WEP Warwick Evans Publishing

Transactions on Materials, Biotechnology and Life Sciences
ISSN: 2960-1932, eISSN: 2960-2319 | Volume 7
MISBP 2024

Progress in Structural Modification and Anti-Tumor Activity of Plant Polysaccharides: Enhancing Efficacy and Bioavailability

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Abstract. Plant polysaccharides are a class of widely distributed biomolecules with significant and diverse bioactivities, such as anti-tumor, anti-inflammatory, antioxidant, antimicrobial and immunoregulation, making them promising candidates for anti-tumor biopharmaceuticals. In this review, recent advancements in the anti-tumor research of plant polysaccharides are summarized from three perspectives: the inherent anti-tumor activity of plant polysaccharides, the enhancement of this activity through chemical modifications, and the development of polysaccharide-based drug delivery systems. Chemical modifications, especially sulfation, phosphorylation, acetylation, and carboxymethylation, have been shown to significantly enhance the antitumor efficacy of plant polysaccharides by promoting apoptosis and modulating immune responses. Furthermore, polysaccharide-based drug delivery systems have been proven effective in reducing tumor drug resistance and improving bioavailability. Based on these findings, we propose two key directions for future research: first, translating these advancements into clinical applications to benefit patients, and second, deepening interdisciplinary research to further enhance our understanding and application of plant polysaccharides in cancer therapy.

Keywords: Plant Polysaccharides, Anti-tumor, Artificial modification, Polysaccharide material.

1. Introduction

Plant polysaccharides are biomolecules consisting of various monosaccharide units, such as glucose, galactose, mannose, xylose, arabinose, and ribose, linked by glycosidic bonds. Common plant polysaccharides include starch, xyloglucan, mannose, and cellulose [1]. These polysaccharides are widely distributed across different plant parts, including leaves, pods, flowers, and fruits, making them a diverse and abundant biological resource [2]. In addition to their structural diversity, plant polysaccharides exhibit a range of biological activities. These include anti-angiogenesis, immunomodulation, modulation of the tumor microenvironment, induction of apoptosis, and cell cycle arrest. Such properties make plant polysaccharides promising candidates as natural anti-tumor agents with relatively fewer side effects [3]. As a result, they have garnered significant attention in the field of anti-tumor research.

However, despite these promising characteristics, the current research on the anti-tumor activities of plant polysaccharides is still far from comprehensive. The majority of studies have focused on a limited number of polysaccharides, leaving a vast number of potentially beneficial polysaccharides underexplored. Furthermore, although natural polysaccharides have demonstrated significant anti-tumor potential, the enhancement of their activity through artificial modifications, such as sulfation, phosphorylation, acetylation, and carboxymethylation, has become a research hotspot. These modifications can improve the biological activity of polysaccharides, thereby enhancing their anti-tumor effects [4].

Additionally, the application of plant polysaccharides in the preparation of nanocomposites has shown promise in improving drug stability and bioavailability, further expanding their potential in cancer treatment. Despite these advances, there is still a lack of comprehensive reviews that systematically summarize the current progress in this field and highlight the existing challenges.

Based on the above analysis, we hypothesize that a systematic review of the current research on plant polysaccharides' anti-tumor activities, including both natural and artificially modified polysaccharides, will provide valuable insights that can guide future research in this area. Therefore, this study aims to summarize recent research progress, identify key gaps in the existing literature, and offer a perspective on future directions in the field of plant polysaccharides and their potential as anti-tumor agents.

2. Anti-tumor activity of natural plant polysaccharides

2.1. Direct action of natural plant polysaccharides on tumor cells

As a prospective anti-tumor therapeutic strategy, research has demonstrated that plant polysaccharides can directly affect the physiological activity of tumor cells through several pathways, such as apoptosis, ferroptosis and anti-angiogenesis, etc.

The polysaccharide CF1 was isolated from wolfberry pollens (WPPs) and demonstrated dose-dependent anti-tumor effects. Furthermore, the anti-tumor activity of CF1 was associated with apoptosis in vitro. This finding lends support to the potential value of plant polysaccharides in anti-tumor therapy [5]. Ferroptosis is a non-apoptotic type of cell death. Use Red ginseng polysaccharide (RGP) extracted from *Panax ginseng C. A. Meyer (Araliaceae)*, to treat A549 and MDA-MB-231 tumor cells. The results show that RGP treatment can significantly inhibited the proliferation and promoted ferroptosis induction in lung or breast cancer cells. This suggests that plant polysaccharides can exert anti-tumor mechanisms through ferroptosis induction [6] *Dendrobium huoshanense* stem polysaccharide (cDHPS) showed the effect of tumor angiogenesis, which presents a molecular weight- and *O*-acetyl group-dependent manner. This is also a key mechanism for inhibiting tumor growth [7].

Edible polysaccharide components derived from the seaweed *Gracilariopsis lemaneiformis* have also been observed to exhibit anti-tumor activity. The mechanism of action is to inhibit tumor proliferation by activating the Fas/FasL pathway-mediated apoptosis in cancer cells. This suggests that the anti-tumor effects of natural plant polysaccharides may involve multiple cell signaling pathways [8]. Plant polysaccharides show modulation of signaling pathways in many anti-tumor activities (Table 1).

Table 1 Signaling pathways involved in the anti-tumor activity of plant polysaccharides

plant polysaccharide	Signaling pathways	Biological Activity	References
Astragalus polysaccharide (APS)	Wnt/β-catenin	Tumor migration and invasion	[9]
Gracilariopsis lemaneiformis edible polysaccharide	Fas/FasL	Tumor proliferation	[8]
Polysaccharide of sunflower (*Helianthus annuus L.*) stalk pith	TNF signaling pathway	Inhibit tumor proliferation and metastasis	[10]
Tea polysaccharide	mTOR-TFEB signaling pathway	Target lysosome to induce cytotoxic autophagy	[11]
Polysaccharide from corn silk	EGFR/PI3K/AKT/CREB signaling pathway	induce cell apoptosis and arrest the cell cycle progression in S phase	[12]

2.2. Suppression of tumor cell activity through immune modulation

In addition to directly affecting the physiological activity of tumor cells, immunomodulation has shown considerable promise in the context of anti-tumor therapy [13]. Polysaccharides, as natural products with multiple anti-tumor mechanisms, offer a novel approach to tumor immunotherapy. For instance, the principal component of the Chinese herb Astragalus, astragalus polysaccharide, has been demonstrated to stimulate the expression of surface molecules CD80 and CD86, facilitate the maturation of dendritic cells, and activate cytotoxic T cells, thereby exerting anti-tumor effects [14].

Similarly, Polysaccharides from *Epimedium koreanum* Nakai have been shown to significantly stimulate macrophages to secrete substantial quantities of anticancer cytokines, which, in turn, promote the maturation and antigen-presenting function of dendritic cells. This suggests their potential role as immunostimulatory modulators in cancer therapy [15]. Additionally, Ganoderma lucidum polysaccharides (GLPs) have been found to activate various immune cells, including macrophages, natural killer cells, neutrophils, T lymphocytes, B lymphocytes, and cytotoxic T lymphocytes. GLPs also promote the expression of cytokines such as TNF-α, IFN-γ, and IL-1β, which collectively contribute to their anti-tumor effects. Notably, the anti-tumor mechanism of GLPs primarily involves the enhancement of the host immune system rather than direct toxicity to tumor cells [16].

Overall, natural plant polysaccharides function as anti-tumor therapeutic agents through a variety of mechanisms, including the induction of apoptosis, modulation of signaling pathways, and immunomodulation (Figure 1). These studies not only highlight the significance of plant polysaccharides in anti-tumor therapy but also provide a scientific foundation for the development of novel anti-tumor drugs based on these natural compounds.

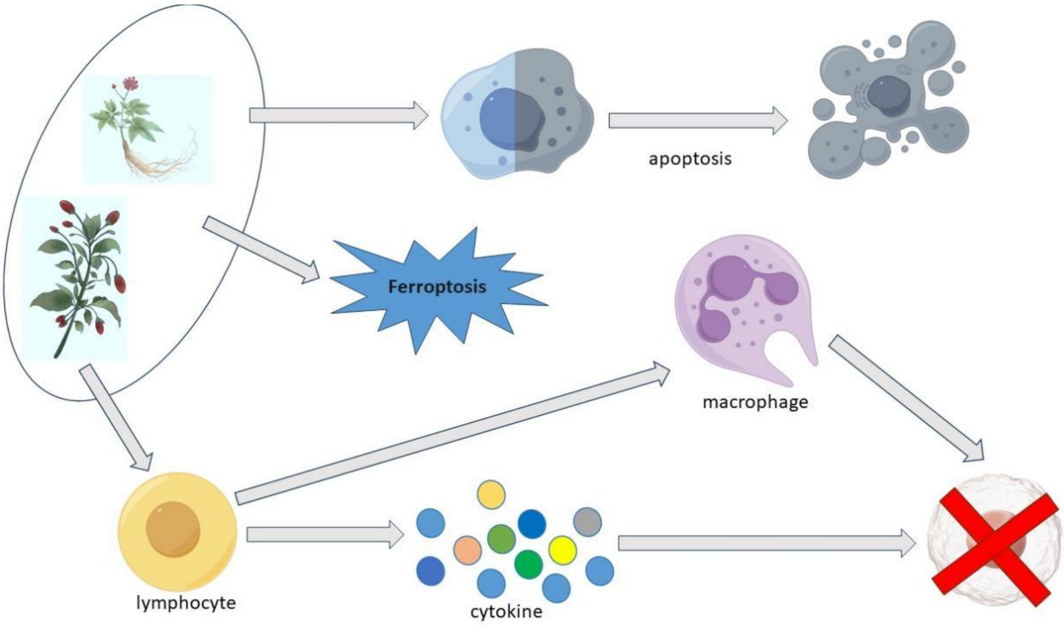

Figure 1 Anti-tumor mechanism of natural plant polysaccharides

3. Chemical modification of plant polysaccharides enhances anti-tumor activity

The inherent chemical and physical properties of natural polysaccharides often limit their therapeutic efficacy in tumor treatment. However, artificial modifications can significantly alter the structure and properties of these polysaccharides, thereby markedly enhancing their antitumor activity. Modifications such as acetylation, sulfation, and methylation target the structure and properties of natural polysaccharides, leading to products with enhanced antitumor functions [17,18]. For example, the sulfated derivative of SGP-1, a natural polysaccharide derived from *Siraitia grosvenorii*, has been shown to exert significant inhibitory effects on the proliferation of human hepatocellular carcinoma cells (HepG2), human breast cancer cells (MDA-MB-231), and human non-small-cell lung carcinoma cells (A549) in vitro. This underscores the importance of sulfated modifications in enhancing the antitumor efficacy of polysaccharides [19]. Similarly, the sulfated derivative of the polysaccharide extracted from *Undaria pinnatifida*, known as S-UPPS-B1, has demonstrated superior antitumor effects. After sulfation, the antitumor activity of S-UPPS-B1 surpassed that of the original UPPS at equivalent doses, further confirming the effectiveness of sulfation in augmenting the antitumor activity of polysaccharides [20]. A summary of various chemical modifications is presented in Table 2.

Table 2. Properties and biological activities of polysaccharides with different chemical modifications

Method	Physicochemical Property	Biological Activity	Example	References
Sulfation	Regulation of the molecular weight of polysaccharides	Regulation of apoptosis-related protein expression	Therapeutic efficacy of SGP-1 derivatives against tumors	[19] [20]
Phosphorylation	Increase in the number of polysaccharide molecular particles	Enhancement of immune response and antioxidant activity	Superior anti-tumor effects of UPPS derivatives	[21] [22]
Acetylation	Changes in the monosaccharide composition of polysaccharides	Modification of hydrophobicity and tumor cell interaction	Immune System Activation Targeting A540 Tumor Cells	[23]
Carboxymethylation	Enhancement of solubility due to hydroxyl group exposure	Promotion of solubility, bioavailability, and apoptosis	Inhibits tumor cell proliferation and induces apoptosis by promoting the expression of pro-apoptotic proteins.	[24] [25]

One crucial mechanism by which chemical modifications enhance the antitumor activity of plant polysaccharides is through altering their solubility. Since most physiological activities depend on an aqueous environment, the water solubility of polysaccharides significantly impacts their biological functions. Artificial chemical modifications can enhance the antitumor activity of polysaccharides by modulating their water solubility and hydrophobicity. For instance, treatment of Undaria pinnatifida brown alga polysaccharides with aspirin resulted in the formation of acetylated polysaccharides, designated ASA-UPFUC. This treatment increased the charge density of ASA-UPFUC, which led to a decrease in particle diameter and an increase in water solubility. These modifications resulted in enhanced antitumor effects against human non-small cell lung cancer A549 cells [23].

Furthermore, the same polysaccharide can enhance its antitumor effect through multiple chemical modifications. For instance, the anti-breast cancer activities of the derivatives of asparagus polysaccharide (GEP) were significantly enhanced by both sulfation (SGEP) and acetylation (AcGEP), with the acetylated product AcGEP exhibiting the most pronounced antitumor effect. Future studies could further explore the effects of different types of chemical modifications on the antitumor bioactivity of the same polysaccharide, aiming to discover and develop more efficient chemical modifications [26].

These findings illustrate that chemical modification of polysaccharides is an effective approach to enhancing their antitumor activity. Future research could focus on the impact of these modifications on the physical and chemical characteristics of polysaccharides, as well as on optimizing the antitumor activity of polysaccharide structures through rational design.

4. The efficacy of plant polysaccharide materials in tumor treatment

In addition to their direct bioactivities on tumors, natural plant polysaccharides are considered promising candidates for nano drug delivery systems due to their excellent biodegradability and biocompatibility. Incorporating polysaccharides into nanocomplexed drug delivery systems has shown potential in enhancing delivery and targeting to tumor cells. For instance, studies have demonstrated that nanocomplexed polysaccharides exhibit enhanced stability, bioavailability, and targeted anti-tumor efficacy in vitro [27-29]. The formation of cross-links within polysaccharides results in more stable and robust structures, which subsequently enhance their anti-tumor activity [30]. Specifically, experiments with two hybridized materials, oligohyaluronic acid-mannose-folic acid (oHA-Man-FA, HMF) and astragalus polysaccharide-dithiodipropionic acid-paeoniflorol (APS-S-Pae, ASP), have shown that these materials can self-assemble in water to form hybridized nanoparticles (HP-NPs) co-loaded with paclitaxel and baicalin. In vitro studies demonstrated that the combination of these drugs with hybridized particles could better overcome tumor resistance and produce superior tumor inhibition compared to free paclitaxel and baicalin [31].

Moving to in vivo studies, cross-linked polysaccharides have shown enhanced resistance to degradation and prolonged activity, resulting in sustained antitumor effects in animal models. For example, natural polysaccharide-Pt nanodrugs were found to readily form 100-300 nm nanospheres, reducing platinum toxicity and improving drug stability in plasma and cellular uptake, leading to improved therapeutic outcomes in tumor-bearing animals [32].

These findings indicate that polysaccharides can inhibit tumor growth through various mechanisms, not only by direct tumor inhibition but also by enhancing drug delivery systems. This suggests their potential in future clinical applications, where such polysaccharide-based delivery systems could be further optimized to improve therapeutic efficacy in cancer patients.

5. Conclusion

Plant polysaccharides, a class of biomolecules widely found in nature, have been extensively studied for their potential anti-tumor properties. Future research on these molecules could greatly benefit from a focus on the biosynthesis and spatial structure analysis of polysaccharides. The biosynthesis of plant polysaccharides is viewed as a promising avenue for the large-scale production of anticancer drugs. For example, L. barbarum polysaccharide (LBP), a key component of Lycium chinense, has demonstrated notable anti-tumor bioactivity and is already widely used in the health market. However, the conventional production methods rely heavily on the cultivation of natural LBP, which significantly limits its yield. Identifying key enzymes in LBP synthesis and using engineered yeast for large-scale production via synthetic biology could expand the application of antitumor polysaccharides. In addition, the structural diversity of plant polysaccharides plays a crucial role in influencing their antitumor activity. These polysaccharides have the ability to form complex structures through various covalent and non-covalent interactions. Further investigation is necessary to understand how these advanced structures impact tumor activity. This understanding is expected to lead to the development of more effective antitumor drugs with fewer side effects, based on insights into polysaccharide structures.

In summary, plant polysaccharides hold significant potential for therapeutic effects on tumors, both through their biological activity and structural characteristics. As our understanding of their antitumor mechanisms deepens, there will be opportunities to optimize the structure of specific polysaccharides to develop more effective antitumor drugs. Given their promising potential as anti-tumor agents, plant polysaccharides should remain a focal point of future research.

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