Research progress on plant polysaccharides in the prevention and treatment of tumors (Review)

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Abstract. With the increasing global burden of cancer, traditional chemotherapy is limited by issues such as high toxicity and poor targeting, making the development of new therapeutic strategies an urgent priority. As natural bioactive macromolecules, herbal polysaccharides have become a hotspot in antitumor research due to their multi-target effects, low toxicity, and excellent biocompatibility. The present review summarizes recent advances in the mechanisms of plant polysaccharides in antitumor activity and their applications in drug delivery systems. It highlights their synergistic antitumor effects through multiple pathways, including regulation of the immune microenvironment, induction of programmed cell death, modulation of the microbiota-immune axis, and inhibition of angiogenesis and metastasis. These compounds significantly enhance the efficacy of chemotherapy and immunotherapy while reversing drug resistance. Novel formulations such as polysaccharide-based nano-delivery systems, selenium-modified complexes and gel platforms have further improved drug targeting, stability, and immunomodulatory efficacy, providing a solid theoretical foundation and innovative directions for integrated traditional Chinese and Western medicine in cancer treatment.

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Abbreviations: DOX, doxorubicin; TIME, tumor immune microenvironment; Tregs, T cells; TAMs, tumor-associated macrophages; MDSCs, myeloid-derived suppressor cells; NK, natural killer; PD-L1, programmed death-ligand 1; TGF-β, transforming growth factor-beta; IL, interleukin; PD-1, programmed cell death protein 1; DCs, dendritic cells; IFN-γ, interferon-gamma; TNF-α, tumor necrosis factor-alpha; CD, cluster of differentiation; NF-κb, nuclear factor kappa B; MyD88, myeloid differentiation primary response 88; CXCL9, C-X-C motif chemokine ligand 9; Bcl-2, B-cell lymphoma 2; GPX4, glutathione peroxidase 4; ROS, reactive oxygen species; EMT, epithelial-mesenchymal transition; CCK-8, Cell Counting Kit-8; NSCLC, VEGF, vascular endothelial growth factor; 5-FU, 5-fluorouracil; PEI, polyethyl-enimine; FA, folic acid; PDT, photodynamic therapy; SeNPs, selenium nanoparticles; HA, hyaluronic acid; GL, glycyrrhizic acid; EPR, enhanced permeability and retention; PK, pharmacokinetic; PD, pharmacodynamic

Key words: plant polysaccharides, tumor, clinical research, drug delivery system, vaccine adjuvant

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1. Introduction

Cancer remains a major global public health challenge. Data indicate ~52,900 new cases and 27,000 deaths occur daily worldwide. By 2040, annual new cases are projected to exceed 28 million, with deaths reaching 16.2 million (1), highlighting an extremely severe prevention and control situation. Current main treatment modalities include surgery, chemotherapy, radiotherapy and immunotherapy. Although certain outcomes have been achieved, each has significant limitations (2). Surgery can remove primary tumors and metastatic lymph nodes but may not completely eradicate cancer cells, potentially even causing intraoperative dissemination and increasing the risk of metastasis and recurrence. Meanwhile, surgical trauma, anesthetic agents and other intraoperative management factors (such as pain, blood transfusion, fluctuations in body temperature and blood pressure) can collectively lead to immunosuppression, reduce antitumor immune responses, and affect patient prognosis (3). Radiotherapy, on the other hand, often damages surrounding normal tissues, inducing radioactive toxicities along with irreversible side effects such as hair

loss, nerve damage, weight changes and anemia, severely impacting patients' quality of life (4). For instance, doxorubicin (DOX) causes severe hair loss in patients with breast cancer (BC) (5), while some patients with prostate cancer (PC) and BC even experience treatment-related metabolic disorders and weight gain (6). Furthermore, tumor heterogeneity and drug resistance mechanisms limit the efficacy of conventional treatments (7). The high cost of therapy also imposes a heavy burden on patients and society. Although some synthetic drugs show potential effects in areas such as radioprotection, their clinical application remains limited due to significant toxicity and side effects.

Against this backdrop, natural plant polysaccharides have emerged as a promising strategy for adjuvant cancer therapy due to their multi-target effects, low toxicity, and excellent biocompatibility (8). Since their antitumor activity was first reported in 1946 (9), plant polysaccharides have been confirmed to possess dual mechanisms of immune regulation and direct antitumor effects: They not only activate innate and adaptive immune systems indirectly but also directly induce tumor cell apoptosis and inhibit proliferation. Moreover, they exhibit significant synergistic effects when combined with conventional chemotherapeutic agents. Furthermore, it has been recently revealed that plant polysaccharides can inhibit metastasis and invasion, induce various forms of programmed cell death (for example, apoptosis, pyroptosis and ferroptosis), regulate the cell cycle, remodel the immune microenvironment, and reverse multidrug resistance, demonstrating unique advantages in mitigating the toxic side effects of radiotherapy and chemotherapy (10). Currently, *Astragalus membranaceous* (Fisch.) Bunge polysaccharide (APS) injection is used to enhance immune function as an adjuvant in cancer treatment (11), and lentinan (a β-glucan polysaccharide isolated from the shiitake mushroom, *Lentinula edodes*) has been adopted as an adjuvant cancer therapy in some Asian countries, including Japan and China (12), offering new pathways for integrated traditional Chinese and Western medicine. More notably, plant polysaccharides show broad prospects in drug delivery systems. For example, the chitosan-guar gum/Cu_2O nanocomposite developed by Cheng *et al* (13) effectively inhibits lung cancer cells with low toxicity to normal cells. As an integrated 'therapeutic-carrier' system, plant polysaccharides possess biodegradability, hydrophilicity, ease of modification and intrinsic immunomodulatory activity. Their mucoadhesive properties and controllable degradation not only improve drug solubility and targeted delivery efficiency but also protect drugs from enzymatic degradation, enhancing treatment precision (14), thereby synergistically improving antitumor efficacy. Examples of plants with antitumor properties are illustrated in Fig. 1. Nevertheless, it must be acknowledged that the translational potential of plant polysaccharides is currently constrained by a lack of human pharmacokinetic (PK) and pharmacodynamic (PD) data, a critical gap that the present review also seeks to highlight.

The present review systematically summarizes recent advances over the past years in the antitumor mechanisms and drug delivery applications of plant polysaccharides, with a focus on their roles in modulating the immune microenvironment, inducing programmed cell death, regulating the microbiota-immune axis, inhibiting tumor metastasis and angiogenesis, and enhancing combined therapies. It aims to provide theoretical support and practical directions for developing novel antitumor formulations.

2. Antitumor effects of plant polysaccharides

Plant polysaccharides exert antitumor effects by modulating the tumor immune microenvironment (TIME). The TIME is a complex network composed of various immune cells, cytokines and physicochemical characteristics, playing a central regulatory role in the initiation and progression of tumors. Within this microenvironment, immunosuppressive cells such as regulatory T cells (Tregs), M2-type tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs) inhibit the function of cytotoxic T lymphocytes and natural killer (NK) cells by expressing molecules such as programmed death-ligand 1 (PD-L1), transforming growth factor-beta (TGF-β) and interleukin (IL)-10, thereby promoting immune escape. Tumor cells can also upregulate PD-L1, which binds to programmed cell death protein 1 (PD-1) on T cells, leading to T cell exhaustion. Meanwhile, features of the TIME, such as hypoxia, acidity and metabolic dysregulation, further impair immune cell function and facilitate angiogenesis and metastasis. Nevertheless, immune-promoting components, including M1-type macrophages, dendritic cells (DCs), and effector T cells, can still be activated to exert antitumor effects through the secretion of factors such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) (15,16), as illustrated in Fig. 2.

In recent years, numerous studies have demonstrated that plant polysaccharides exert antitumor effects by regulating key components of the TIME. Liu *et al* (17) found that *Bletilla striata* (Thunb.) Rchb.f. polysaccharides could activate TAMs, lymphocytes and NK cells, modulate the proportions of immune cell subsets, and inhibit tumor cell proliferation while promoting apoptosis (17). Yu *et al* (18) reported that APS inhibited self-renewal of melanoma stem cells, downregulated the expression of stem cell markers such as cluster of differentiation (CD)133, BMI1, and CD47, reduced PD-L1 expression, and promoted the infiltration of $CD4^+$ and $CD8^+$ T cells into tumor tissues (increasing by 2.3-fold and 3.1-fold, respectively) in a B16 melanoma mouse model. Wang *et al* (19) demonstrated that *Dendrobium officinale* Kimura and Migo polysaccharide (DOP) promoted the polarization of TAMs toward the M1 phenotype via Toll-like receptor (TLR) 2-mediated signaling, thereby inhibiting tumor growth. Liu *et al* showed that *Polygonatum sibiricum* Redouté polysaccharide (PSP) significantly inhibited the growth of castration-resistant PC-3 PC xenografts in nude mice and induced tumor cell apoptosis by downregulating the expression of PI3K, Akt, nuclear factor kappa B (NF-κB) p65 proteins and their phosphorylated forms in the PI3K/Akt and NF-κB signaling pathways, while upregulating caspase-3 expression. After 30 days of intervention, the tumor suppression effect of the high-dose PSP group was comparable to that of the docetaxel group (20). Similarly, PSP could polarize tumor-associated TAMs from the M2 to the M1 phenotype via theTLR4-mediated myeloid differentiation primary response 88 (MyD88)-dependent signaling pathway, significantly inhibiting liver cancer growth (21). Liang *et al* (22) purified a

Figure 1. Plants with antitumor activity. The image was created using Figdraw (www.figdraw.com).

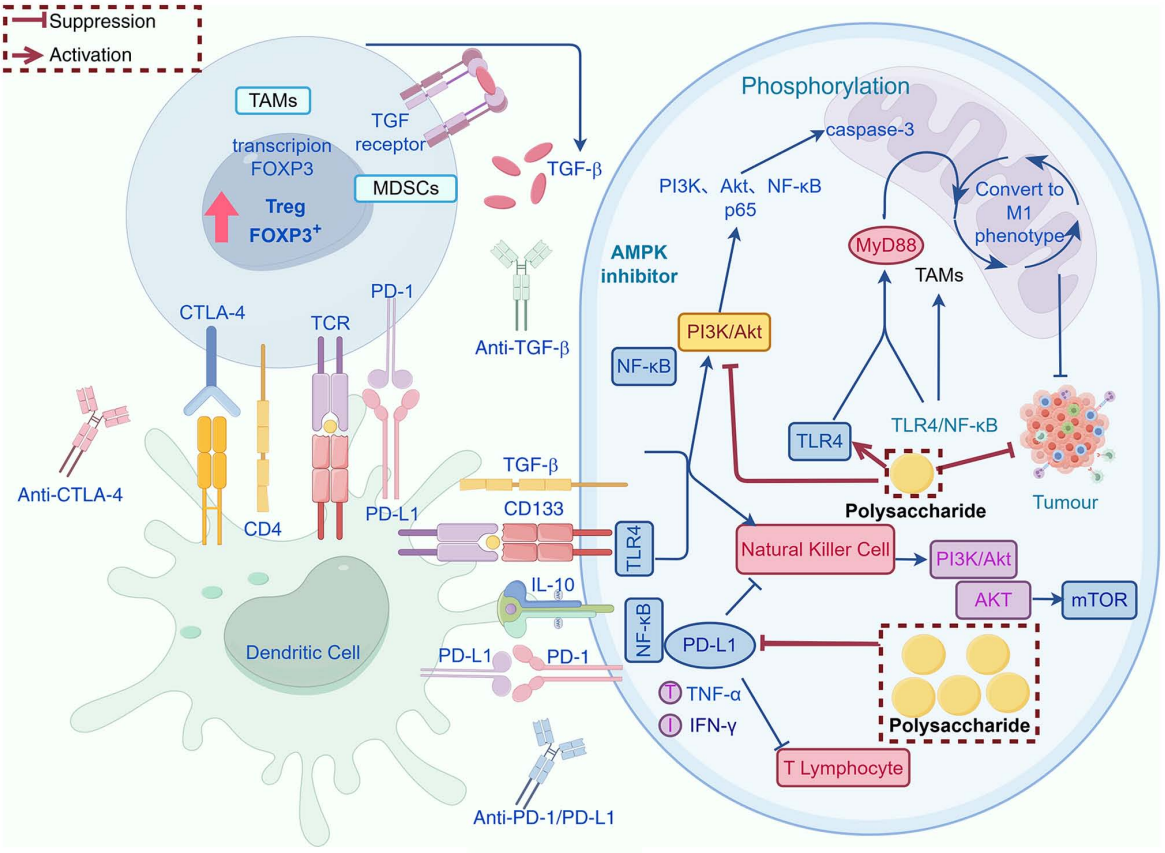

Figure 2. Plant polysaccharides modulate the TIME. The image was created using Figdraw (www.figdraw.com). TAMs, tumor-associated macrophages; MDSCs, myeloid-derived suppressor cells; IFN-γ, interferon-gamma; TNF-α, tumor necrosis factor-alpha; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TGF-β, transforming growth factor-beta; NF-κb, nuclear factor kappa B; TLR4, Toll-like receptor 4.

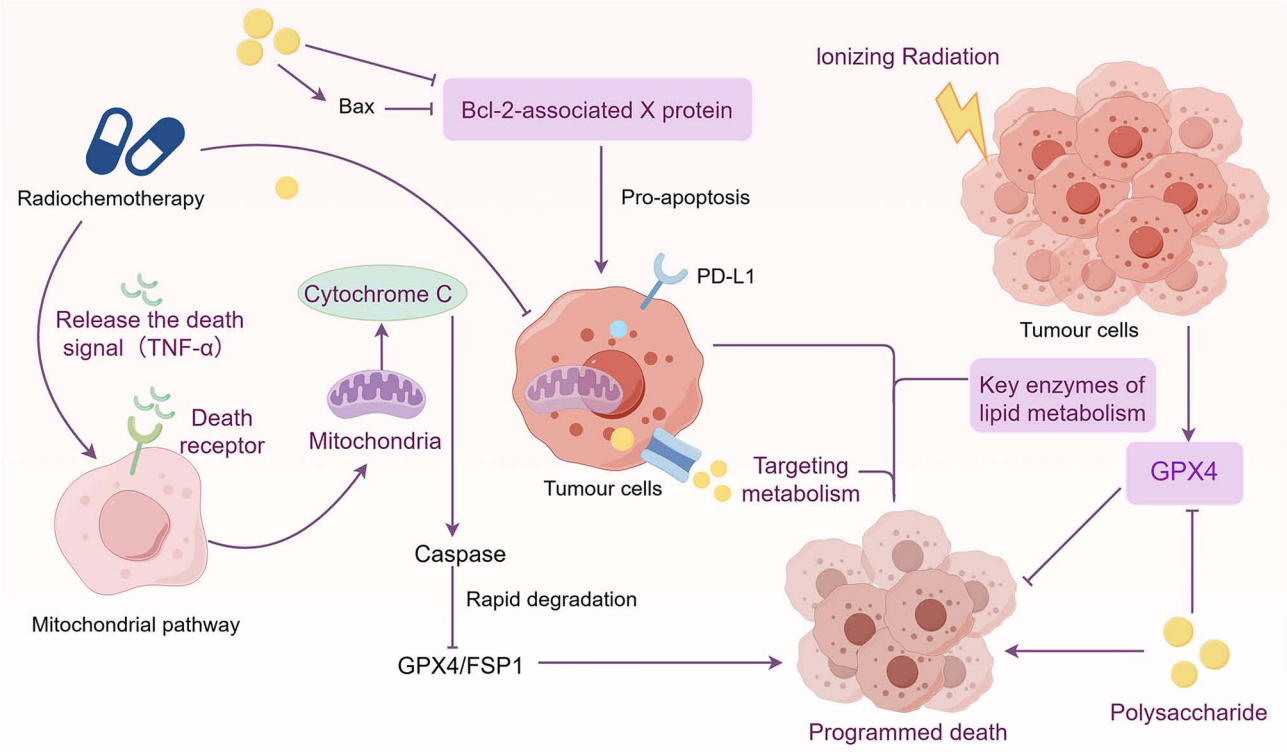

Figure 3. Plant polysaccharides induce programmed cell death in tumor cells. The image was created using Figdraw (www.figdraw.com). TNF-α, tumor necrosis factor-alpha; PD-L1, programmed death-ligand 1; GPX4, glutathione peroxidase 4; Bcl-2, B-cell lymphoma 2.

glucan, ASPN-1, from *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim., which elevated levels of IL-2, IFN-γ, and TNF-α, while reducing TGF-β and IL-10, thereby suppressing colorectal cancer (CRC) growth. Liao *et al* (23) indicated that *Crataegus pinnatifida* Bunge polysaccharide AF2 promoted the secretion of IL-1β, IL-6 and TNF-α by TAMs through the TLR4/NF-κB pathway. Wang *et al* (24) demonstrated that *Moringa oleifera* Lam. leaf polysaccharide reprogrammed tumor-associated TAMs from the pro-tumor M2 phenotype to the antitumor M1 phenotype by targeting TLR4 in a Lewis lung carcinoma-bearing mouse model, promoting the expression of C-X-C motif chemokine ligand 9 (CXCL9) and CXCL10, increasing intratumoral T cell infiltration, and thus remodeling the TIME to exert anti-lung cancer effects. Zhang *et al* (25) proved that two polysaccharide fractions, PLP-I and PLP-II, isolated and purified from *Plantago asiatica* L., significantly promoted the maturation of DCs, reduced the endocytic activity of DCs, stimulated the secretion of the inflammatory cytokine IL-12 p70, and markedly decreased tumor weight. Additionally, *Trachycarpus fortune* (Hook.) H.Wendl. polysaccharide induced tumor tissue necrosis and leukocyte infiltration by modulating oxidative stress and inflammatory responses without affecting normal metabolic functions (26).

Plant polysaccharides exert antitumor effects by inducing programmed cell death in tumor cells. Programmed cell death primarily includes apoptosis, pyroptosis and ferroptosis, and its dysregulation is closely associated with tumor initiation, progression and therapeutic response. On one hand, tumor cells can evade programmed cell death through various mechanisms, such as altering the B-cell lymphoma 2(Bcl-2)/Bcl-2-associated X protein (Bax) ratio to inhibit mitochondrial pathway apoptosis, thereby achieving sustained proliferation and acquiring drug resistance. On the other hand, inducing programmed cell death in tumor cells has become an important strategy in antitumor therapy. Conventional treatments such as chemotherapy and radiotherapy can activate caspase-dependent apoptotic pathways, while emerging strategies such as inducing ferroptosis [for example, by inhibiting key factors like glutathione peroxidase 4 (GPX4)] can specifically kill certain drug-resistant tumor cells. Furthermore, immune checkpoint inhibitors (for example, anti-PD-1/PD-L1 antibodies) can indirectly enhance the apoptosis-inducing effects of T cells on tumor cells by restoring T cell function. Therefore, targeting programmed cell death pathways has become a significant direction in antitumor drug development (27,28), as illustrated in Fig. 3.

Recent studies have shown that various plant polysaccharides can exert antitumor effects by inducing different forms of programmed cell death. *Salicornia europaea* L. polysaccharide SabPS-1 significantly inhibits the proliferation of HepG-2 cells (cell viability: 47.90±4.14% at 400 μg/ml) and induces apoptosis by regulating the expression of caspase 3, caspase 8, Bax and Bcl-2, demonstrating excellent antitumor properties (29). *Panax ginseng* C.A.Mey. acidic polysaccharide induces apoptosis in MGC803 cells via the mitochondrial pathway, improves the state of immune organs in H22 tumor-bearing mice, enhances immune cell activity, and increases serum cytokine levels. At a dose of 200 mg/kg, the tumor inhibition rate reaches 45.70% (30). *Zingiber officinale* Roscoe polysaccharide reduces lipid droplet accumulation by regulating key enzymes in lipid metabolism, cuts off the

energy supply of MDSCs, upregulates the pro-apoptotic protein caspase 9, and downregulates the anti-apoptotic protein Bcl-2, thereby inhibiting the proliferation and promoting the apoptosis of MSC-2 cells (31). Red *Panax ginseng* C.A.Mey. polysaccharide induces ferroptosis by downregulating GPX4 expression, inhibiting the growth of human lung cancer A549 cells (IC_{50}=376.2 μg/ml) and BC MDA-MB-231 cells (IC_{50}=311.3 μg/ml) (32). *Taraxacum mongolicum* Hand.-Mazz. leaf polysaccharide inhibits the proliferation of hepatocellular carcinoma cells in a dose-dependent manner by inducing apoptosis in HepG2 cells (manifested as morphological changes such as cell shrinkage and cytoskeleton disintegration) and arresting the cell cycle in the S-phase (33). Additionally, *Hemerocallis citrina* Baroni polysaccharide HcBPS2 significantly inhibits the proliferation of liver cancer cells without affecting normal liver cells by inducing G2/M phase arrest and mitochondrial-dependent apoptosis (34). Xiao *et al* (35) extracted polysaccharide CVP-2 from the whole plant of *Christia vespertilionis* (L.f.) Bakh.f., which at a concentration of 1,000 μg/ml, inhibits A549 lung cancer cells by 49.63% and HepG2 liver cancer cells by 28.56% by arresting the G1/S phase cell cycle and reducing the Bcl-2/Bax protein ratio. It also significantly promotes apoptosis while having no significant effect on 16HBE and LX-2 normal cells (inhibition rate <13%). *Alpinia officinarum* Hance polysaccharide AHP-3a can scavenge free radicals and inhibit the proliferation, migration and invasion of liver cancer cells (36). *Coriandrum sativum* L. polysaccharide significantly inhibits tumor growth in H22 liver cancer-bearing mice and exerts antitumor activity by inducing apoptosis and cell cycle arrest (37). *Platycodon grandiflorus* (Jacq.) A.DC. polysaccharide promotes ferroptosis in H1299 lung cancer cells by inducing mitochondrial dysfunction, lipid peroxidation and excessive reactive oxygen species (ROS) production, and inhibits cell migration by regulating the expression of epithelial-mesenchymal transition (EMT)-related proteins (38). Studies have shown that two novel heteropolysaccharides, YCJP-1 and YCJP-2, isolated from *Chloranthus japonicus* Siebold, along with the crude polysaccharide YCJP and its purified components, significantly inhibit the proliferation of MGC-803 and AGS gastric cancer (GC) cells as confirmed by Cell Counting Kit-8 (CCK-8) assay and colony formation assay. AGS cells are more sensitive, with YCJP-2 exhibiting superior anti-GC activity (39). *Aralia elata* (Miq.) Seem. polysaccharide also exerts antitumor effects by regulating apoptosis (40).

Plant polysaccharides inhibit tumors by regulating the gut microbiota-immune axis. The gut microbiota-immune axis plays a central regulatory role in the occurrence, development and treatment response of tumors. On one hand, specific beneficial microbiota can promote the maturation and activation of Tregs and DCs, thereby enhancing antitumor immune responses. On the other hand, dysbiosis may induce the accumulation of MDSCs and M2-type TAMs, forming an immunosuppressive microenvironment that promotes tumor progression (41), as shown in Fig. 4.

Recent studies have shown that various plant polysaccharides can enhance tumor treatment efficacy by regulating the gut microbiota-immune axis. For example, Huang *et al* (42) found that the combination of *Panax ginseng* C.A.Mey. polysaccharide and α-PD-1 monoclonal antibody (mAb) could reshape the gut microbiota structure (increasing the abundance of *Parabacteroides distasonis* and *Bacteroides vulgatus*) and metabolic profile (elevating valeric acid and reducing the kynurenine/tryptophan ratio), thereby improving the treatment response to PD-1 inhibitors in non-small cell lung cancer. In a mouse model transplanted with gut microbiota from non-responding patients, this combination strategy induced effector T cell expansion and suppressed Tregs, significantly enhancing anti-PD-1 immunotherapy efficacy (42). Zhang *et al* (43) also reported that *Dioscorea oppositifolia* L. polysaccharide synergistically enhanced the antitumor effect of αPD-1 mAb. Its mechanisms included optimizing gut microbiota composition (enriching beneficial bacteria such as *Clostridia* UCG-014 and reducing pathogenic bacteria such as *Enterorhabdus*), reversing tumor-associated metabolic disorders (inhibiting deoxyguanosine-mediated M2-type macrophage polarization), and improving the immune microenvironment (reducing $CD206^+$ M2-type TAMs and increasing $CD8^+$ T cell infiltration) (43). Furthermore, multi-omics analysis revealed that *Ocimum basilicum* L. polysaccharide could modulate the gut microbiota and its metabolites, enhancing the antitumor effect of gefitinib in a drug-resistant xenograft model. Its mechanism involved regulating cancer-related signaling pathways and lung resistance-related protein expression, further confirming the potential of plant polysaccharide-microbiota-host metabolic interactions in antitumor therapy (44).

Plant polysaccharides inhibit tumor angiogenesis and metastasis. Tumor angiogenesis and metastasis are two closely related biological processes in malignant tumor progression, collectively promoting invasive tumor growth and therapy resistance. Tumor cells secrete pro-angiogenic factors such as vascular endothelial growth factor (VEGF) to induce the formation of structurally abnormal neo-vessels from host blood vessels. These neo-vessels not only supply oxygen and nutrients to the tumor but also serve as channels for tumor cells to invade the circulatory system and undergo distant metastasis. Tumor cells enhance their migratory and invasive capabilities through EMT, subsequently infiltrating blood vessels to achieve hematogenous metastasis and form metastatic foci in distant organs (45). Therefore, inhibiting tumor angiogenesis has become an important strategy in antitumor therapy, as it can both cut off the tumor's nutrient supply and block metastasis pathways (Fig. 5).

Recent studies have found that various plant polysaccharides can exert antitumor effects by inhibiting angiogenesis and metastasis. *Glehnia littoralis* F.Schmidt ex Miq. polysaccharide inhibits angiogenesis by regulating the VEGF/VEGF receptor 2 (VEGF/VEGFR-2) signaling pathway, while simultaneously activating immune responses through interactions with TLR-4 and PD-1, thereby suppressing tumor development and metastasis (46). *Platycodon grandiflorus* (Jacq.) A.DC. polysaccharide PGP40-2B exhibits non-cytotoxic antitumor properties by targeting both VEGF and PD-1, simultaneously inhibiting angiogenesis and activating immune responses (47). *Rhodiola rosea* L. polysaccharide HJBP85-1 significantly inhibits tumor proliferation (93%) and metastasis (85%) in a zebrafish model. Its mechanisms include direct inhibition of

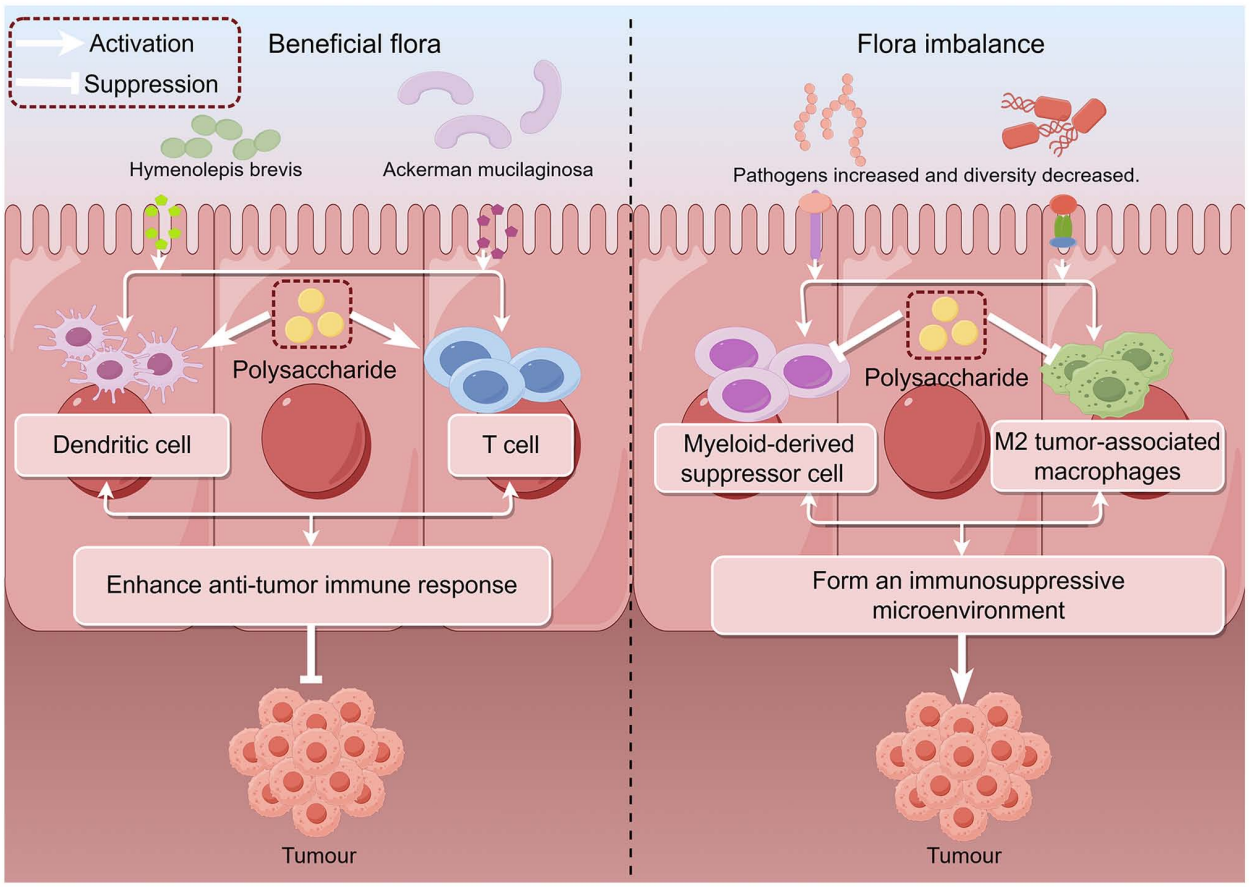

Figure 4. Role of the gut microbiota-immune axis in tumors. The image was created using Figdraw (www.figdraw.com).

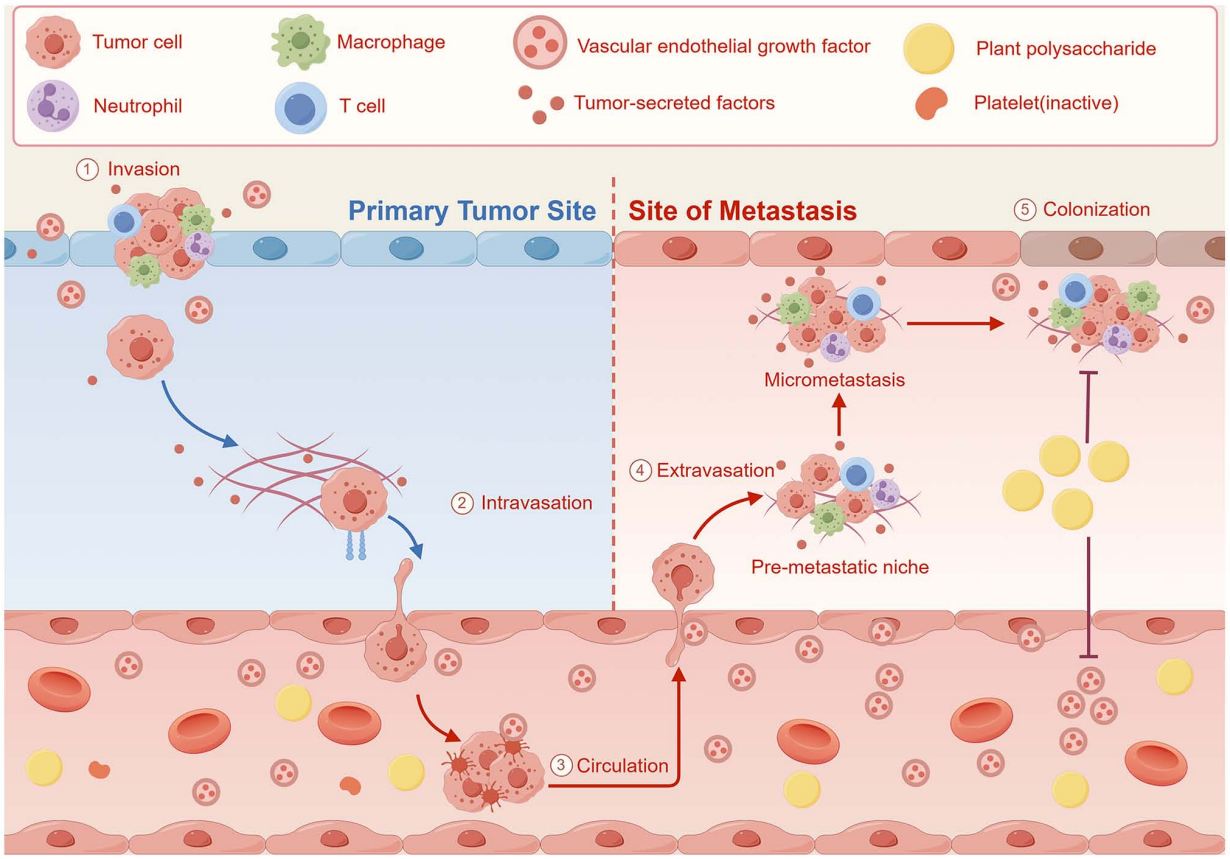

Figure 5. Plant polysaccharides inhibit tumor angiogenesis and metastasis. The image was created using Figdraw (www.figdraw.com).

angiogenesis and tumor cell migration, as well as modulation of the immune microenvironment by promoting M1 macrophage polarization and DC maturation (48). *Aconitum coreanum* (H.Lév.) Rapaics polysaccharide ACP1 and its derivatives can inhibit the migration and motility of BC cells by disrupting the dynamic remodeling of the actin cytoskeleton (49). Additionally, *Helianthus annuus* L. stem pith polysaccharide effectively inhibits tumor proliferation and metastasis by reducing TNF-α secretion from TAMs, significantly prolonging the survival of tumor-bearing mice (50).

Plant polysaccharides as synergistic agents in combination therapy. Plant polysaccharides can be combined with chemotherapy drugs to achieve multiple effects, including synergistic sensitization, reversal of drug resistance, and reduction of toxic side effects. In DOX treatment, APS enhances endoplasmic reticulum stress by reducing O-linked N-acetylglucosamine (O-GlcNAc) glycosylation levels, thereby promoting DOX-induced apoptosis in liver cancer cells and synergistically inhibiting tumor growth (51). *In vitro* experiments showed that *Codonopsis pilosula* (Franch.) Nannf. polysaccharide (CPP) exhibited the strongest antitumor activity (inhibition rate nearly equivalent to the 10 μg/ml DOX group at 125 μg/ml concentration). It significantly promoted nitric oxide secretion in macrophages. When combined with DOX, it achieved superior therapeutic effects compared with DOX alone through synergistic immunomodulation and direct cytotoxic effects (52). To address cisplatin resistance (53), *Angelica sinensis* (Oliv.) Diels polysaccharide effectively reverses cisplatin resistance in ovarian cancer cells by inhibiting GPX4 expression to induce ferroptosis, with a favorable safety profile (54). To improve the low oral bioavailability of genistein (55), pH-responsive nanoparticles constructed with genistein and *Lentinus edodes* polysaccharide simultaneously induce oxidative stress/apoptosis in tumor cells and promote the maturation and activation of DCs to initiate immune responses, demonstrating synergistic effects in inhibiting tumor growth and metastasis (12). 5-Fluorouracil (5-FU) is one of the most commonly used anticancer drugs approved by the U.S. Food and Drug Administration for the treatment of various solid tumors. It is a cornerstone of systemic combination chemotherapy for head and neck cancer, BC, CRC, and other gastrointestinal malignancies. However, 5-FU can induce oxidative stress leading to cardiotoxicity, clinically manifested as angina pectoris, pulmonary edema, congestive heart failure, myocardial infarction or ischemia, arrhythmias, and sudden cardiac death. It also easily leads to drug resistance (56,57). Chen *et al* (58) experimentally demonstrated that large-leaf yellow tea polysaccharide (ULYTP-1) can protect against chemotherapy drug toxicity by promoting autolysosome formation, activating autophagy, and alleviating 5-FU-induced oxidative stress and inflammatory responses. In a 4T1 tumor-bearing mouse model, ULYTP-1 reduced 5-FU toxicity by modulating the gut microbiota, while protecting immune organs and the liver, and enhancing the tumor-suppressive effect of 5-FU. This provides a new strategy for optimizing clinical chemotherapy regimens, as shown in Fig. 6.

In summary, various plant polysaccharides exert antitumor effects through multiple pathways. A summary of their biological and pharmacological activities is provided in Table I.

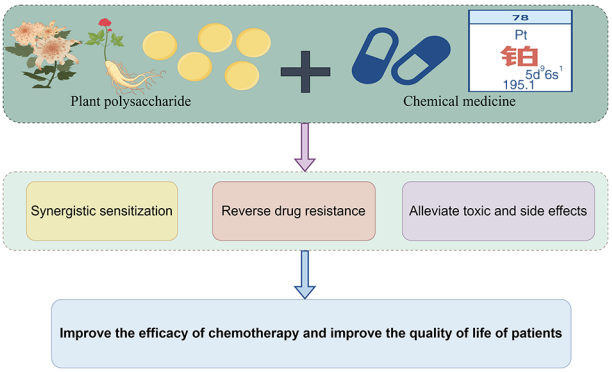

Figure 6. Synergistic antitumor effects of plant polysaccharides and chemical drugs. The image was created using Figdraw (www.figdraw.com).

3. Clinical trials on the antitumor effects of plant polysaccharides

Although modern medicine has yet to develop completely non-toxic drugs capable of curing tumors, traditional Chinese herbal medicine, a valuable legacy of East Asian traditional medicine, has demonstrated unique value in cancer treatment over thousands of years of practice. These herbs not only effectively alleviate clinical symptoms in patients but also significantly reduce the toxic side effects of radiotherapy and chemotherapy, providing an important complementary strategy within modern comprehensive cancer treatment systems. In recent years, plant polysaccharides, as key active components of Chinese herbal medicine, have garnered increasing attention for their antitumor effects. They not only directly inhibit tumor cells (for example, by inducing apoptosis and suppressing proliferation) but also indirectly exert antitumor effects by modulating the body's immune functions (for example, activating macrophages and T cells) and improving the tumor microenvironment (TME). Their diverse mechanisms of action, low toxicity, and multi-target characteristics make them an attractive research direction in the field of cancer therapy. The progress of clinical research on the antitumor effects of selected plant polysaccharides is summarized in Table II, providing a clearer understanding of their potential applications.

Despite these encouraging clinical observations, no plant polysaccharide has yet undergone a complete human PK and PD evaluation. Most clinical studies remain small-scale, open-label, or non-randomized, and none have reported complete human PK parameters such as plasma peak concentration, half-life, area under the curve, or absolute bioavailability. The major obstacles include: i) A lack of sensitive and validated analytical methods for detecting polysaccharides in biological fluids; ii) the widespread belief that polysaccharides are not systemically absorbed, which has led to the neglect of PK/PD studies; and iii) the structural heterogeneity of polysaccharide preparations, which complicates standardized quantification. Future research must prioritize dedicated human PK/PD trials using modern analytical techniques to address these gaps.

Table I. Biological and pharmacological activities of polysaccharides.

First author/s, year	Polysaccharide	Family	Average molecular weight	Properties	Antitumor	Optimal dose	Model	Pharmacological activity	Extraction/ Purification methods	(Refs.)
Liu and Liu, 2022	*Bletilla striata* (Thunb.) Rchb.f.	Orchidaceae	22.9 kDa	Neutral polysaccharide	Liver cancer	200 mg/kg	*In vivo*: H22 solid tumor mouse model	Protects immune organs and activates macrophages/ lymphocytes/ NK cells; modulates the ratio of lymphocyte subsets	Ethanol precipitation + DEAE-cellulose column chromatography	(17)
Yu *et al*, 2024	*Astragalus membranaceus* (Fisch.) Bunge	Fabaceae (Leguminosae)	-	-	Melanoma	200 mg/kg	*In vitro*: Melanoma stem cell model; *In vivo:* B16 melanoma mouse model	Inhibits the self-renewal capacity of cancer stem cells, reduces the expression of CD133/BMI1/CD47, and increases $CD4^+/CD8^+$ T cell immune infiltration	Hot water extraction + ethanol precipitation	(18)
Wang *et al*, 2022	*Dendrobium officinale* Kimura & Migo	Orchidaceae	-	-	Liver, lung, gastric and colon cancer	200 mg/kg	*In vivo*: Tumor-bearing mouse model	Orally targets TLR2 on TAMs, promotes the polarization of TAMs toward the M1 phenotype, with an inhibition rate of 72.61%.	Hot water extraction + ethanol precipitation	(19)
Liu *et al*, 2025	*Polygonatum sibiricum* Redouté	Liliaceae	-	Acidic polysaccharide	Prostate cancer	400 mg/kg	*In vivo*: PC-3 prostate cancer nude mouse xenograft model	Downregulates the PI3K/Akt and NF-κB pathways; upregulates caspase-3	-	(20)

Table I. Continued.

First author/s, year	Polysaccharide	Family	Average molecular weight	Properties	Antitumor	Optimal dose	Model	Pharmacological activity	Extraction/ Purification methods	(Refs.)
Leng *et al*, 2025			5.97 kDa	Neutral polysaccharide	Liver cancer	200 μg/ml/ 200 mg/kg	*In vitro*: Mouse macrophage cell line RAW264.7, human normal hepatocyte L02, mouse hepato-cellular carcinoma cell H22; *In vivo*: H22 hepato-cellular carcinoma subcutaneous xenograft model	Activates the TLR4/ MyD88-dependent signaling pathway, reverses TAMs from the M2 to M1 phenotype, promotes the secretion of immunomodulatory factors such as NO, TNF-α, and IL-12 p70, and enhances the $CD4^+/CD8^+$ T cell ratio	-	(21)
Liang *et al*, 2025	*Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim.	Araliaceae	33.31 kDa	Neutral polysaccharide	Colorectal cancer	200 mg/kg	*In vivo*: CT26.WT mouse colon cancer model; *In vitro*: BALB/c mouse	Increases IL-2, IFN-γ, and TNF-α; decreases TGF-β and IL-10; achieves a tumor inhibition rate of 52.78%.	-	(22)
Liao *et al*, 2024	*Crataegus pinnatifida* Bunge	Rosaceae	111.7 kDa	Acidic polysaccharide	-	400 μg/ml	*In vitro*: RAW264.7 mouse macrophage cell line	Activates the NF-κB signaling pathway, downregulates inhibitor of kappa B alpha, upregulates	-	(23)

Table I. Continued.

First author/s, year	Polysaccharide	Family	Average molecular weight	Properties	Antitumor	Optimal dose	Model	Pharmacological activity	Extraction/ Purification methods	(Refs.)
								phosphorylated IκBα and NF-κB P65, and promotes the secretion of IL-1β, IL-6, and TNF-α		
Wang *et al*, 2023	*Moringa oleifera* Lam. leaf	Moringaceae	17.35 kDa	Neutral polysaccharide	Lung cancer	200 μg/ml	*In vivo*: Lewis lung carcinoma-bearing mouse model; *In vitro*: Bone marrow-derived macrophage model	Targets TLR4 to reverse TAMs from the M2 to M1 phenotype and promotes the expression of CXCL9 and CXCL10	-	(24)
Zhang *et al*, 2025	*Plantago asiatica* L.	Plantaginaceae	1.42 kDa/ 12.73 kDa	Neutral/Acidic polysaccharide	Breast cancer	*In vitro* 5 μg/ml; *In vivo* 10 mg/kg	*In vitro*: Dendritic cell model, 4T1 breast cancer cells; *In vivo*: 4T1 breast cancer xenograft model	Promotes DC maturation, up-regulates MHC-II, CD80, and CD86, reduces the endocytic activity of DCs, and promotes the secretion of IL-12 p70. *In vivo*, significantly increases the proportion of $CD4^+$ and $CD8^+$ T cells in lymph nodes and elevates serum IFN-γ levels	Hot water extraction + ethanol precipitation + DEAE-Sepharose chromatography	(25)
de Oliveira *et al*, 2024	*Trachycarpus fortunei* (Hook.)	Arecaceae (Palmaceae)	70 kDa	Acidic polysaccharide	Ehrlich ascites	50 mg/kg	*In vivo*: Ehrlich	Decreases glutathione; increases	-	(26)

Table I. Continued.

First author/s, year	Polysaccharide	Family	Average molecular weight	Properties	Antitumor	Optimal dose	Model	Pharmacological activity	Extraction/ Purification methods	(Refs.)
	H.Wendl.				carcinoma tumor-bearing		ascites carcinoma-bearing mouse model	lipid peroxidase and NO; decreases IL-1β; increases TNF-α and N-acetyl-β-D-glucosaminidase		
Wang *et al*, 2024	*Salicornia europaea* L.	Chenopodiaceae	32.4 kDa	Acidic polysaccharide	Liver cancer	400 µg/ml	*In vitro*: HepG-2 hepato-cellular carcinoma cell model	Upregulates caspase-3, caspase-8, and Bax; downregulates Bcl-2	-	(29)
Dai *et al*, 2025	*Panax ginseng* C.A.Mey. acidic	Araliaceae	6,050 kDa	A*cid*ic polysaccharide	Gastric cancer	200 mg/kg	*In vitro*: MGC803 cells; *In vivo*: H22 tumor-bearing mice	Induces tumor cell apoptosis through the mitochondrial pathway; enhances immune organ function, improves immune cell activity and pro-apoptotic protein expression; achieves a tumor inhibition rate of 45.70%	-	(30)
Song *et al*, 2023	*Zingiber officinale* Roscoe	Zingiberaceae	-	-	MDSCs	200 µg/ml	*In vitro*: MSC-2 cells	Inhibits fatty acid synthase and diacylglycerol O-acyltransferase 2, reduces fatty acid synthesis and lipid droplet accumulation; upregulates caspase-9 and downregulates Bcl-2	-	(31)

Table I. Continued.

First author/s, year	Polysaccharide	Family	Average molecular weight	Properties	Antitumor	Optimal dose	Model	Pharmacological activity	Extraction/ Purification methods	(Refs.)
Zhai *et al*, 2022	Red *Panax ginseng* C.A.Mey.	Araliaceae	-	Neutral polysaccharide	Lung cancer	200 μg/ml	*In vitro*: A549 lung cancer and MDA-MB-231 breast cancer cell models	Targets and inhibits GPX4 expression, promotes lipid reactive ROS accumulation and lactate dehydrogenase release	-	(32)
Chen *et al*, 2022	*Taraxacum mongolicum* Hand.-Mazz.	Asteraceae (Compositae)	1,640 kDa	Acidic polysaccharide	Liver cancer	800 μg/ml	*In vitro*: HepG2 hepatocellular carcinoma cell model	Induces cell shrinkage and cytoskeleton disruption; arrests the cell cycle in the S-phase; cell viability is 29.4%	-	(33)
Sang *et al*, 2023	*Hemerocallis citrina* Baroni	Liliaceae	-	Acidic polysaccharide	Liver cancer	50-100 μg/ml	*In vitro*: Human hepatocellular carcinoma cell lines HepG2 and Bel-7402	Downregulates cyclin B1 and cyclin D1; upregulates p21; reduces mitochondrial membrane potential; promotes cytochrome c release; activates caspase-9 and caspase-3; and modulates the Bcl-2/Bax ratio	-	(34)
Xiao *et al*, 2025	*Christia vespertilionis* (L.f.) Bakh.f.	Fabaceae (Leguminosae)	92.92 kDa	Neutral polysaccharide	Lung cancer, Liver cancer	1,000 μg/ml	*In vitro*: A549 lung cancer and HepG2 hepatocellular carcinoma cell models	Decreases the Bcl-2/Bax protein ratio; arrests the cell cycle at the G1/S phase; achieves an inhibition rate of 49.63%	-	(35)

Table I. Continued.

First author/s, year	Polysaccharide	Family	Average molecular weight	Properties	Antitumor	Optimal dose	Model	Pharmacological activity	Extraction/ Purification methods	(Refs.)
Wen *et al*, 2024	*Alpinia officinarum* Hance	Zingiberaceae	484 kDa	Acidic polysaccharide	Liver cancer	0.5 mg/ml	*In vitro*: HepG2 and Huh7 hepatocellular carcinoma cell models	Inhibits cell proliferation, migration, and invasion	-	(36)
Chang *et al*, 2022	*Coriandrum sativum* L.	Apiaceae (Umbelliferae)	1,300 kDa	Acidic polysaccharide	Liver cancer	300 µg/ml	*In vivo*: H1299 human NSCLC cells	Induces mitochondrial pathway apoptosis in cancer cells; arrests the cell cycle in the S-phase; protects immune organ function	-	(37)
Wu *et al*, 2025	*Platycodon grandiflorus* (Jacq.) A.DC.	Campanulaceae	7.036 kDa	Neutral polysaccharide	NSCLC	200 µg/ml	*In vitro*: H1299 lung cancer cell model	Induces ferroptosis and regulates EMT-related proteins	Ultrasound-assisted + natural deep eutectic solvent extraction + ethanol precipitation	(38)
Liu *et al*, 2024	*Chloranthus japonicus* Siebold	Chloranthaceae	0.848-5.81 kDa	Neutral polysaccharide	Gastric cancer	600 µg/ml	*In vitro*: MGC-803 and AGS gastric cancer cell models	CCK-8 and colony formation assays confirm anticancer effects	-	(39)
Liang *et al*, 2025	*Aralia elata* (Miq.) Seem.	Araliaceae	7.809 kDa	Acidic polysaccharide	Osteosarcoma, lung cancer, lung cancer, melanoma	1,000 µg/ml	*In vitro*: U2OS, LLC, A549, and B16 cell models	Binds with high affinity to the TLR4 receptor and activates the mitogen-activated protein kinase and NF-κB signaling pathways	-	(40)

Table I. Continued.

First author/s, year	Polysaccharide	Family	Average molecular weight	Properties	Antitumor	Optimal dose	Model	Pharmacological activity	Extraction/ Purification methods	(Refs.)
Huang *et al*, 2022	*Panax ginseng* C.A.Mey.	Araliaceae	-	-	Lung cancer	200 mg/kg	*In vivo*: Syngeneic mouse model	Modulates the gut microbiota, inhibits Tregs, and activates effector T cells to enhance the efficacy of PD-1 inhibitors; tumor growth inhibition rates are 75.2 and 65.1%, respectively	-	(42)
Zhang *et al*, 2025	*Dioscorea oppositifolia* L.	Dioscoreaceae	-	Neutral polysaccharide	Colorectal cancer	100 mg/kg	*In vitro*: C57BL/6 colorectal cancer cell model; *In vivo*: C57BL/6 mice and BALB/c mice	Enriches beneficial bacteria such as Clostridia UCG-014 and reduces pathogenic bacteria such as *Enterorhabdus*; inhibits deoxyguanosine-mediated M2 macrophage polarization; reduces $CD206^+$ M2-type TAMs and increases $CD8^+$ T cell infiltration	-	(43)
Feng *et al*, 2024	*Ocimum basilicum* L.	Lamiaceae (Labiatae)	-	Acidic polysaccharide	Lung cancer	200 mg/kg	*In vivo*: Immunodeficient gefitinib-resistant xenograft mouse model	Modulates gut microbiota and their metabolites, affecting the expression of lung cancer drug resistance-related proteins	-	(44)

Table I. Continued.

First author/s, year	Polysaccharide	Family	Average molecular weight	Properties	Antitumor	Optimal dose	Model	Pharmacological activity	Extraction/ Purification methods	(Refs.)
Liu *et al*, 2024	*Glehnia littoralis* F.Schmidt ex Miq.	Apiaceae (Umbelliferae)	7.76 kDa	Neutral polysaccharide	Liver cancer	400 μg/ml	*In vivo*: Zebrafish tumor model; *In vitro*: HepG2 and DC2.4 cells	Activates the TLR-4 pathway to promote the maturation of DC2.4 cells and macrophages; strongly interacts with PD-1 to alleviate immuno-suppression; regulates the VEGF/VEGFR-2 signaling pathway	-	(46)
Liu *et al*, 2024	*Platycodon grandiflorus* (Jacq.) A.DC.	Campanulaceae	7.05 kDa	Acidic polysaccharide	Solid malignant tumors	400 μg/ml	*In vivo*: Zebrafish model	Targets and inhibits tumor angiogenesis and acts on PD-1 to activate immune responses	-	(47)
Chen *et al*, 2025	*Rhodiola rosea* L.	Crassulaceae	13 kDa	Neutral polysaccharide	Liver cancer	400 μg/ml	*In vivo*: Zebrafish xenograft model	Directly inhibits tumor cell migration and blocks angiogenesis; promotes M1 macro-phage polarization and dendritic cell maturation; achieves proliferation and metastasis inhibition rates of 93 and 85%, respectively	-	(48)
Zhang *et al*, 2017	*Aconitum coreanum* (H.Lév.) Rapaics	Ranunculaceae	67.6 kDa	Neutral polysaccharide	Breast cancer	400 μg/ml	*In vitro*: Human breast cancer cell line MDA-MB-435s	Inhibits cell migration, disrupts actin cytoskeleton reorganization, and blocks signal molecule phosphorylation	-	(49)

Table I. Continued.

First author/s, year	Polysaccharide	Family	Average molecular weight	Properties	Antitumor	Optimal dose	Model	Pharmacological activity	Extraction/ Purification methods	(Refs.)
Meng *et al*, 2024	*Helianthus annuus* L. stem pith	Asteraceae (Compositae)	472 kDa	Acidic polysaccharide	Lung cancer	250 mg/kg	*In vivo*: Lung cancer metastasis syngeneic mouse model	Reduces TNF-α secretion by macrophages; prolongs the survival of tumor-bearing mice and inhibits metastasis	-	(50)
Li *et al*, 2023	*Astragalus membranaceous* (Fisch.) Bunge	Fabaceae (Leguminosae)	-	-	Liver cancer	50 mg/kg	*In vivo*: Hep3B xenograft tumor model	Reduces O-GlcNAc glycosylation levels to enhance endoplasmic reticulum stress; promotes DOX-induced apoptosis in hepatocellular carcinoma cells and synergistically inhibits tumor growth	Hot water extraction + ethanol precipitation	(51)
Li *et al*, 2023	*Codonopsis pilosula* (Franch.) Nannf.	Campanulaceae	60-100 kDa	Neutral polysaccharide	Melanoma	125 μg/ml	*In vitro*: B16-F10 cells; *In vivo*: Melanoma model	Directly inhibits tumor cell proliferation *In vitro*; increases the M1/M2 macrophage ratio *In vivo*	-	(52)
Guo *et al*, 2024	*Angelica sinensis* (Oliv.) Diels	Apiaceae (Umbelliferae)	-	Acidic polysaccharide	Ovarian cancer	200 μg/ml	*In vivo*: Xenograft model	Inhibits GPX4 expression to induce ferroptosis	-	(54)
Lin *et al*, 2024	Lentinan	Marasmiaceae	18 kDa	Neutral polysaccharide	Lung cancer, Liver cancer	*In vitro* 4.8 μg/ml 9.6 μg/ml *In vivo* 46-124 μg/ml	*In vitro*: Human lung cancer cells A549, human hepatocellular carcinoma cells	Promotes dendritic cell maturation and upregulates the expression of costimulatory molecules CD40, CD80, CD86, and MHC-II	Hot water extraction + ethanol precipitation + ultrafiltration centrifugation	(12)

Table I. Continued.

First author/s, year	Polysaccharide	Family	Average molecular weight	Properties	Antitumor	Optimal dose	Model	Pharmacological activity	Extraction/ Purification methods	(Refs.)
							HepG2, mouse dendritic cells DC2.4; *In vivo*: Zebrafish embryo xenograft model			
Chen *et al*, 2024	Large-leaf yellow tea	Theaceae	12.9 kDa	Acidic polysaccharide	Breast cancer	200 mg/kg	*In vivo*: BALB/c female mice, 4T1 breast cancer xenograft model	Enhances the antitumor effect of 5-Fu and reduces its hepatotoxicity; activatesthe PTEN-induced putative kinase 1/Parkin pathway and modulates gut microbiota; reduces oxidative stress and inflammation	-	(58)

"-" indicates that the specific value was not clearly reported in the original reference, or that the original reference did not provide specific extraction/purification methods (only mentioned "extraction" or "purification" without detailed steps); MHC-II, major histocompatibility complex class II; NSCLC, non-small cell lung cancer.

Table II. Summary of clinical trials on the antitumor effects of plant polysaccharides.

First author/s, year	Polysaccharide	Study type and participants	Main outcomes and findings	(Refs.)
Shen *et al*, 2024	*Astragalus membranaceous* (Fisch.) Bunge	Randomized, placebo-controlled trial in 66 breast cancer patients undergoing anthracycline-based chemotherapy (Phase II)	The APS group showed significantly less deterioration in global fatigue scores among premenopausal patients compared to the placebo group (P<0.05), along with significantly greater improvement in overall quality of life, without increasing chemotherapy-related toxicity	(59)
Tsao *et al*, 2021		Retrospective analysis of 53 lung cancer patients treated with immune checkpoint inhibitors combined with chemotherapy	APS injection resulted in a reduction or stabilization of the NLR in 91.3% of patients, which was significantly higher than the control group (63.3%, P=0.028). Additionally, the NLR in the APS group decreased significantly by 31.60% from baseline (P=0.012), while no significant change was observed in the control group	(60)
Li *et al*, 2022		Randomized control trial in 248 patients with breast cancer or malignant lymphoma	The polysaccharide group demonstrated significant advantages in cardiac protection: at the 6-month follow-up, left ventricular ejection fraction and parameters assessing ventricular diastolic function were significantly higher (P<0.05), while markers of myocardial injury and the incidence of cardiotoxicity were significantly lower (P<0.05)	(61)
Hsieh *et al*, 2020		Phase II trial in 17 patients with advanced head and neck squamous cell carcinoma	APS injection significantly reduced the incidence of severe treatment-related adverse events and improved patient quality of life in terms of pain, appetite, and social eating behavior	(62)
Ma *et al*, 2014	*Panax ginseng* C.A.Mey.	RCT in 96 patients with NSCLC	In the polysaccharide combined with chemotherapy group, serum levels of IFN-γ, IL-2, and the Th1/Th2 ratio were significantly increased (P<0.05), while levels of IL-4, IL-5, and Functional Assessment of Cancer Therapy-Lung scores were significantly decreased (P<0.01)	(63)
Wang *et al*, 2024	Lentinan	Meta-analysis including 52 RCTs involving patients with advanced malignant tumors	Polysaccharide combination therapy significantly improved treatment efficacy (risk ratio, RR=1.40) and quality of life (RR=1.45), while reducing the risk of gastrointestinal reactions (RR=0.86), without increasing overall adverse reactions	(64)

NLR, neutrophil-to-lymphocyte ratio; RCT, randomized controlled trial.

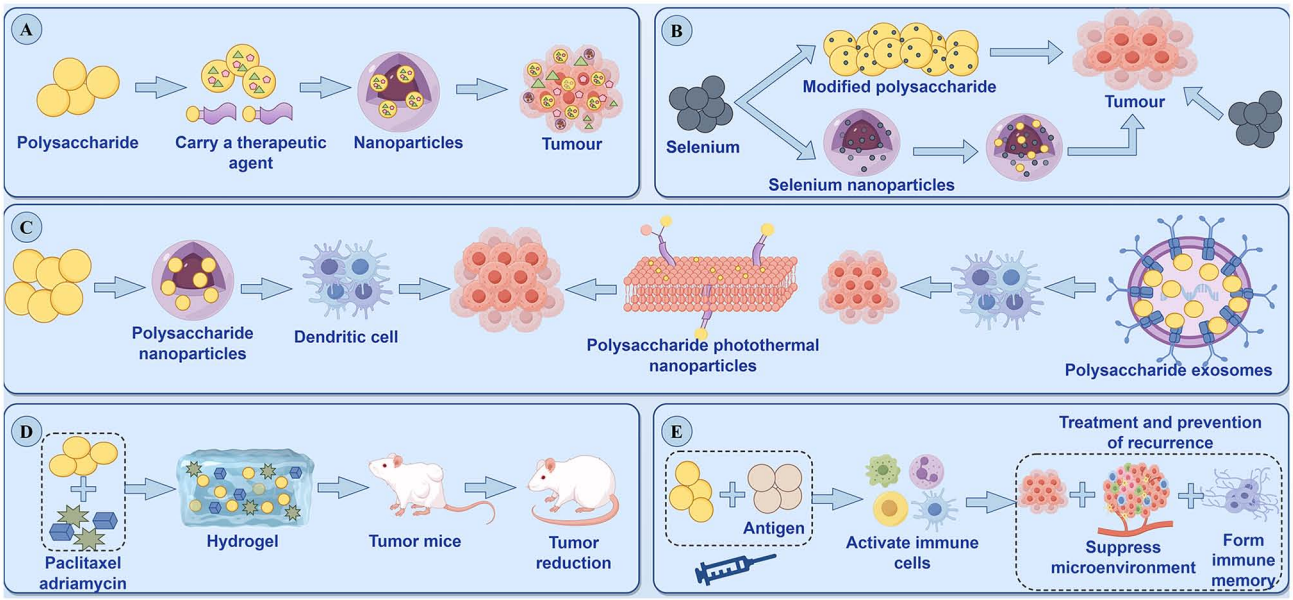

Figure 7. Synergistic antitumor effects of plant polysaccharide-based drug delivery systems. (A) Polysaccharides modified with various therapeutic agents in nano-delivery systems for antitumor effects. (B) Antitumor effects of selenium-modified polysaccharides or polysaccharide nano-selenium. (C) Antitumor effects of polysaccharide nano-delivery systems, polysaccharide-based photothermal nanoparticles and exosome-polysaccharide composite systems. (D) Antitumor effects of glycosyl-based gels. (E) Antitumor effects of polysaccharides as vaccine adjuvants. The image was created using Figdraw (www.figdraw.com).

4. Drug delivery systems based on plant polysaccharides

In recent years, the emergence of nanomedicine has opened a promising new avenue for cancer treatment. Among various materials, polysaccharides play a significant role in nanodrug delivery systems due to their unique properties. They can serve as a 'shell' for hydrophilic nanoparticles, ensuring drug stability during blood circulation. Meanwhile, some polysaccharides possess cross-linking and adhesive properties, facilitating sustained and controlled drug release. Owing to these advantages, drug delivery systems constructed from plant polysaccharides demonstrate superior performance in targeting, biocompatibility, tissue permeability, and immunomodulation compared with non-polysaccharide-based nanoparticles (65). Furthermore, polysaccharide-based delivery systems can effectively evade phagocytosis by the reticuloendothelial system, prevent degradation of biomolecules, and enhance the bioavailability of small molecules, thereby maximizing therapeutic efficacy (66). Studies have confirmed that surface modification of drug delivery systems with polysaccharides not only effectively addresses limitations of conventional systems, such as poor stability, rapid clearance *in vivo*, tendency to aggregate and fuse, and susceptibility of phospholipid molecules to degradation, hydrolysis and oxidation, but also synergizes with other functional materials to construct novel composite delivery systems. This significantly improves the physical stability of formulations, controlled release profiles, and cellular uptake efficiency (67). For example, Lee *et al* (68) developed plant polysaccharide nanoparticles with CD44 receptor-binding affinity via a simple one-pot nanoprecipitation method. These polysaccharide nanoparticles self-assembled for active targeting without requiring chemical modification. Paclitaxel-loaded plant polysaccharide nanoparticles exhibited stronger anticancer activity in CD44-positive cancer cells (SCC7 cells). In SCC7 tumor-bearing mice, the accumulation of these nanoparticles in tumor tissues was 3.7-fold higher than that of free dye, confirming the efficient targeted drug delivery capability of plant polysaccharide nanocarriers (Fig. 7A-E).

Polysaccharide-modified nano-delivery systems. Polysaccharides can carry various therapeutic agents and combine with nanoparticles to achieve targeted delivery and stimulus-responsive release, significantly enhancing tumor accumulation and cellular internalization efficiency of drugs, as shown in Fig. 7A. For example, Ma *et al* (69) constructed a functional gene vector by grafting polyethyl-enimine (PEI) onto the backbone of *Panax notoginseng* (Burkill) F.H.Chen polysaccharide (PNP), which was then loaded with shRNA targeting PD-L1 to form therapeutic nanoparticles termed PNP-PEI/shPD-L1. Experiments confirmed that these nanoparticles efficiently delivered shPD-L1 to B16-F10 tumor cells and significantly inhibited PD-L1 expression. Meanwhile, PNP-PEI promoted the polarization of macrophages from the M2 to M1 phenotype and facilitated the maturation of DCs, thereby enhancing the host immune response and improving antitumor efficacy. This demonstrates the dual functionality of natural polysaccharides as both carriers and immunomodulators in combined gene-immunotherapy.

Gong *et al* (70) experimentally demonstrated that manganese dioxide nanoparticles modified with APS polysaccharide and an indocyanine green analog IR820 (MnO_2@APS-IR820; 193.4±1.7 nm) responded to glutathione in the TME to release Mn^{2+}, which significantly promoted the maturation of bone marrow-derived DCs and induced the repolarization of TAMs from the M2 to M1 phenotype. When combined with APS-IR820 nanoparticles (220.1±11.2 nm) loaded with squamocin (Squ), the treatment achieved ~92% tumor suppression in a 4T1 tumor-bearing mouse model by activating both innate and adaptive immune responses. Tao *et al* (71) demonstrated that nanoparticles constructed using immunomodulatory DOP as the carrier and folic acid (FA) as the targeting ligand

(FA@Dox nanoparticles) delivered Dox to BC sites via dual passive and active targeting mechanisms. The released Dox directly eliminated tumor cells, while DOP enhanced immunogenic cell death through multiple immunomodulatory effects, including promoting NK cell proliferation and DC maturation. *In vivo* experiments significantly inhibited primary tumor growth and prevented lung metastasis. When DOP was modified with cholesterol to form an amphiphilic nano-system loaded with a cationic aggregation-induced emission photosensitizer TPA-3BCP, the system not only promoted dendritic cell maturation via DOP itself, but also effectively captured tumor antigens released after photodynamic therapy (PDT) and enhanced antigen uptake by DCs due to its positive surface charge. Under light irradiation, the high reactive ROS generation capability of TPA-3BCP synergized with the immunomodulatory function of DOP, significantly enhancing the antitumor immune response post-PDT (72).

Antitumor applications of selenium-modified polysaccharides and selenium nanoparticles. In drug delivery systems, selenium can serve as a carrier or modifying group for antitumor drugs, enhancing their targeting capability and antitumor efficacy, as illustrated in Fig. 7B. Liu *et al* (73) experimentally demonstrated that polysaccharide YDOP-1 (molecular weight 13,456 Da, identified as an O-acetylated glucomannan) isolated from *Dendrobium officinale* Kimura & Migo exhibited moderate inhibitory activity against GC cells. After selenium modification, the resulting YDOP-Se, formed via Se-O bonds, significantly enhanced its anti-GC effects by effectively inhibiting the proliferation of MGC-803 cells and inducing apoptosis through regulation of apoptotic proteins such as Bax, Bcl-2 and Caspase-7. These findings indicate that selenium modification markedly improves the antitumor activity of DOP. Similarly, *Dioscorea oppositifolia* L. polysaccharides modified with different selenium contents, prepared by controlling the amount of sodium selenite added, showed not only significantly improved emulsification, foaming, and antioxidant capacities compared with unmodified *Dioscorea oppositifolia* L. polysaccharides, but also enhanced tolerance to simulated gastrointestinal environments (74).

Selenium nanoparticles (SeNPs), as a novel anticancer agent, exhibit higher bioactivity and lower toxicity compared with traditional selenium compounds. However, they tend to aggregate into large black elemental selenium particles, limiting their clinical application (75). To address this, researchers have utilized polysaccharides to stabilize SeNPs, which not only significantly improves the stability of the nanocomplexes but also enhances their antitumor efficacy, offering a new strategy for developing highly effective and low-toxicity nano-selenium antitumor drugs (76,77). Zhang *et al* (78) employed *Prunella vulgaris* L. heteroxylan polysaccharide PVP3-1 as a stabilizer to successfully construct zero-valent red spherical SeNPs (PVP3-1-SeNPs) with an average diameter of ~60 nm and high stability in aqueous solution. *In vitro* antitumor experiments against pancreatic cancer demonstrated that PVP3-1-SeNPs inhibited cancer cell proliferation and migration and induced both apoptosis and autophagy by blocking the mTOR signaling pathway, confirming the potential application value of polysaccharide-stabilized SeNPs in pancreatic cancer therapy.

Novel polysaccharide-based drug delivery approaches for antitumor therapy. Due to their unique immunomodulatory activity and excellent biocompatibility, natural polysaccharides have become ideal components for constructing synergistic antitumor systems. They cannot only directly participate in reprogramming the immune microenvironment as active ingredients but also serve as intelligent carriers to achieve the integration of chemotherapy, photothermal/photodynamic therapy, and immunotherapy, significantly enhancing antitumor efficacy and overcoming drug resistance issues, as illustrated in Fig. 7C. In the context of immuno-chemotherapy synergy, Lin *et al* (79) developed pH-responsive nanoparticles utilizing *Physalis peruviana* L. polysaccharide to promote dendritic cell maturation, synergizing with honokiol-induced reactive ROS-mediated apoptosis pathways. This system demonstrated a dual enhancement mechanism in inhibiting the growth of MCF-7 and HeLa tumor (79). For immuno-photothermal synergistic strategies, Chen *et al* (80) constructed *Prunus persica* (L.) Batsch polysaccharide-based photothermal nanoparticles, which not only achieved near-infrared-triggered mild photothermal therapy but also reversed the immunosuppressive microenvironment by polarizing macrophages toward the M1 phenotype. These nanoparticles significantly suppressed CT26 tumor progression via the mitochondrial apoptosis pathway, characterized by upregulation of Bax, downregulation of Bcl-2, and cytochrome C release (80). Zhang *et al* (81) pioneered a novel approach using an exosome-polysaccharide composite system: Encapsulating *Lonicera japonica* Thunb. polysaccharide into exosomes enabled effective targeting of lymph nodes and enhanced the antigen-presenting capacity of DCs, thereby eliciting a robust $CD8^+$ T cell response in immune-cold tumors (81). Collectively, these cases demonstrate that natural polysaccharides integrate diverse therapeutic modalities through multiple mechanisms, showing strong application prospects in the field of synergistic antitumor therapy.

Antitumor effects of polysaccharide-based gels. Polysaccharide-constructed three-dimensional gel networks enable sustained and controlled drug release, mitigate the toxic side effects of conventional chemotherapy, and enhance local therapeutic efficacy, as depicted in Fig. 7D. For instance, Wang *et al* (82) developed a dual-responsive nanogel that co-delivers APS and baicalein. This system not only improves drug solubility but also effectively suppresses lung cancer progression through the synergistic effects of immunomodulation and chemotherapy, achieving a 35% increase in inhibition rate *in vitro* (82). Zhao *et al* (83) developed a novel hydroalcoholic physical gel based on CPP-G. This gel forms a physically cross-linked network via hydrophobic association of polysaccharide chains, exhibiting excellent mechanical strength and self-recovery properties. *In vitro* experiments demonstrated that the CPP-G loaded with paclitaxel and DOX enabled sustained drug release and exhibited synergistic antitumor effects against 4T1 and MCF-7 BC cell lines, confirming the potential of natural polysaccharides in constructing injectable drug-loaded gel systems.

Halder *et al* (84) experimentally demonstrated that a nanofiber-based local delivery system constructed from hyaluronic acid (HA) and loaded with glycyrrhizic acid (GL) and methotrexate possesses excellent mechanical properties (breaking force: 50 g) and muco-adhesiveness (153 gm/cm^2).

This system significantly enhanced the apoptosis-inducing effect of methotrexate on oral epidermal carcinoma cells (KB cells), achieving an apoptosis rate of 63.97±1.99% at 24 h. In a mouse model of Ehrlich ascites carcinoma, the nanofiber system effectively promoted tumor regression through the synergistic anti-inflammatory effect of GL while reducing mucositis-related inflammation, confirming that the HA-based nanofiber system improves oral cancer treatment efficacy via the localized co-delivery of chemotherapeutic and anti-inflammatory agents.

Adjuvant function of polysaccharides in tumor vaccines. Vaccination, as one of the most influential public health prevention measures in human history, has garnered broad recognition within the scientific community for its effectiveness. In the cutting-edge field of cancer immunotherapy, tumor vaccines have attracted significant research interest due to their unique advantages. As a highly promising approach for cancer prevention and treatment, the rational selection of adjuvants is a critical aspect of vaccine development. Although adjuvant vaccine delivery platforms have demonstrated remarkable potential in achieving antigen-targeted delivery and eliciting potent immune responses, very few candidate adjuvants have met the stringent criteria of being non-toxic and safe for human use despite comprehensive evaluation over the past few decades (85,86), as shown in Fig. 7. A novel and biosafe nanoparticle adjuvant system was constructed by loading *Dioscorea oppositifolia* L. polysaccharide as an immuno-enhancer onto aluminum hydroxide nanoparticles, which significantly enhanced immune responses (87). APS has been used as an immunomodulator to enhance immune responses due to its non-toxicity (88). For example, Cao *et al* (89) demonstrated through *in vitro* and *in vivo* experiments that a nano-vaccine (NP-TCL@APS) prepared by co-loading colorectal tumor cell lysate and APS into poly(lactic-co-glycolic acid) nanoparticles significantly promoted DC uptake and activation. In a mouse model, it enhanced antigen-specific $CD8^+$ T cell responses, suppressed tumor growth, and exhibited favorable biocompatibility.

Similarly, Li *et al* (90) extracted two polysaccharides with different molecular weights (APS, 12.19 kDa and APSHMw, 135.67 kDa) and constructed ovalbumin (OVA)/APS nano-vaccines (APS-NVs) via microfluidic technology. These nano-vaccines, coated with a shedable calcium phosphate layer for enhanced stability, were efficiently taken up by DCs. Experiments confirmed that APS-NVs activate DCs via dectin-1/TLR2/4 pathways and promote antigen cross-presentation. In a B16-OVA melanoma model, they significantly enhanced cytotoxic T cell infiltration and suppressed tumor growth (outperforming the OVA + Alum group). Experiments in nude mice verified that the antitumor effect depends on adaptive immune responses, demonstrating the dual functionality of APS as both a nano-vaccine carrier and an immune adjuvant, without systemic side effects.

Targeting mechanisms of polysaccharide-based nanocarriers. Polysaccharide-based nanocarriers achieve tumor-specific drug delivery through multiple mechanisms, primarily including receptor-mediated active targeting, passive targeting via the enhanced permeability and retention (EPR) effect, and microenvironment-stimuli-responsive release.

Receptor-mediated targeting is the most widely used strategy, in which different polysaccharides recognize distinct receptors due to their structural diversity: i) Mannose receptors are highly expressed on macrophages and DCs. APS and DOP can bind to mannose receptors, promote the polarization of TAMs toward the M1 phenotype, enhance the antigen-presenting capacity of DCs, and thereby reverse the immunosuppressive microenvironment (19,70,89). ii) Dectin-1 receptor is the primary recognition receptor for β-glucans. Lentinan and APS can activate innate immune responses by binding to Dectin-1, promote DC maturation and cytotoxic T lymphocyte activation, which underlies its function as a tumor vaccine adjuvant and immunomodulator (12,90). iii) TLR family receptors are key targets for the immunological activity of polysaccharides. APS, DOP and *Moringa oleifera* Lam. leaf polysaccharide can activate the downstream MyD88/NF-κB pathway through TLR2 or TLR4 signaling, induce macrophage polarization and inflammatory cytokine secretion, and subsequently remodel the TIME (19,21,24). iv) CD44 receptors are overexpressed on the surface of various tumor cells. Polysaccharides such as chitosan and hyaluronic acid can achieve active targeted delivery by binding to CD44. The plant polysaccharide nanoparticles developed by Lee *et al* (68) utilized this property to achieve CD44-targeted drug delivery without chemical modification. Passive targeting is primarily achieved through the EPR effect. Polysaccharide nanoparticles with a particle size in the range of 50-200 nm can selectively accumulate in tumor tissues due to the leaky vasculature and impaired lymphatic drainage, which is a core mechanism enabling the efficient tumor enrichment of various polysaccharide nanocarriers, such as MnO_2@APS-IR820 and FA@DOP nanoparticles (70,71). Stimuli-responsive release further enhances the precision of drug delivery. The weakly acidic TME (pH 6.0-6.8) and the even lower pH within endosomes/lysosomes (pH 4.5-5.5) can trigger the cleavage of pH-sensitive bonds. The pH-responsive *Physalis peruviana* L. polysaccharide nanoparticles developed by Lin *et al* (79) utilized this property to achieve the simultaneous release of chemotherapeutic drugs and immunoadjuvants. Meanwhile, the high concentration of glutathione in tumor cells can cleave redox-responsive linkers such as disulfide bonds, enabling intracellular-specific drug release. In addition, polysaccharide nanocarriers can prolong their retention time in the gastrointestinal tract or at the tumor site through mucoadhesive properties. The injectable CPP-G formed a three-dimensional network via hydrophobic association of polysaccharide chains, achieving long-term controlled drug release and enhanced local efficacy (83).

In summary, polysaccharide nanocarriers integrate multiple mechanisms including receptor recognition, the EPR effect, stimuli responsiveness, and muco-adhesion, enabling selective accumulation in tumor tissues, precise regulation of immune cells, and controlled drug release. This represents a key technological advancement for plant polysaccharides, transitioning them from 'active ingredients' to 'intelligent delivery systems'. The characteristics of representative polysaccharide-based nanocarriers are compared in Table III.

5. Conclusions and prospects

In recent years, plant polysaccharides have achieved groundbreaking progress in cancer prevention and treatment. Their

Table III. Comparison of different plant polysaccharide-based nanocarriers.

First author/s, year	Polysaccharide	Targeting receptor/mechanism	Drug loading efficiency	Key advantage	Limitation	(Refs.)
Lin *et al*, 2024	Lentinan	Dectin-1 receptor	Low to moderate	Triple-helix structure provides stability; clinically used in Asia	Poor water solubility for high-molecular-weight fractions	(12)
Cheng *et al*, 2025	Chitosan	CD44 receptor, muco-adhesion	Moderate to high	Biodegradable, easily chemically modifiable, low toxicity	Poor solubility at neutral pH; requires acidification	(13)
Wang *et al*, 2022; Tao *et al*, 2025; Tao *et al*, 2023	DOP	Mannose receptor, TLR2	Moderate	Dual function: intrinsic immune activity plus targeted carrier capability	High raw material cost; limited supply	(19,71,72)
Li *et al*, 2023; Zhao *et al*, 2023	CPP	Physical cross-linking network (gel), muco-adhesion	High	Injectable physical gel enables long-term controlled drug release	Mechanical strength needs further improvement	(52,83)
Gong *et al*, 2025; Cao *et al*, 2024; Li *et al*, 2024	APS	Mannose receptor, TLR2/ TLR4, Dectin-1	Moderate	Intrinsic immunomodulatory activity synergizes with carrier function; enhances anti-tumor immunity	Limited chemical modification sites; batch-to-batch variability	(70,89,90)
Lin *et al*, 2025	*Physalis peruviana* L.	pH-responsive acidic (tumor microenvironment)	High	pH-responsive nanoparticles enable chemo-immunotherapy synergy	Degradation rate control requires further optimization	(79)
Chen *et al*, 2025	*Prunus persica* (L.) Batsch	M1 macrophage polarization, mitochondrial apoptosis pathway	Moderate	Combines photothermal conversion capability with immunomodulatory function	Photothermal stability requires optimization	(80)
Zhang *et al*, 2025	*Lonicera japonica* Thunb.	Lymph node targeting, DC antigen presentation	Moderate	Efficient lymph node targeting after exosome encapsulation; enhances $CD8^+$ T cell response	Complex exosome extraction process	(81)
Halder *et al*, 2024	Hyaluronic acid	CD44 receptor (high affinity)	Moderate to high	Natural CD44 ligand; excellent biocompatibility	Expensive; susceptible to enzymatic degradation by hyaluronidase	(84)

DOP, *Dendrobium officinale* Kimura and Migo polysaccharide; CPP, *Codonopsis pilosula* (Franch.) Nannf. polysaccharide; APS, *Astragalus membranaceous* (Fisch.) Bunge polysaccharide.

unique bioactivities and structural plasticity offer a novel paradigm for oncology therapy. Studies have shown that polysaccharides from dozens of medicinal plants, including species from Araliaceae, Orchidaceae and Asteraceae, exert antitumor effects by modulating multiple pathways such as ferroptosis, immune microenvironment remodeling, and cell cycle arrest. Moreover, these polysaccharides exhibit synergistic effects with chemotherapeutic agents like cisplatin and docetaxel, enhancing efficacy while significantly reducing toxic side effects.

The innovative design of polysaccharide-based nano-delivery systems has further overcome the limitations of conventional chemotherapy. Through targeted delivery, stimulus-responsive release, and immunomodulatory functions, these systems enable chemo-immunotherapy combinations. In addition, the development of selenium-modified polysaccharides and polysaccharide-based vaccine adjuvants has expanded their applications in precision medicine. Clinical trials have confirmed that formulations such as APS can effectively improve patients' quality of life, marking a significant transition from basic research to clinical application.

Despite these achievements, several critical limitations remain unaddressed. First, current studies rely heavily on *in vitro* cell lines and rodent models, while human PK and PD data are extremely scarce; indeed, no complete human PK profile for any plant polysaccharide has been published to date. The oral bioavailability of plant polysaccharides is generally presumed to be low due to high molecular weight and poor intestinal permeability, yet this presumption has never been rigorously tested in humans. Systematic human PK/PD studies are urgently needed to determine absorption, distribution, metabolism and excretion characteristics. Second, most antitumor mechanisms have been demonstrated only in homogeneous tumor models, failing to reflect the heterogeneity of human cancers. Third, the structure-activity relationship of polysaccharides remains poorly defined, hindering rational drug design.

Safety and toxicity considerations also warrant attention. Although plant polysaccharides are generally regarded as safe, systematic toxicological evaluation remains underreported. Commonly used polysaccharides such as lentinan and APS exhibit low acute toxicity in animal models (LD_{50} >2 g/kg). However, potential adverse effects include mild gastrointestinal discomfort, rare immunogenic reactions (for example, cytokine release syndrome at high doses), and risks of heavy metal contamination from crude extracts. Future studies should adhere to standardized toxicological evaluation guidelines (for example, OECD 423) and report complete histopathology, serum biochemistry, and organ toxicity data, especially for nano-formulated polysaccharides where altered biodistribution may introduce new safety concerns.

Looking forward, with the increasing integration of structure-activity relationship studies, nanotechnology, and biomedicine, the application prospects of plant polysaccharides in oncology are expanding. Future research should prioritize the following directions:

i) Basic research: Precise structural elucidation and functional modification of polysaccharides, employing synthetic biology to construct intelligent responsive delivery systems for spatiotemporally controlled drug release and immune microenvironment programming.

ii) Mechanism exploration: Integration of artificial intelligence and multi-omics technologies to establish structure-function correlation models, elucidate how polysaccharides regulate the microbiota-immune-metabolism network, and identify novel biomarkers and combination targets.

iii) Quality control: Standardization of raw material cultivation and extraction processes to improve polysaccharide consistency and stability.

iv) Drug delivery: Development of environment-responsive polysaccharide carriers to achieve precise drug delivery.

v) Combination therapy: Thorough investigation of synergistic mechanisms between polysaccharides and emerging therapies such as immunotherapy and gene editing to promote multimodal combination strategies.

vi) Clinical translation: Large-sample, multi-center trials to establish evidence-based medication guidelines and quality control standards, with particular emphasis on reversing drug resistance, inhibiting metastasis, and synergizing with cutting-edge technologies such as chimeric antigen receptor T-cell therapy and mRNA vaccines.

In summary, plant polysaccharides have not only deepened our understanding of antitumor molecular mechanisms but also provided a rich natural molecular library and novel technological platforms for developing highly effective, low-toxicity anticancer drugs. Through interdisciplinary collaboration and industry-academia partnerships, plant polysaccharides are expected to lead the way toward a new era of highly effective, low-toxicity, and personalized cancer treatment, providing solutions for global cancer control.

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Availability of data and materials

Not applicable.

Authors' contributions

JKW conceptualized the study, developed methodology, prepared the original draft, and conducted formal analysis and investigation. YHW conducted data validation, wrote, reviewed and edited the manuscript, and performed project administration and visualization. XWZ curated data, provided resources, supervised the study, and acquired funding. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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