterogeneity and batch-to-batch variability of natural polysaccharides pose major challenges for quality control. This heterogeneity primarily stems from differences in source materials (species and growth environments) and inconsistencies in extraction and purification processes, leading to significant variations in molecular weight distribution, monosaccharide composition, and branching structure among different batches. These factors directly impact the stability and reproducibility of their pharmacological activities. In terms of formulation development and clinical translation, most existing polysaccharide-based nanodelivery systems still exhibit notable limitations. While these nanocarriers demonstrate excellent drug-loading capacity and controlled release properties *in vitro*, data on their *in vivo* pharmacokinetics, biodistribution, and long-term safety remain insufficient. Key issues such as the degradation behavior of polysaccharide nanoparticles, immunogenicity risks, and their interactions with biological barriers (e.g., the blood-milk barrier) urgently need clarification. Additionally, the generally low bioavailability and short half-life of polysaccharides significantly limit their clinical efficacy. In the era of precision medicine, developing personalized polysaccharide-based therapies for breast diseases presents another major challenge due to their high heterogeneity. Furthermore, while natural polysaccharides exhibit broad-spectrum anti-tumor activities across multiple breast cancer models, future studies should strive to systematically evaluate their efficacy and mechanisms in the context of distinct molecular subtypes (e.g., ER⁺, HER2⁺, and TNBC). Such comparative analyses could reveal whether certain structural features or formulations confer enhanced activity against specific subtypes, thereby informing the development of polysaccharide-based precision therapeutics. Furthermore, to bridge the gap between preclinical models and clinical reality, future research must explicitly compare and contrast findings across different disease models (e.g., LPS-induced murine mastitis vs. bacterial infection in bovine models, or xenograft vs. genetically engineered mouse models for breast cancer). This will help critically assess the

translational relevance of each model and identify core mechanisms that are conserved across species and contexts. Integrating subtype-specific omics data with functional assays will be crucial to uncover potential biomarkers of response and optimize combinatorial strategies with existing targeted or immunotherapies.

To address these challenges, future research must adopt innovative interdisciplinary strategies that integrate cutting-edge technologies across multiple fields. For structural optimization, artificial intelligence should be fully leveraged to analyze vast polysaccharide structure-activity datasets through deep learning algorithms, enabling the establishment of predictive models for rational design - exemplified by using generative adversarial networks (GANs) to simulate optimal bioactive structures coupled with automated synthesis platforms for targeted preparation. In drug delivery system development, priority should be given to constructing intelligent responsive carriers such as ROS-sensitive polysaccharide nanoparticles specifically activated by tumor microenvironment or bioinspired delivery systems capable of traversing multiple biological barriers. At the translational level, it is imperative to establish more physiologically relevant models like patient-derived mammary organoids for personalized treatment screening and efficacy prediction. Specifically, comparative studies utilizing both standardized rodent models and larger animal models that more closely mimic human disease (e.g., spontaneous mammary tumors in dogs) should be prioritized to validate key findings and assess translational potential more reliably. Particularly promising are combination strategies integrating polysaccharides with emerging immunotherapies, including polysaccharide-modified CAR-T cells with enhanced homing capacity and persistence, or sulfated polysaccharides that reprogram tumor-associated macrophages toward antitumor phenotypes. Furthermore, in-depth investigation of the novel "polysaccharide-gut microbiota-immunomodulation" axis using advanced omics technologies like single-cell sequencing and spatial transcriptomics may uncover groundbreaking therapeutic targets for breast diseases.

To achieve large-scale clinical application of natural polysaccharides in breast disease treatment, it is imperative to establish a comprehensive quality standard system and production protocols. This requires implementing stringent quality control standards for raw materials, developing batch-to-batch consistency evaluation methods based on fingerprint profiling technology, and applying process analytical technology (PAT) for full-process production monitoring. Concurrently, standardized preclinical safety assessments and clinical trial designs must be conducted, with particular attention to long-term medication safety and special population risks (e.g., pregnancy and lactation periods). Through collaborative innovation among industry, academia, research institutions, and medical practitioners, this green therapeutic strategy can be accelerated toward clinical translation, ultimately providing safer, more effective, and personalized treatment options for breast disease patients while achieving a transformative leap from traditional natural medicine to modern precision medicine.

Funding

This work was supported by Nursery Project of the Affiliated Tai'an City Central Hospital of Qingdao University (2024MPZ08), Shandong Province medical system staff science and technology innovation plan project (SDYWZGKCJHLH202451). National Natural Science Foundation of China (82472139).

Data availability

No data was used for the research described in the article.

References

- [1] N. Zaatout, D. Hezil, A meta-analysis of the global prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) isolated from clinical and subclinical bovine mastitis, *J Appl Microbiol.* 132 (2022) 140-154. <https://doi.org/10.1111/jam.15192>.
- [2] D. Vijay, J.S. Bedi, P. Dhaka, et al., Qualitative Study on Antimicrobial Usage and Resistance in the Dairy Chain: A Situation Analysis and Solutions by Stakeholders from Punjab, India, *Antibiotics* (Basel). 11 (2022) <https://doi.org/10.3390/antibiotics11091229>.
- [3] B.H.P.C. Mastitis Prevention and Treatment and Breastfeeding Promotion Group, China Association of Maternal and Child Health Care, Chinese guidelines for the diagnosis and treatment of lactational mastitis, *Chinese Journal of Breast Disease.* 14 (2020) 10–14. <https://doi.org/10.3877/cma.j.issn.1674-0807.2020.01.005>.
- [4] K.W. Chamberlin, C. Li, Z. Luo, et al., Use of nonsteroidal anti-inflammatory drugs and poor olfaction in women, *Int Forum Allergy Rhinol.* 14 (2024) 639-650. <https://doi.org/10.1002/alr.23241>.
- [5] H.R. Khoja, B.R. Barala, S. Sharma, et al., Role of centchroman versus danazol in treatment of benign breast disorders, *International Surgery Journal.* 8 (2021) 616.
- [6] L.C. Hartmann, A.C. Degnim, R.J. Santen, et al., Atypical hyperplasia of the breast--risk assessment and management options, *N Engl J Med.* 372 (2015) 78-89. <https://doi.org/10.1056/NEJMsr1407164>.
- [7] W.s.H.B. Breast Health and Breast Disease Prevention and Treatment Group, Chinese Preventive Medicine Association, Expert consensus on the diagnosis and treatment of mammary gland hyperplasia, *Chinese Journal of Practical Surgery.* 36 (2016) 759–762. <https://doi.org/10.7504/CJPS.ISSN1005-2208.2016.07.13>.
- [8] H. Sung, J. Ferlay, R.L. Siegel, et al., Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries, *CA Cancer J Clin.* 71 (2021) 209-249. <https://doi.org/10.3322/caac.21660>.
- [9] W.J. Gradishar, B.O. Anderson, J. Abraham, et al., Breast Cancer, Version 3.2020, NCCN Clinical Practice Guidelines in Oncology, *J Natl Compr Canc Netw.* 18 (2020) 452-478. <https://doi.org/10.6004/jnccn.2020.0016>.
- [10] M.D.T.D. Melo, A.L.C. Almeida, A.J.D.O.M. Neto, et al., Which therapeutic strategy is less cardiotoxic in the treatment of breast cancer: Using paclitaxel before or after doxorubicin?, *Journal of Clinical Oncology.* 39 (2021) e12617-e12617.
- [11] D. Liu, Z. Zheng, S. Zhang, et al., Analysis of risk factors related to acute radiation dermatitis in breast cancer patients during radiotherapy, *J Cancer Res Ther.* 18 (2022) 1903-1909. https://doi.org/10.4103/jcr.t.jcr.t_1203_22.
- [12] X. Wu, H. Yang, X. Yu, et al., Drug-resistant HER2-positive breast cancer: Molecular mechanisms and overcoming strategies, *Front Pharmacol.* 13 (2022) 1012552. <https://doi.org/10.3389/fphar.2022.1012552>.
- [13] M. Yan, X. Wang, J. Zhang, et al., Extraction, structural characterization, and in vitro immunomodulatory activities of *Saccharomyces cerevisiae* spore wall β -glucan, *Journal of Agriculture and Food Research.* 22 (2025) 102116. <https://doi.org/10.1016/j.jafr.2025.102116>.
- [14] M. Dhahri, S. Sioud, R. Dridi, et al., Extraction, Characterization, and Anticoagulant Activity of a Sulfated Polysaccharide from *Bursatella leachii* Viscera, *ACS Omega.* 5 (2020) 14786-14795. <https://doi.org/10.1021/acsomega.0c01724>.
- [15] J.A. Panggabean, S.P. Adiguna, S.I. Rahmawati, et al., Antiviral Activities of Algal-Based Sulfated Polysaccharides, *Molecules.* 27 (2022) <https://doi.org/10.3390/molecules27041178>.
- [16] L. Hu, S. Nomura, Y. Sato, et al., Anti-inflammatory effects of differential molecular weight Hyaluronic acids on UVB-induced calprotectin-mediated keratinocyte inflammation, *J Dermatol Sci.* 107 (2022) 24-31. <https://doi.org/10.1016/j.jdermsci.2022.06.001>.
- [17] L.Q. Zhao, Z.Q. Li, Y.F. Liu, et al., Ultrasonic complexation with *Lycium barbarum* polysaccharide significantly enhances the aqueous solubility and bioavailability of curcumin, *Ultrason Sonochem.* 123 (2025) 107673. <https://doi.org/10.1016/j.ultsonch.2025.107673>.

- [18] J. Li, H. Guo, Y. Dong, et al., Polysaccharides from Chinese herbal medicine: a review on the hepatoprotective and molecular mechanism, *Chin J Nat Med.* 22 (2024) 4-14. [https://doi.org/10.1016/s1875-5364\(24\)60558-3](https://doi.org/10.1016/s1875-5364(24)60558-3).
- [19] Y. Liu, Q. Sun, X. Xu, et al., *Platycodon grandiflorus* polysaccharides combined with hesperidin exerted the synergistic effect of relieving ulcerative colitis in mice by modulating PI3K/AKT and JAK2/STAT3 signaling pathways, *Chin J Nat Med.* 23 (2025) 848-862. [https://doi.org/10.1016/s1875-5364\(25\)60913-7](https://doi.org/10.1016/s1875-5364(25)60913-7).
- [20] M.Q. Liu, C.J. Bao, X.F. Liang, et al., Specific molecular weight of *Lycium barbarum* polysaccharide for robust breast cancer regression by repolarizing tumor-associated macrophages, *Int J Biol Macromol.* 261 (2024) 129674. <https://doi.org/10.1016/j.ijbiomac.2024.129674>.
- [21] F.N. Razali, S.K. Sinniah, H. Hussin, et al., Tumor suppression effect of *Solanum nigrum* polysaccharide fraction on Breast cancer via immunomodulation, *Int J Biol Macromol.* 92 (2016) 185-193. <https://doi.org/10.1016/j.ijbiomac.2016.06.079>.
- [22] R. Liu, H. Zhu, J. Zhao, et al., *Lycium barbarum* Polysaccharide Inhibits E. coli-Induced Inflammation and Oxidative Stress in Mammary Epithelial Cells of Dairy Cows via SOCS3 Activation and MAPK Suppression, *Agriculture (Switzerland).* 12 (2022) 598. <https://doi.org/10.3390/agriculture12050598>.
- [23] Z. Lin, Y. Zhou, R. Chen, et al., Protective Effects of Chitosan Oligosaccharide Against Lipopolysaccharide-Induced Inflammatory Response and Oxidative Stress in Bovine Mammary Epithelial Cells, *Mar Drugs.* 23 (2025) <https://doi.org/10.3390/md23010031>.
- [24] H. Yin, G. Xue, A. Dai, et al., Protective Effects of Lentinan Against Lipopolysaccharide-Induced Mastitis in Mice, *Front Pharmacol.* 12 (2021) 755768. <https://doi.org/10.3389/fphar.2021.755768>.
- [25] J. Li, W. Yin, Y. Liang, et al., Pomegranate flower polysaccharide improves mastitis in mice by regulating intestinal flora and restoring the blood-milk barrier, *Front Pharmacol.* 15 (2024) 1427355. <https://doi.org/10.3389/fphar.2024.1427355>.
- [26] Y.-K. Xie, X.-Y. Pan, X.-R. Liang, et al., Research progress on structural characterization and bioactivities of *Poria cocos* and *Ganoderma* polysaccharides, *Food & Medicine Homology.* 2 (2025) 9420040. <https://doi.org/10.26599/FMH.2025.9420040>.
- [27] A. Coatrini-Soares, J.C. Soares, M. Popolin-Neto, et al., Multidimensional calibration spaces in *Staphylococcus Aureus* detection using chitosan-based genosensors and electronic tongue, *Int J Biol Macromol.* 271 (2024) 132460. <https://doi.org/10.1016/j.ijbiomac.2024.132460>.
- [28] P. Yadav, A.B. Yadav, P. Gaur, et al., Bioengineered Ciprofloxacin-Loaded Chitosan Nanoparticles for the Treatment of Bovine Mastitis, *Biomedicines.* 10 (2022) <https://doi.org/10.3390/biomedicines10123282>.
- [29] C.A. Godoy, I. Balic, A.A. Moreno, et al., Antimicrobial and Antibiofilm Activity of Chitosan Nanoparticles Against *Staphylococcus aureus* Strains Isolated from Bovine Mastitis Milk, *Pharmaceutics.* 17 (2025) <https://doi.org/10.3390/pharmaceutics17020186>.
- [30] B.N. Tran, H.T. Nguyen, J.O. Kim, et al., Combination of a chemopreventive agent and paclitaxel in CD44-targeted hybrid nanoparticles for breast cancer treatment, *Arch Pharm Res.* 40 (2017) 1420-1432. <https://doi.org/10.1007/s12272-017-0968-0>.
- [31] J. Xiong, B. Jiang, Y. Luo, et al., Multifunctional Nanoparticles Encapsulating *Astragalus* Polysaccharide and Gold Nanorods in Combination with Focused Ultrasound for the Treatment of Breast Cancer, *Int J Nanomedicine.* 15 (2020) 4151-4169. <https://doi.org/10.2147/ijn.S246447>.
- [32] F. Zheng, D. Tan, Y. Zheng, et al., A chitosan-based deep tumor-penetrating nano-photothermal agent for enhanced chemo-photothermal combination therapy, *Materials Today Chemistry.* 45 (2025) 102676. <https://doi.org/https://doi.org/10.1016/j.mtchem.2025.102676>.
- [33] Y.-L. Cui, B. Li, Hypoglycemic effects of edible fungus polysaccharides: A mini review, *Food & Medicine Homology.* 2 (2025) 9420046. <https://doi.org/10.26599/FMH.2025.9420046>.
- [34] X. Ran, Y. Li, W. Guo, et al., *Angelica sinensis* Polysaccharide Alleviates *Staphylococcus aureus*-Induced Mastitis by Regulating The Intestinal Flora and Gut Metabolites, *J Agric Food Chem.* 72 (2024) 24504-24517. <https://doi.org/10.1021/acs.jafc.4c06094>.

- [35] K. Li, X. Ran, J. Han, et al., *Astragalus* polysaccharide alleviates mastitis disrupted by *Staphylococcus aureus* infection by regulating gut microbiota and SCFAs metabolism, *Int J Biol Macromol.* 286 (2025) 138422. <https://doi.org/10.1016/j.ijbiomac.2024.138422>.
- [36] D. Zhang, G. Jin, W. Liu, et al., *Salvia miltiorrhiza* polysaccharides ameliorates *Staphylococcus aureus*-induced mastitis in rats by inhibiting activation of the NF- κ B and MAPK signaling pathways, *BMC Vet Res.* 18 (2022) 201. <https://doi.org/10.1186/s12917-022-03312-6>.
- [37] J.S. Moon, H.K. Kim, H.C. Koo, et al., The antibacterial and immunostimulative effect of chitosan-oligosaccharides against infection by *Staphylococcus aureus* isolated from bovine mastitis, *Appl Microbiol Biotechnol.* 75 (2007) 989-998. <https://doi.org/10.1007/s00253-007-0898-8>.
- [38] V. Felipe, M.L. Breser, L.P. Bohl, et al., Chitosan disrupts biofilm formation and promotes biofilm eradication in *Staphylococcus species* isolated from bovine mastitis, *Int J Biol Macromol.* 126 (2019) 60-67. <https://doi.org/10.1016/j.ijbiomac.2018.12.159>.
- [39] J.C. Soares, A.C. Soares, M. Popolin-Neto, et al., Detection of *Staphylococcus aureus* in milk samples using impedance spectroscopy and data processing with information visualization techniques and multidimensional calibration space, *Sensors and Actuators Reports.* 4 (2022) 100083. <https://doi.org/https://doi.org/10.1016/j.snr.2022.100083>.
- [40] A. Coatrini-Soares, J. Coatrini-Soares, M. Popolin Neto, et al., Microfluidic E-tongue to diagnose bovine mastitis with milk samples using Machine learning with Decision Tree models, *Chemical Engineering Journal.* 451 (2023) 138523. <https://doi.org/https://doi.org/10.1016/j.cej.2022.138523>.
- [41] M. Eskandari, Z. Abdolmaleki, F. Moosakhani, et al., Antimicrobial Efficacy of Cloxacillin-Loaded Chitosan Nanoparticles Against *Staphylococcus aureus* Biofilms in Subclinical Mastitis, *Curr Microbiol.* 82 (2025) 65. <https://doi.org/10.1007/s00284-024-04030-y>.
- [42] J. Tong, X. Hou, D. Cui, et al., A berberine hydrochloride-carboxymethyl chitosan hydrogel protects against *Staphylococcus aureus* infection in a rat mastitis model, *Carbohydr Polym.* 278 (2022) 118910. <https://doi.org/10.1016/j.carbpol.2021.118910>.
- [43] J. Tong, Z. Liu, K. Zhou, et al., Thermosensitive bovine lactoferricin-loaded chitosan hydrogels for sustained antibacterial release: An alternative to antibiotics for treating bovine mastitis, *Int J Biol Macromol.* 303 (2025) 140673. <https://doi.org/10.1016/j.ijbiomac.2025.140673>.
- [44] M.S. Orellano, P. Isaac, M.L. Breser, et al., Chitosan nanoparticles enhance the antibacterial activity of the native polymer against bovine mastitis pathogens, *Carbohydr Polym.* 213 (2019) 1-9. <https://doi.org/10.1016/j.carbpol.2019.02.016>.
- [45] P. Rivera Aguayo, T. Bruna Larenas, C. Alarcón Godoy, et al., Antimicrobial and Antibiofilm Capacity of Chitosan Nanoparticles against Wild Type Strain of *Pseudomonas sp.* Isolated from Milk of Cows Diagnosed with Bovine Mastitis, *Antibiotics (Basel).* 9 (2020) <https://doi.org/10.3390/antibiotics9090551>.
- [46] Y. Ping, C. Li, L. Wang, et al., Effects of *Atractylodes Macrocephala* Rhizoma polysaccharide on intestinal microbiota composition in rats with mammary gland hyperplasia, *Front Endocrinol (Lausanne).* 13 (2022) 1102605. <https://doi.org/10.3389/fendo.2022.1102605>.
- [47] H. Zhao, Y. Yang, Y. Zhou, et al., The anti-hyperplasia effect of polysaccharide from *Prunella vulgaris* L. on mammary gland hyperplasia in rats through regulation of the AKT-FOXO3a signaling pathway and intestinal flora, *J Sci Food Agric.* 104 (2024) 8190-8200. <https://doi.org/10.1002/jsfa.13652>.
- [48] C. Wang, W. Lin, Z. Sun, et al., *Porphyr* *haitanensis* polysaccharide (PH) attenuates cell hyperplasia via remodeling the cross-talk between Hippo/YAP and mTOR pathways, *Food Science and Human Wellness.* 12 (2023) 424-430. <https://doi.org/https://doi.org/10.1016/j.fshw.2022.07.044>.
- [49] X. Qiao, B. Wang, Z. Yuan, et al., The polysaccharides from Yiqi Yangyin complex attenuated mammary gland hyperplasia: Integrating underlying biological mechanisms and network pharmacology, *Journal of Functional Foods.* 88 (2022) 104878. <https://doi.org/https://doi.org/10.1016/j.jff.2021.104878>.
- [50] J. Zhang, K. Liu, T. Yang, et al., Mechanism of *Astragalus* Polysaccharide in Alleviating Bovine Mammary Fibrosis Through ROS/NLRP3 Inhibition and EMT Regulation, *Antioxidants (Basel).* 14 (2025) <https://doi.org/10.3390/antiox14050503>.

- [51] W. Li, X. Hu, Y. Li, et al., Cytotoxicity and growth-inhibiting activity of *Astragalus* polysaccharides against breast cancer via the regulation of EGFR and ANXA1, *J Nat Med.* 75 (2021) 854-870. <https://doi.org/10.1007/s11418-021-01525-x>.
- [52] C.I. Jen, L.T. Ng, Physicochemical Properties of Different Sulfated Polysaccharide Components from *Laetiporus sulphureus* and Their Anti-Proliferative Effects on MDA-MB-231 Breast Cancer Cells, *J Fungi (Basel)*. 10 (2024) <https://doi.org/10.3390/jof10070457>.
- [53] H.C. Lin, J.Y. Lin, GSF3, a polysaccharide from guava (*Psidium guajava* L.) seeds, inhibits MCF-7 breast cancer cell growth via increasing Bax/Bcl-2 ratio or Fas mRNA expression levels, *Int J Biol Macromol.* 161 (2020) 1261-1271. <https://doi.org/10.1016/j.ijbiomac.2020.06.057>.
- [54] Y. Zhang, D. Sun, Q. Meng, et al., *Grifola frondosa* polysaccharides induce breast cancer cell apoptosis via the mitochondrial-dependent apoptotic pathway, *Int J Mol Med.* 40 (2017) 1089-1095. <https://doi.org/10.3892/ijmm.2017.3081>.
- [55] N. Qin, S. Lu, N. Chen, et al., Yulangsan polysaccharide inhibits 4T1 breast cancer cell proliferation and induces apoptosis in vitro and in vivo, *Int J Biol Macromol.* 121 (2019) 971-980. <https://doi.org/10.1016/j.ijbiomac.2018.10.082>.
- [56] Z. Luo, X. Hu, H. Xiong, et al., A polysaccharide from Huaier induced apoptosis in MCF-7 breast cancer cells via down-regulation of MTDH protein, *Carbohydr Polym.* 151 (2016) 1027-1033. <https://doi.org/10.1016/j.carbpol.2016.06.046>.
- [57] Y.Z. Wu, J. Sun, Y.B. Wang, Selective estrogen receptor modulator: A novel polysaccharide from *Sparganii Rhizoma* induces apoptosis in breast cancer cells, *Carbohydr Polym.* 163 (2017) 199-207. <https://doi.org/10.1016/j.carbpol.2017.01.062>.
- [58] M. Xue, X. Ji, C. Xue, et al., Caspase-dependent and caspase-independent induction of apoptosis in breast cancer by fucoidan via the PI3K/AKT/GSK3 β pathway *in vivo* and *in vitro*, *Biomed Pharmacother.* 94 (2017) 898-908. <https://doi.org/10.1016/j.biopha.2017.08.013>.
- [59] Z. Li, M. Zhang, Y. Liu, et al., Advances in the Preparation, Structure-Activity Relationship, and Biological Mechanisms of *Agaricus* Polysaccharides, *Food Science and Human Wellness.* (2025) 1-26. <https://link.cnki.net/urlid/10.1750.ts.20250325.1317.006>
- [60] Z.-X. Wang, K. Huang, K.-L. Pu, et al., *Naematelia aurantialba*: a comprehensive review of its medicinal, nutritional, and cultivation aspects, *Food & Medicine Homology.* 2 (2025) 9420072. <https://doi.org/10.26599/FMH.2025.9420072>.
- [61] G.-Q. Fu, Y.-X. Li, Y. He, et al., Extraction, structure and bioactivity of *Tremella Fuciformis* polysaccharides: A review, *Food & Medicine Homology.* 2 (2025) 9420038. <https://doi.org/10.26599/FMH.2025.9420038>.
- [62] W.-Y. Fan, X.-X. Fan, Y.-J. Xie, et al., Research progress on the anti-aging effects and mechanisms of polysaccharides from Chinese herbal medicine, *Food & Medicine Homology.* 3 (2026) 9420108. <https://doi.org/10.26599/FMH.2026.9420108>.
- [63] W. Li, J. Wang, H. Hu, et al., Functional polysaccharide Lentinan suppresses human breast cancer growth via inducing autophagy and caspase-7-mediated apoptosis, *Journal of Functional Foods.* 45 (2018) 75-85. <https://doi.org/https://doi.org/10.1016/j.jff.2018.03.024>.
- [64] H.Y. Xu, L.Y. Liu, M. Ding, et al., Effect of *Ganoderma applanatum* polysaccharides on MAPK/ERK pathway affecting autophagy in breast cancer MCF-7 cells, *Int J Biol Macromol.* 146 (2020) 353-362. <https://doi.org/10.1016/j.ijbiomac.2020.01.010>.
- [65] N. Zhang, M. Xue, Q. Wang, et al., Inhibition of fucoidan on breast cancer cells and potential enhancement of their sensitivity to chemotherapy by regulating autophagy, *Phytother Res.* 35 (2021) 6904-6917. <https://doi.org/10.1002/ptr.7303>.
- [66] Y. Zhang, W. Wu, L. Kang, et al., Effect of *Aconitum coreanum* polysaccharide and its sulphated derivative on the migration of human breast cancer MDA-MB-435s cell, *Int J Biol Macromol.* 103 (2017) 477-483. <https://doi.org/10.1016/j.ijbiomac.2017.05.084>.
- [67] Y. Tian, J. Wu, L. Zeng, et al., Huaier polysaccharides suppress triple-negative breast cancer metastasis and epithelial-mesenchymal transition by inducing autophagic degradation of Snail, *Cell Biosci.* 11 (2021) 170. <https://doi.org/10.1186/s13578-021-00682-6>.
- [68] J.Y. Park, M.S. Shin, S.N. Kim, et al., Polysaccharides from Korean Citrus hallabong peels inhibit angiogenesis and breast cancer cell migration, *Int J Biol Macromol.* 85 (2016) 522-529. <https://doi.org/10.1016/j.ijbiomac.2016.01.015>.
- [69] X. He, M. Xue, S. Jiang, et al., Fucoidan Promotes Apoptosis and Inhibits EMT of Breast Cancer Cells, *Biol Pharm Bull.* 42 (2019) 442-447. <https://doi.org/10.1248/bpb.b18-00777>.

- [70] S. Yang, S. Sun, W. Xu, et al., *Astragalus* polysaccharide inhibits breast cancer cell migration and invasion by regulating epithelial-mesenchymal transition via the Wnt/ β -catenin signaling pathway, *Mol Med Rep.* 21 (2020) 1819-1832. <https://doi.org/10.3892/mmr.2020.10983>.
- [71] L. Wang, L. Zhao, F.L. Gong, et al., Modified citrus pectin inhibits breast cancer development in mice by targeting tumor-associated macrophage survival and polarization in hypoxic microenvironment, *Acta Pharmacol Sin.* 43 (2022) 1556-1567. <https://doi.org/10.1038/s41401-021-00748-8>.
- [72] Z. Guan, Y. Liu, P. Liu, et al., Lentinan regulates the immune efficacy of macrophage for lung metastasis in triple negative breast, *Journal of Functional Foods.* 105 (2023) 105560. <https://doi.org/https://doi.org/10.1016/j.jff.2023.105560>.
- [73] J. Wu, H. Li, X. Wang, et al., Effect of polysaccharide from *Undaria pinnatifida* on proliferation, migration and apoptosis of breast cancer cell MCF7, *Int J Biol Macromol.* 121 (2019) 734-742. <https://doi.org/10.1016/j.ijbiomac.2018.10.086>.
- [74] X. Wan, X. Jin, M. Xie, et al., Characterization of a polysaccharide from *Sanghuangporus vaninii* and its antitumor regulation via activation of the p53 signaling pathway in breast cancer MCF-7 cells, *Int J Biol Macromol.* 163 (2020) 865-877. <https://doi.org/10.1016/j.ijbiomac.2020.06.279>.
- [75] C.I. Jen, L.T. Ng, F2-sulfated polysaccharides of *Laetiporus sulphureus* suppress triple-negative breast cancer cell proliferation and metastasis through the EGFR-mediated signaling pathway, *Int J Biol Macromol.* 306 (2025) 141407. <https://doi.org/10.1016/j.ijbiomac.2025.141407>.
- [76] C.J. Bao, M.Q. Liu, Y.N. Liu, et al., A structurally distinct arabinose-bridged arabinogalactan from *Lycium barbarum* as a TLR4-activating adjuvant for nanovaccine-based cancer immunotherapy, *Carbohydr Polym.* 373 (2026) 124618. <https://doi.org/10.1016/j.carbpol.2025.124618>.
- [77] J.L. Duan, M.Q. Liu, Y.N. Liu, et al., Comparative study on physicochemical characterization and immunomodulatory activities of neutral and acidic *Lycium barbarum* polysaccharides, *Biomed Pharmacother.* 181 (2024) 117659. <https://doi.org/10.1016/j.biopha.2024.117659>.
- [78] W. Li, K. Song, S. Wang, et al., Anti-tumor potential of *astragalus* polysaccharides on breast cancer cell line mediated by macrophage activation, *Mater Sci Eng C Mater Biol Appl.* 98 (2019) 685-695. <https://doi.org/10.1016/j.msec.2019.01.025>.
- [79] J. Ding, Y. Guo, X. Jiang, et al., Polysaccharides Derived from *Saposhnikovia divaricata* May Suppress Breast Cancer Through Activating Macrophages, *Onco Targets Ther.* 13 (2020) 10749-10757. <https://doi.org/10.2147/ott.S267984>.
- [80] G. Jia, X. Shao, R. Zhao, et al., *Portulaca oleracea* L. polysaccharides enhance the immune efficacy of dendritic cell vaccine for breast cancer, *Food Funct.* 12 (2021) 4046-4059. <https://doi.org/10.1039/d0fo02522d>.
- [81] J. Gao, Y.N. Zhang, J. Cui, et al., A Polysaccharide From the Whole Plant of *Plantago asiatica* L. Enhances the Antitumor Activity of Dendritic Cell-Based Immunotherapy Against Breast Cancer, *Front Pharmacol.* 12 (2021) 678865. <https://doi.org/10.3389/fphar.2021.678865>.
- [82] A. Deng, R. Fan, J. Gou, et al., Innovative PDK1-Degrading PROTACs Transform Cancer Aerobic Glycolysis and Induce Immunogenic Cell Death in Breast Cancer, *Exploration (Beijing).* 5 (2025) e20240031. <https://doi.org/10.1002/exp.20240031>.
- [83] G. Deng, H. Lin, A. Seidman, et al., A phase I/II trial of a polysaccharide extract from *Grifola frondosa* (Maitake mushroom) in breast cancer patients: immunological effects, *J Cancer Res Clin Oncol.* 135 (2009) 1215-1221. <https://doi.org/10.1007/s00432-009-0562-z>.
- [84] F. Lyu, C. Xie, L. Zhang, et al., Nanotubes fabricated from a triple helix polysaccharide as a novel carrier delivering doxorubicin for breast cancer therapy, *Int J Biol Macromol.* 242 (2023) 124153. <https://doi.org/10.1016/j.ijbiomac.2023.124153>.
- [85] H. Jang, K. Zhi, J. Wang, et al., Enhanced therapeutic effect of paclitaxel with a natural polysaccharide carrier for local injection in breast cancer, *Int J Biol Macromol.* 148 (2020) 163-172. <https://doi.org/10.1016/j.ijbiomac.2020.01.094>.
- [86] R. Malviya, S. Raj, S. Fuloria, et al., Evaluation of Antitumor Efficacy of Chitosan-Tamarind Gum Polysaccharide Polyelectrolyte Complex Stabilized Nanoparticles of Simvastatin, *Int J Nanomedicine.* 16 (2021) 2533-2553. <https://doi.org/10.2147/ijn.S300991>.
- [87] L. Paoletti, N. Zoratto, M. Benvenuto, et al., Hyaluronan-estradiol nanogels as potential drug carriers to target ER+ breast cancer cell line, *Carbohydr Polym.* 314 (2023) 120900. <https://doi.org/10.1016/j.carbpol.2023.120900>.

-
- [88] L. Sun, X. Wang, B. Ma, et al., The study of the treatment of breast cancer by the combined photothermal therapy of *Lycium barbarum* polysaccharide doxorubicin gel, *Journal of Drug Delivery Science and Technology*. 93 (2024) 105429. <https://doi.org/https://doi.org/10.1016/j.jddst.2024.105429>.
- [89] J. Sui, M. He, Y. Yang, et al., Reversing P-Glycoprotein-Associated Multidrug Resistance of Breast Cancer by Targeted Acid-Cleavable Polysaccharide Nanoparticles with Lapatinib Sensitization, *ACS Appl Mater Interfaces*. 12 (2020) 51198-51211. <https://doi.org/10.1021/acsami.0c13986>.
- [90] B. Chen, X. Liu, Y. Li, et al., iRGD Tumor-Penetrating Peptide-Modified Nano-Delivery System Based on a Marine Sulfated Polysaccharide for Enhanced Anti-Tumor Efficiency Against Breast Cancer, *Int J Nanomedicine*. 17 (2022) 617-633. <https://doi.org/10.2147/ijn.S343902>.
- [91] B. Wang, C. Guo, Y. Liu, et al., Novel nano-pomegranates based on *astragalus* polysaccharides for targeting ER α -positive breast cancer and multidrug resistance, *Drug Deliv*. 27 (2020) 607-621. <https://doi.org/10.1080/10717544.2020.1754529>.
- [92] K. Ghosal, S. Ghosh, D. Ghosh, et al., Natural polysaccharide derived carbon dot based in situ facile green synthesis of silver nanoparticles: Synergistic effect on breast cancer, *Int J Biol Macromol*. 162 (2020) 1605-1615. <https://doi.org/10.1016/j.ijbiomac.2020.07.315>.
- [93] Y. Qi, Y. Yuan, Z. Qian, et al., Injectable and Self-Healing Polysaccharide Hydrogel Loading Molybdenum Disulfide Nanoflakes for Synergistic Photothermal-Photodynamic Therapy of Breast Cancer, *Macromol Biosci*. 22 (2022) e2200161. <https://doi.org/10.1002/mabi.202200161>.
- [94] L. Sun, B. Ma, C. Zuo, et al., Combination of chemotherapy with low-dose doxorubicin/*Lycium barbarum* polysaccharide and photothermal therapy with polypyrrole nanoparticles for treating breast cancer, *Journal of Drug Delivery Science and Technology*. 84 (2023) 104442. <https://doi.org/https://doi.org/10.1016/j.jddst.2023.104442>.