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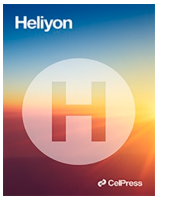

Review article

Review on active components and mechanism of natural product polysaccharides against gastric carcinoma☆

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ABSTRACT

One of the malignant tumors with a high occurrence rate worldwide is gastric carcinoma, which is an epithelial malignant tumor emerging from the stomach. Natural product polysaccharides are a kind of natural macromolecular polymers, which have the functions of regulating immunity, anti-oxidation, anti-fatigue, hypoglycemia, etc. Natural polysaccharides have remarkable effectiveness in preventing the onset, according to studies, and development of gastric cancer at both cellular and animal levels. This paper summarizes the inhibitory mechanisms and therapeutic significance of plant polysaccharides, fungi polysaccharides, and algal polysaccharides in natural product polysaccharides on the occurrence and development of gastric cancer in recent years, providing a theoretical basis for the research, development, and medicinal value of polysaccharides.

1. Introduction

According to the GLOBOCAN 2020 report, the new global cancer data released by the International Agency for Research on Cancer (IARC) in December 2020 indicates that the incidence rate of female gastric cancer ranks eighth among all cancers, while the incidence rate of male gastric cancer ranks fourth. Gastric cancer is a result of multiple pathogenic factors, with Helicobacter pylori infection, precancerous lesions, diet, environment, and genetic factors being the most common causes [1]. Currently, gastric cancer prevalence among young people is increasing in some countries. The etiology and progression of gastric cancer, as well as the corresponding drug research and development, have become a hot topic of research in recent years [2].

Natural product polysaccharides, characterized by intricate structures and a wide range of biological activities, have garnered growing interest in recent years due to their distinctive chemical composition and pharmacological properties. Notably, these

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Table 1
Summary of research information on anti-gastric cancer activity of plant polysaccharides.

Polysaccharides	Model	Dose	The experiment	Inspection indicators	Molecular mechanism	Reference
Dendrobium huoshanense polysaccharides	4-week-old BALB/c male mice	cDHPS-H 262.80 mg/kg/d, cDHPS-M 131.40 mg/kg/d, cDHPS-L 65.70 mg/kg/d	ELISAanalysis, Flow cytometry analysis, qRT-PCR analysis	The tumor tissue weights and volumes	Bax, Bcl-2, Caspase-9, Caspase-3, VEGF, CD34	[20]
Astragalus polysaccharides	SGC-7901 cells, human gastric epithelial cells, the adriamycin-resistant GC cell line SGC-7901/ADR	APS (100–400 μg/mL) 24–72 h	Apoptosis, Cell Viability assay, Western blot analysis	SEMA3F, P21WAF1/CIP1, FBXW7	Caspase-3	[17,21]
Lycium barbarum polysaccharide	BCG-823, GES-1, MKN-45, SGC-7901 cells	LBP (100, 200, 400, 800, 1000 mg/L	MTT assay, Cell cycle analysis, Western blot analysis	_	miR-202-5p/PIK3CA axis inGC, PIK3CA/AKT/mTOR, Bax/Bcl-2, Caspase-3, Caspase-7, Bax, Bcl-2	[18,19]
Panax ginseng polysaccharide	HGC-27, AGS (human normal gas tric epithelial cells)	PGPw, PGP1, PGP2, PGP3, PGP4 (25, 50, 100, 200, 400, 800 μg/mL)	Cell proliferation, Cell apoptosis and Cell cycle, Apoptosis GC, Western blot Analysis, Cell cycle assay	Activation of Bcl-2 family proteins	Caspase-3, Caspase-9, PARP	[22]

polysaccharides exhibit various activities such as anti-tumor, anticoagulant, antioxidant, antiviral, hypertension prevention, and anti-hepatitis effects [3,4]. Among these activities, extensive research has been conducted on the anti-tumor properties of polysaccharide components, particularly in the context of lung cancer, revealing a complex mechanism of action. Research on the anti-tumor properties of polysaccharide components is currently underway for various types of cancer, including lung cancer, liver cancer, cervical cancer, and colon cancer [5–8]. Additionally, the investigation of polysaccharide components, particularly fungal polysaccharides, has demonstrated promising potential in the study of gastric cancer [9].

The intricate nature of the anti-tumor activity exhibited by natural product polysaccharides encompasses a multitude of targets and signaling pathways. These polysaccharides possess the capability to impede the expression of oncogenes within tumor cells, as well as modulate the activity of kinases and phosphatases [10,11]. Overall, natural product polysaccharides have the potential to modulate the immune response of the body, hinder the proliferation of tumor cells, induce apoptosis in tumor cells, and disrupt the metastatic abilities of tumor cells.

Among them, the regulation of immune response stands out as a significant mechanism contributing to the anti-tumor activity of natural product polysaccharides. These polysaccharides have the ability to stimulate various immune cells, including macrophages, dendritic cells, T lymphocytes, and B lymphocytes, leading to the release of cytokines such as interleukin, interferon, and tumor necrosis factor. Furthermore, they enhance the cytotoxic activity of T lymphocytes against tumor cells [12,13].

This article aims to provide a comprehensive overview of the research progress concerning the active constituents of natural product polysaccharides and their mechanism of action in inhibiting the metastasis of tumor cells, specifically in the context of gastric cancer. These polysaccharides have been found to modulate the expression and functionality of matrix metalloproteinases, cell adhesion molecules, and other associated proteins, thereby impeding the adhesion, migration, and invasion of tumor cells. For further in-depth research in the future, to explore its pharmacological activity and mechanism of action, and to provide new ideas and strategies for cancer treatment.

2. Research on the prevention of gastric carcinoma by various polysaccharides

Natural polysaccharides come from a variety of sources and have gentle qualities. They have incredible potential in the food, health care, and other industries owing to their therapeutic properties and very low toxicity [14,15]. Therefore, we discuss the therapeutic applications of plant polysaccharides, fungal polysaccharides, and algal polysaccharides for gastric cancer.

2.1. Plant polysaccharides

Through the study of some plants, it is found that the polysaccharide in many plants can achieve the effect of inhibiting gastric carcinoma. Plant polysaccharides are widely distributed in natural plant tissues. According to current research, plant polysaccharides have good biological activities, such as ginseng polysaccharides [16], *astragalus* polysaccharides [17], *Lycium barbarum* polysaccharides, etc [18,19]. Research has shown that plant polysaccharides like those found in ginseng and *astragalus* have a strong inhibitory impact on gastric carcinoma. Liu et al. discussed the effect of *Dendrobium huoshanense* stem polysaccharide (cDHPS) on the body in the process of inhibiting gastric cancer, and whether the molecular weight and O-Acetyl group of cDHPS have any impact on how well it inhibits gastric carcinoma [20]. *Astragalus* polysaccharides (APS) by themselves were the subject of research by Song et al. and APS combined with doxorubicin (0.1 μg/mL) on gastric carcinoma cell apoptosis. The MTT algorithm was used to test the effect of APS on cell viability for 24–72 h at concentrations that varied between 50 μg/mL to 200 μg/mL. Meanwhile, Caspase-3 cleavage and phosphorylated AMPK were detected by Western blot analysis. APS dramatically reduced the cell viability of gastric cancer cells and increased cell death, according to the findings. Furthermore, when combined with doxorubicin and APS, it can produce a reduction in the ability to survive and death of gastric cancer cells. APS may be employed as a chemosensitizer because it can independently cause apoptosis in gastric cancer cells and increase doxorubicin's apoptosis-promoting effects [21]. Li et al. [22] extracted crude polysaccharide from the degreased root of *Panax ginseng* with distilled water, and added 4 vol of 95.00% ethanol for precipitation. In order to investigate the apoptosis of HGC-27 cells induced by the anti-tumor polysaccharide (PGP2a) from ginseng roots, four drug concentrations (0, 100, 200, and 400 μg/mL) of PGP2a were used to treat HGC-27 cells for 48 h. After applying the four medication concentrations, the number of apoptotic cells increased from 6.60% to 21.70%, 42.10%, and 65.00%, respectively. Using flow cytometry, the impact of PGP2a on cell cycle progression was investigated. It was shown that compared to 6.00% of PGP2a cells in untreated control samples, the number of G2/M cells that were subjected to 100 μg/mL~400 μg/mL increased from 14.70% to 46.90%.

Through experimental research, they concluded that PGP2a can act as a new anti-tumor drug in Twist related genes to treat human gastric carcinoma [18]. The relevant information of the above polysaccharide research are described in Table 1.

At present, it is known that the ways in which plant polysaccharides act on gastric cancer are mostly by inhibiting the proliferation of gastric cancer cells and induce apoptosis of tumor cells by regulating the expression of relevant anti-cancer factors. However, the impact of plant polysaccharides on other aspects cannot be ignored. For example, they may also have anti-inflammatory and antioxidant effects. In addition, plant polysaccharides can also regulate the gut microbiota and improve intestinal health. Therefore, we need to delve deeper into the mechanism of action of plant polysaccharides in order to better utilize them for the prevention and treatment of gastric cancer.

2.2. Fungi polysaccharides

In addition to plant polysaccharides playing a good role in gastric cancer, it has been found through research that fungal polysaccharides also have excellent biological activity against gastric cancer.

2.2.1. Grifola frondosa polysaccharide

Some researchers have found that the polysaccharide component of *Grifola frondosa* can play an anti-gastric cancer role. Liu et al. isolated a type of polysaccharide from *Grifola frondosa* as well as investigated which is preliminary structure as well as the inhibitory effect it has on human cancer of the gastric MKN-45 cells via the Fas/FasL comprehensiveness receptor apoptotic pathway. The cells were then treated with GFP-4 at concentrations of 0, 100, 200, or 400 μg/mL, for 24 h, and cells were then detected by flow cytometry stained with PI. At the same time, S-phase cells decreased in varying degrees ($P < 0.05$). These results suggest that GFP-4 severely blocks the MKN-45 cell cycle in the G0/G1 phase. The experimental results show that GFP-4 has a dose-dependent inhibitory impact on MKN-45 cell growth. This research provides an intellectual basis for future GFP-4 implementations [23]. Cui et al. isolated a new polysaccharide peptide named GFPPS1*b* from the Mycelium of *Grifola frondosa* GF9801, and studied its biological function. After treatment with GFPS1a and GFPS1b, the findings of the study suggest that GFPS1b can prevent SGC-7901 cells from growing, which lowers cell survival by preventing cell cycle and promoting tumor cell death [24].

2.2.2. Hericium erinaceus polysaccharide

After studying the components of *Hericium erinaceus*, it is found that its polysaccharide can achieve the effect of anti-gastric cancer. *Hericium erinaceus* polysaccharides have many biological activities, such as tumor inhibition, ant-gastric ulcer, liver protection, anti hyperlipidemia, fatigue relief, antioxidant, and so on [25]. Wang et al. purified a polysaccharide with anti-gastric ulcer and ant-gastritis activities from the cultured *Hericium erinaceus* mycelia. To see if EP-1 inhibited MC cells (GES-1 cells produced through N-methyl-N′-nitro-N-nitrosoguanidine nitroguanidine). Proliferation by flow cytometry, calculate the percentage of MC cells treated with utilizing EP-1 at 0.1 and 0.5 mg/mL dosages by flow cytometry. Preliminary research has found that this polysaccharide can effectively prevent gastric cancer [26]. Zan et al. Purified a novel polysaccharide protein HEG-5 from *Hericium erinaceus*. Conduct cell proliferation experiments on SGC-7901 cells. According to the experimental findings, HEG-5 had a proliferative inhibitory detrimental effect on SGC-7901 cells ($P < 0.05$). Meanwhile, after treating SGC-7901 cells with polysaccharides at a concentration of 200 μg/mL for 48 h, the highest inhibition rate was 93.40%. In addition, differences in gene expression were found after detecting the effects of cell cycle and apoptosis related gene expression in SGC-7901 cells treated with HEG-5 using qRT-PCR technology. HEG-5 may substantially increase mRNA expression by acting on these 5 proteins (p53, Bad, Bax, Caspase-8, Caspase-3). When HEG-5 inhibits these four proteins (CDK4, Bcl-2, PI3K, and Akt), mRNA expression drops, with dosage and time effects ($P < 0.05$) [27].

2.2.3. Other fungi polysaccharides

Other fungi polysaccharides have also been found to inhibit gastric cancer. Sun et al. studied the relationship between ncRNAs and genetic cancer in the way of Meta-analysis, and discussed the role and mechanism of *cordyceps* polysaccharide. Finally, some non-

Table 2
Summary of research information on anti-gastric cancer activity of fungal polysaccharides.

Polysaccharides	Model	Dose	The experiment	Molecular mechanism	Reference
Grifola frondosa polysaccharide	Human gastric cancer MKN-45 cells	GFP-4: 25, 50, 75, 100, 200, 400, 600, 800 μg/mL	High-performance gel permeation chromatography, fourier-transform infrared spectroscopy, Apoptosis, Cell proliferation, Cell cycle, Western blot analysis	*p*-AKT, AKT	[23]
Hericium erinaceus polysaccharide	SGC-7901		Western blot analysis, apoptosis, Cell cycle arrest	Bax, Bcl-2, Caspase-3, Caspase-8, p53, CDK4	[24]
Inonotus obliquus polysaccharide	SGC-7901, nude mice Cells (3–5 weeks old, weighing 20 ± 2 g)	ISP2a: 25, 50,100, 150, 200 μg/mL	Spleen lymphocyte proliferation assay, Macrophage phagocytosis assay, Assayof TNF-secretion	_	[29]
Pleurotus ostreatus mycelium polysaccharides	BGC-823	POMP2: 25, 50, 100, 200,400 mg/L	Cell migration assay, colony formation assay, in vivo antitumor tests	_	[30]
Ganoderma lucidum polysaccharides	MKN28,AGS, NCI–N87, noncancerous gastric cell line	LBSGLP: 0, 7.5, 10, 12.5,15; RSGLP: 0, 2, 3, 4, 5 mg/mL for 24 h, 48 h, 72 h	Cell viability assay, Hoechst 33342 staining assay, mRFP-GFP-LC3 adenovirus transfection, Colocalization analysis, Western blot analysis, Cell death, apoptosis	Bcl-2, pro-Caspase-3	[31]

coding RNAs, such as H19 and mir-21 had strong associations with clinical and pathological features of gastric cancer [28]. Fan et al. studied the anti-tumor and immunomodulatory activities of water colloid polysaccharide from *Inonotus obliquus* (ISP2a). The dosages of ISP2a were 25, 50, 100, 150, 200 μg/mL, respectively. After receiving 10 days of treatment, it was found that the tumor growth of mice treated with ISP2a was significantly inhibited ($P < 0.05$), and the inhibition rate was 39.02% when the concentration of ISP2a was 50 mg/kg; when the concentration of ISP2a is 75 mg/kg, the inhibition rate is 48.24%; while the concentration of ISP2a is 100 mg/kg, the inhibition rate is 57.45%. The final research results showed that ISP2a has potential application as a natural anti-tumor drug with immunomodulatory activity [29]. For specific information from the above-mentioned research, see Table 2. *Pleurotus ostreatus* mycelium has been employed to extract a specific kind of POMP2 (*Pleurotus ostreatus* Mycelium Polysaccharides 2). According to in vitro tumor experiments, varying quantities of POMP2 can regulate the expansion of BGC-823 cells in an amount and time dependent way ($P < 0.05$). At a concentration of 400 mg/L and the maximum concentration, the inhibition rate of the drug after 72 h of action reached 35.60%; the experimental results showed that POMP2 also exhibited inhibitory effects on the invasion of BGC 823 cells ($P < 0.05$). In addition, the effect of POMP2 on the growth of primary xenograft tumors in nude mice was also studied. As a result, it was found that the tumor weight and volume of the control group mice were significantly higher than those treated with POMP2 (100, 200 mg/kg) ($P < 0.05$) [30]. Zhong et al. studied the impact of polysaccharides on cancer extracted from *Ganoderma lucidum* spores after removing spores (RSGLP). Using methods such as cell viability assay, cell proliferation and apoptosis assay, mRFP-GFP-LC3 adenovirus transfection, and co localization analysis, it was found that *Ganoderma lucidum* (*G. lucidum*) polysaccharide (BSGLP) has a lower inhibitory effect on gastric cancer cell viability than RSGLP. At the same time, RSGLP can become a member of future autophagy inhibitors for gastric cancer treatment [31].

The mechanism of action of fungal polysaccharides on colon cancer is similar to that of plant polysaccharides, both of which involve the regulation of the immune system. Fungal polysaccharides and plant polysaccharides can both activate immune cells, promote inflammatory responses, and thus have an inhibitory effect on tumor cells. In addition, they can also inhibit the proliferation and metastasis of tumor cells, as well as promote apoptosis of tumor cells. However, research on fungal polysaccharides is more comprehensive because they have stronger anti-tumor activity and can induce some special immune factors, enhancing their anti-cancer effects.

2.3. Algal polysaccharides

It has been found that polysaccharide in algae can also inhibit gastric cancer cells. Fucoidan is a type of acidic polysaccharide widely present in the cell walls of brown algae. Chen et al. investigated two non-small cell cancer of the lungs cell lines, A549 and H1650. Different concentrations of brown algae polysaccharides were applied to both types of cells for in vitro experiments such as cell proliferation, apoptosis, and Western blot analysis. Additionally, 4-week-old mice were selected for in vivo tests on A549 cells. The final experimental results found that brown algae polysaccharides can stop the spread of two kinds of cells through the mTOR signaling pathway, while also inhibiting the expression of VEGF, inhibiting the invasion and epithelial mesenchymal transition of both types of cells, and inducing apoptosis of both types of cells. Brown algal polysaccharides have been discovered in vivo to decrease the formation of A549 tumors in mice [32]. The impact of brown algal polysaccharides on MKN45 gastric cancer cells was investigated by Miwa et al. Conduct ASK1 research on inhibiting tumor cell proliferation and downregulating cell cycle regulated kinase phosphorylation. Using the BrdU technique, MKN45 cell proliferation was discovered, and the cytotoxicity of alginate polysaccharide was detected by LDH method and cloning method. It was concluded that the inhibition effect of alginate polysaccharide on the cell cycle of MKN45 was about 50.00%, and the cell proliferation was inhibited. The last study found that brown algae polysaccharides disrupt the ASK1-p38 signaling pathway by phosphorylating ASK1, preventing MKN45 cell growth and DNA synthesis [33]. Han et al. assessed the structural properties of *Sargassum henslowianum*, as well as its immunomodulatory effect on rats with cancer of the stomach. The findings of the experiment revealed that the rats in the control group had substantially higher spleen and thymus scores than the rats in the group given N-methyl-N′-nitro nitrosoguanidine (MNNG) ($P < 0.001$), indicating that the immune system can be suppressed when the tumor is induced by MNNG. However, compared to the spleen and thymus indices of the model group rats, both indices of the rats treated

Table 3
Summary of research information on Anti-gastric cancer activity of other polysaccharides.

Polysaccharides	Model	Dose	The experiment	Inspection indicators	Molecular mechanism	Reference
Fucoidan Polysaccharides	MKN45, Elutriated neutrophils	_	Western blot analysis, ELISA assay, Human neutrophils' spontaneous apoptosis is delayed, Caspase activation is inhibited, Up-regulates Mcl-1 expression	_	Caspase-3, IL-1β, IL-6, IL-8, TNF-α PI3K/AKT pathways	[32,33]
Sargassum henslowianum Polysaccharides	Male Wistar rats (150–200 g), 6 weeks old	SHPPB2-L200 mg/kg/day, SHPPB2-M 400 mg/kg/day, SHPPB2–H 800 mg/kg/day	Immune functional analysis, Cell proliferation, Apoptosis	weight of rat	IL-2, IL-4, IL-6, IL-10, TNF-α	[34]

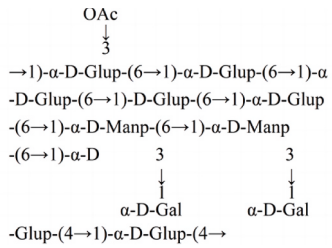
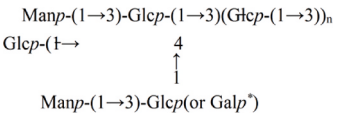
with SHPPB2 increased significantly in a dose-dependent manner ($P < 0.001$). At the same time, this study found that when treated with SHPPB2, the proliferation of splenocyte stimulated by ConA- or LPS- also increased significantly in a dose-dependent manner ($P < 0.001$). However, as compared to the model group rats' spleen and thymus indices, both indices of the rats treated with SHPPB2 rose significantly in a dose-dependent manner ($P < 0.001$). The results show that SHPPB2 can significantly enhance the immune-mediated function in rats with stomach cancer. In the future, SHPPB2 can be further developed as a treatment method for immunotherapy of gastric cancer patients [34]. In addition to the above, there are some other polysaccharides with antitumor activity [35], and we summarize these other polysaccharides with antigastric cancer activity in Table 3.

The inhibitory effects of natural product polysaccharides on gastric cancer have been widely discovered, and the structural features of many polysaccharides have been detected to explore the conformational relationship between polysaccharides and antitumor activity. We summarize the known structures of polysaccharides with antigastric cancer activity in Table 4, with the aim of improving the antitumor activity of natural product polysaccharides from polysaccharide structure in the future.

3. Mechanism of polysaccharide on gastric cancer

Polysaccharides, as a type of natural product, exhibit diverse biological functions. Nevertheless, the underlying mechanism behind the anti-gastric cancer effect of polysaccharides is progressively being investigated. Through an examination of existing research literature on the inhibition of gastric cancer occurrence and progression by polysaccharide constituents, the primary focus of

Table 4
Structural Characterization Information of Polysaccharides from Natural Products with Anti gastric Cancer Activity.

Polysaccharides	Monosaccharide composition (molar ratio)	Extraction method	Chemical structure	Molecular mechanism	Reference
Dendrobium polysaccharides	Glc: Man: Gal = 31:10:8	Hot-water (50°C-60 °C) extraction and ethanol precipitation		_	[36]
Astragalus polysaccharide (APS3)	Rhamnose: Glucose: Galactose: Arabinose = 1:10.76:6.55:12	Water extraction and precipitation with 20%, 40%, 60%, 80% ethanol	_	_	[37]
Panax ginseng polysaccharide	Galactose:Arabinose: Glucose: Galacturonic = 3.7:1.6:0.5:5.4	Water extraction, ethanol precipitation and enzymolysis	_	Twist/ AKR1C2/NF-1	[38]
Polysaccharides	Monosaccharide composition (molar ratio)	Extraction method	Chemical structure	Molecular mechanism	Reference
Radix ginseng Rubra polysaccharide	RGRP-1a: Arabinose, Glucose, Galactose; RGRP-1b: Arabinose galacturonic acid, Glucose, Galactose;	Distilled water extraction, ethanol precipitation	1,4-α-Glcp, with a 1,4,6-α-Glcp branch unit. Its side chains were branched at O-4 position of 1,4,6-α-Glcp, namely, 1)-β-Galp-(4 → 1)-α-Araf-(5 → α-Araf and 1)-β-Galp-(6 → α-Glcp	IL-6, IL-12, TNF-α	[41]
Grifola frondosa polysaccharide	Galactose: Glucose: Mannose = 1.00:3.45:1.19	Water extraction, ethanol precipitation	β-D-GlcpA→, 1,2,6-α-Gal, →2)-α-Manp→, and →3)-α-L-Fucp-(1→	Fas/FasL	[23]
Hericium erinaceus polysaccharide	glucose, mannose, galactose			Bax, Bcl-2, caspase-3	[26]
Sargassum henslowianum polysaccharide	Mannose: glucuronic acid: galactose: xylose: fucose = 17.4: 13.5: 10.5: 16.8: 41.8	95% ethanol to remove lipids, boiling water extraction	_	IL-2, IL-4, IL-6, IL-10, TNF-α	[34]

a. Only around 10% of Galp was connected to the main chain.

investigation centers on the phenotypic alterations observed in gastric cancer cells. These alterations encompass the regulation of cell cycle arrest, facilitation of cell apoptosis, initiation of cell autophagy, control of cell migration and invasion, and modulation of the body's immune function (Fig. 1).

3.1. Regulation of tumor cell cycle

It has been discovered that numerous natural polysaccharides possess the ability to exert an anti-gastric cancer effect by modulating the cell cycle of tumor cells. Gong et al. isolate polysaccharides from *Lycium barbarum* fruit, which were subsequently utilized for the treatment of hepatoma (SMMC-7721 and HepG2), clinical cancer (HeLa), gastric cancer (SGC-7901), and other cancerous cells, as well as human breakthrough cancer cells (MCF-7), in order to observe the impact of polysaccharides on cancer cells. The arabinogalactan derived from *Lycium barbarum* fruit disrupts the cell cycle during the G0/G1 phase, according to the study methodology, it has been observed that there is a correlation between changes in mitochondrial activity, oxidative stress, and modulation of the MAPK signal pathway. This correlation ultimately leads to the induction of apoptosis in tumor cells [39]. In their study, Wu et al. discovered that *Astragalus* polysaccharide (AsPs) inhibits the AKT signal pathway, thereby enhancing the anti-tumor effect of Apatinib on AGS cells derived from gastric cancer. The addition of AsPs impedes the AKT signaling pathway, thereby expanding the anti-tumor effects of Apatinib on AGS cells. Furthermore, the administration of 3-MA reduces the level of autophagy induced by apatinib, consequently increasing the rate of apoptosis. Based on the findings of the study, the combination of apatinib and aspirin may be a suitable pharmacological intervention for the management of gastric cancer [40]. Miwa et al. discovered that marine bioactive compounds possess the ability to modulate the signaling pathway involved in cell cycle regulation during cancer treatment, as well as directly influence the molecules responsible for cell cycle regulation. Through their investigation on the inhibitory effects of fucoidan on cell cycle promotion, they observed that fucoidan effectively suppressed the ASK1-p38 signaling pathway, thereby impeding the proliferation of MKN45 cells [41].

3.2. Inhibitory role by regulating tumor cell death patterns

3.2.1. Cell apoptosis and necroptosis

Apoptosis, a process regulated by genes to maintain cellular homeostasis, refers to the controlled and spontaneous death of cells [42]. Zhong et al. discovered that disrupting autophagic flux through *Ganoderma lucidum* spore polysaccharide can induce apoptosis in

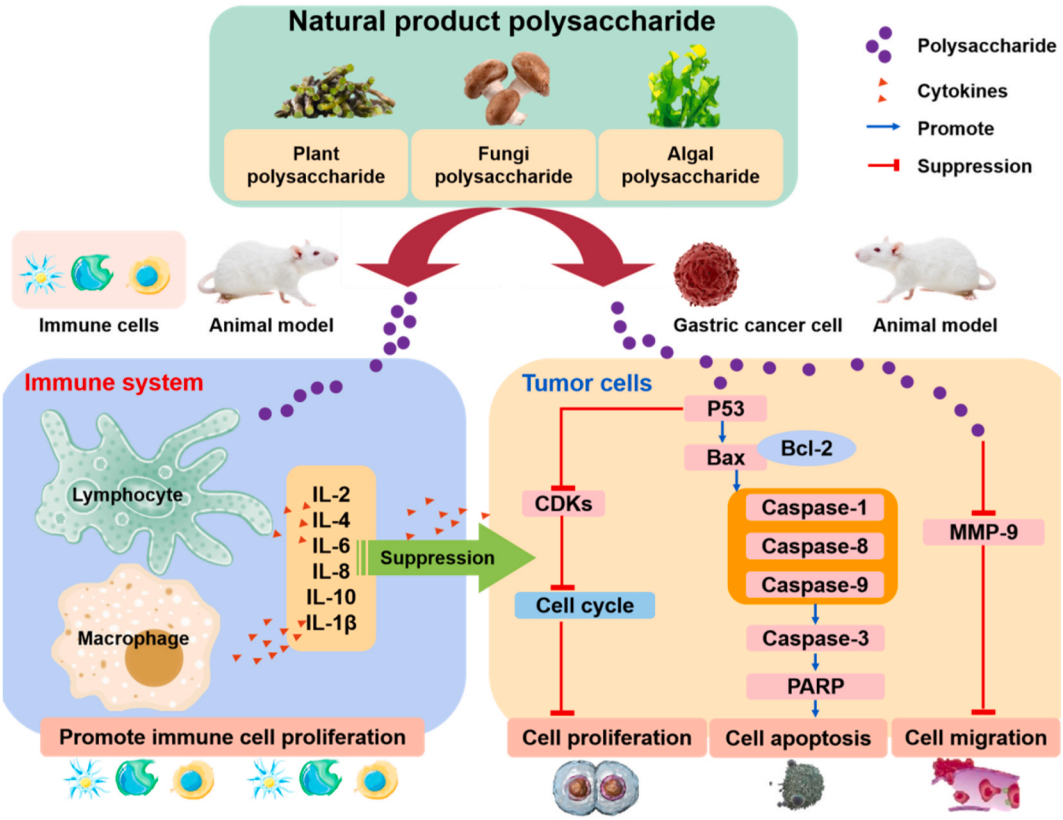


Fig. 1. The impact and mechanism of natural material polysaccharide on stomach cancer.

human gastric cancer cells. The subsequent study demonstrated that the interruption of autophagy induced by sporoderm-removed spores of *G. lucidum* (RSGLP) and the subsequent disruption of autophagy flux contributed at least partially to the apoptosis by RSGLP in AGS cells. These findings provide evidence that RSGLP is more efficacious than BSGLP in reducing gastric cancer cells' ability to survive, and RSGLP may be an alternative autophagic inhibitor for the treatment of gastric cancer [31].

3.2.2. Cell pyroptosis

Cell pyroptosis is a distinct form of cell death that distinguishes itself from apoptosis and necrosis. It is typically triggered by aberrant signal transduction and gene expression within cells, resulting in membrane rupture, extracellular release of cellular contents, and eventual demise of the cell [43]. Certain drugs have been observed to induce cellular pyroptosis [44,45]. *Poria cocos* polysaccharides have been found to inhibit the pyroptosis of intestinal epithelial cells and macrophages, bolster the integrity of the intestinal barrier, and mitigate the onset of hepatitis [46]. Garlic polysaccharides have been found to exert regulatory effects on the expression of proteins such as GPX4, SOD2, HO1, NQO1, and Nrf2, thereby reducing inflammation and inhibiting pyroptosis [47]. Similarly, *Dendrobium officinale* polysaccharides have demonstrated the ability to alleviate pyroptosis induced by uropathogenic Escherichia coli (UPEC) in macrophage cells [48]. Consequently, the modulation of tumor cell pyroptosis through pharmacological interventions holds promise as a potentially effective approach for cancer treatment.

3.2.3. Cell ferroptosis

Ferroptosis, characterized by distinct features and the capacity to recognize physiological conditions and various diseases, including cancer, represents a novel form of cell death. The application of ferroptosis provides broad prospects for cancer treatment [49]. $CD8^+$ T cells have been found to release IFN-γ, which has been shown to promote lipid peroxidation and ferroptosis in tumor cells [50]. Additionally, the combination of $CD8^+$ T cell-derived interferon (IFN)γ and arachidonic acid (AA) has been found to induce immunogenic tumor ferroptosis [51]. Yan Wang et al. pointed out that red ginseng polysaccharides can inhibit ferroptosis in gastric cancer cells by inhibiting the expression of the PI3K/AKT pathway [52]. Furthermore, *astragalus* polysaccharides can alshave been shown to treat ferroptosis in normal human cells and prevent the occurrence of diseases [53]. It is worth noting that various natural product polysaccharide components have been identified to inhibit ferroptosis, enhance immune function, provide neuroprotection, and exhibit anti-tumor effects [54–57].

In summary, natural polysaccharides are also able to inhibit the growth of tumor cells by inducing cellular pyroptosis and ferroptosis, which provides a theoretical basis for research on the treatment of gastric cancer. The mechanisms by which natural product polysaccharides induce tumor cell death are summarized in Table 5. In the future, the anti-tumor activity of natural polysaccharides on gastric cancer can be verified by the aspects of cell pyroptosis and ferroptosis, so as to improve the biological functions of natural polysaccharides.

3.3. Inhibiting the migration and invasion of tumor cells

Numerous studies have demonstrated that natural polysaccharides have the ability to inhibit tumor cell migration and invasion, in addition to their anti-gastric cancer effects. These polysaccharides have also been noted for their ability to regulate the immune system in animals or cells. The role of cancer stem cells (CSCs) in invasion, metastasis, and tumor angiogenesis was studied by Zhu et al. using the gastric cancer cell line SGC-7901 and CSC-G. They found that CSC-G exhibited considerably higher rates of proliferation, drug resistance, migration, invasion, and tumorigenicity than SGC-7901. The proliferation, migration, invasion, and tumorigenicity of gastric cancer cells are all significantly affected by CSC-G [58].

Furthermore, in a recent study, Chen et al. investigated the mechanism of *Lycium barbarum* polysaccharide (LBP) in inhibiting gastric cancer. Their findings suggest that LBP suppresses matrix metalloproteinases (MMPs), thereby slowing the proliferation, migration, and invasion of human gastric cancer cells. LBP achieves this by reducing the transition of cells from an epithelial to mesenchymal (EMT) state [59].

EMT is a critical process associated with the occurrence and metastasis of cancer, and there are various highly regulatory factors associated with EMT in different types of cancers [60]. It has been reported that natural product polysaccharides may inhibit tumor cell migration and invasion by regulating the expression of EMT-related proteins such as N-cadherin and E-cadherin [61].

The underlying mechanisms through which natural product polysaccharides inhibit tumor cell migration and invasion mainly

Table 5
The mechanism of natural product polysaccharides inducing tumor cell death.

Cell death mode	Polysaccharides	Molecular mechanism	Reference
Cell apoptosis and necroptosis	*Ganoderma lucidum* Polysaccharide	Bax, Bcl-2, caspase-3	[31]
Cell pyroptosis	*Poria cocos* polysaccharides, Garlic polysaccharides, *Dendrobium officinale* polysaccharides	PARP-1, TLR2/Myd88/NF-κB, ROS/AMPK, GPX4, SOD2, HO1, NQO1, Nrf2, NLRP3/Caspase-1/GSDMD	[46–48]
Cell ferroptosis	Red ginseng polysaccharide, *Astragalus* polysaccharide, *Dendrobium Nobile* Polysaccharides, *Lycium barbarum* polysaccharides, *Polygonatum cyrtonema* Hua Polysaccharides, *Aureobasidium melanogenum* Polysaccharides	PI3K/Akt, GSH, xCT, Gpx4, NRF2/HO-1,	[52–57]

involve three ways: Firstly, they may directly interact with tumor cells and interfere with their adhesion and migration. Secondly, polysaccharides may regulate the expression of oncogenes and tumor suppressor genes, inhibit the formation of new blood vessels in tumors, and reduce the supply of nutrients for tumor cells since angiogenesis is a necessary condition for tumor growth and metastasis. Thirdly, polysaccharides may regulate the immune function of the body, enhance the body's ability to recognize and kill tumor cells, and prevent the metastasis of tumors [62,63].

Polysaccharides derived from natural products have the ability to bind to specific receptors on the surface of tumor cells due to their unique carbohydrate structure. This interaction leads to a modulation of the expression and activity of signaling molecules within the tumor cells, thereby regulating processes such as cell proliferation, differentiation, and apoptosis. Ultimately, this mechanism can effectively inhibit the metastasis of tumor cells [64,65].

3.4. The immunomodulatory activity of natural polysaccharides

Several natural polysaccharides have been shown to possess anti-gastric cancer effects through immunological regulation in animals or cells. Siedlar et al. investigated the levels of tumor necrosis factor and interleukin-12p40 in patients with gastric cancer, along with their relationship to the expression of the protein IL-1R-associated kinase-1 and the stage of the disease. Their findings suggested an unusual process in advanced stomach cancer, where the reduction of the innate immune system's defenses against tumor cells may be caused or promoted by an impairment in IRAK-1 protein expression [66].

Two chromatography methods (Thin-layer chromatography and Sephadex G-100 chromatography) were used to separate the *Astragalus* polysaccharides extract in a study by Li et al. The study found a significant enhancement in the promotion of peripheral blood lymphocytes stimulated by antigenic receptors in the incidence of gastric cancer ($P < 0.01$). Additionally, the levels of $CD4^+$ and CD4+/CD8+ in model rats were significantly lower than those treated with AP ($P < 0.01$). Bioactivity tests demonstrated that *Astragalus* polysaccharides exhibited anti-inflammatory activity and promoted the proliferation of splenic lymphocytes. The polysaccharides also displayed significant immunoregulatory activity, supporting their potential application in the treatment of gastric cancer [67]. Zhang et al. investigated the structural characteristics, immune regulatory activity, and tumor inhibitory potential of RGRP-1b, a ginseng polysaccharide. The researchers utilized measurements of nitric oxide (NO) levels and cytotoxicity to make their discoveries. They found that the activity of RAW264.7 cells in the negative control group was significantly reduced compared to the concentration of 200-400 μg/mL. Furthermore, cell viability after treatment with RGRP-1b at 200–400 μg/mL indicated no toxicity to macrophages ($P < 0.05$). These findings suggest that RGRP-1b at 200–400 μg/mL does not exhibit toxicity to macrophages. The final outcomes of the study revealed that RGRP-1b has the ability to inhibit Huh 7 growth through immunoregulation and acts as a potent immune modulator [68].

4. Clinical application of polysaccharide preparation in the treatment of gastric cancer

Lentinan is used in the treatment of various malignancies, including liver cancer [69], gastric cancer [70], lung cancer [71], colorectal cancer [72], ovarian cancer [73], pancreatic cancer [74], and others. It plays a significant role in enhancing the effectiveness of chemotherapy and radiotherapy, as well as improving the quality of life during tumor treatment.

In a review by Zhang et al. the clinical use of lentinan in the treatment of various cancers in China over the past 12 years was examined. The inquiry revealed that lentinan was employed as an adjuvant therapy in the treatment of multiple malignancies. Lentinan treatments were administered to over 68.69% of lung cancer patients (3469 cases, 36.62%) and stomach cancer patients (3039 cases, 32.08%). Specifically for gastric cancer, lentinan chemotherapy groups reported overall response rates ranging from 11.10% to 87.50%, compared to 30.60%–71.00% in the chemotherapy groups alone. The findings indicated that all chemotherapy plus lentinan groups demonstrated superior efficacy and response rates compared to the chemotherapy group alone [75].

Higashi et al. conducted a study involving 39 patients diagnosed with unresectable gastric cancer based on preoperative examinations or laparotomy. Among them, 19 patients received treatment with lentinan, while the remaining 20 patients did not. A comparison of the two groups revealed that the lentinan-treated group experienced fewer instances of leukopenia and nausea, as well as a lower frequency of painful events such as finger numbness, stomatitis, and taste disorders during chemotherapy. Although the overall number of adverse events did not change significantly, the lentinan group showed a tendency towards experiencing fewer negative incidents ($P = 0.076$). Ultimately, lentinan is recognized as a promising chemotherapeutic agent that can contribute to maintaining a good quality of life for cancer patients. This underscores the widespread clinical application of lentinan as the most common natural product polysaccharide [76].

5. Discussion

Currently, research on the effects of polysaccharides from animals, plants, and fungi on gastric cancer typically focuses on their inhibitory effects, which are generally determined by assessing cell proliferation and tumor size in animal models [77]. While the anti-tumor impact is achieved through preventing tumor cell migration and invasion, immune system regulation, and direct tumor cell death [78–81]. However, much of the research on the biological functions of polysaccharides is conducted at the cellular level. Furthermore, due to the complex molecular structure of polysaccharides, more precise data should be obtained through cell and animal experiments in future clinical studies. It is recommended to conduct more in-depth research at the animal level and expedite the application of these findings in clinical practice to alleviate the suffering of more patients.

The application of polysaccharides in clinical cancer treatment presents both advantages and disadvantages. Polysaccharides offer

several benefits, including their immunomodulatory effects, which can bolster the immune system of cancer patients [82,83]. Additionally, polysaccharides have the ability to inhibit tumor growth and induce apoptosis in tumor cells. They can also mitigate the side effects of chemotherapy and radiotherapy, ultimately enhancing the quality of life for patients. However, there are drawbacks to polysaccharide therapy for cancer. It may not be universally applicable to all cancer patients due to the complex nature of the disease. As a result, polysaccharide therapy is often employed in combination with other treatment methods to achieve the most effective therapeutic outcome [84].

Currently, fungal polysaccharides have been developed and utilized in the treatment of cancer patients as adjunctive therapies to extend patient survival. In summary, natural product polysaccharides hold promise in the treatment of cancer, but their safety and effectiveness must be substantiated through rigorous scientific research and clinical trials [85].

The majority of research on the inhibitory effect of polysaccharides on gastric cancer utilizes crude polysaccharide components, including some purified polysaccharide components, with a predominant focus on phenotypic studies of the mechanism of action. However, further research is warranted to delve into the specific chemical composition, structure, and mechanism of action of polysaccharide components in the future.

6. Conclusions

This study provides a comprehensive summary of the active constituents and action mechanism of natural polysaccharides. Additionally, it presents the structural characterization information of polysaccharides derived from various natural products exhibiting anti-gastric cancer activity. Currently, the research focus on natural product polysaccharides for gastric cancer primarily revolves around fungi polysaccharides. Notably, lentinan, a specific fungi polysaccharide, has gained significant attention in the food and pharmaceutical industries due to its wide-ranging applications and promising prospects.

Furthermore, a range of natural product polysaccharides exhibit intricate molecular structures and rich bioactivities. Significant progress has been made in regulating the cancer cell cycle, promoting tumor cell death, obstructing tumor cell invasion, and controlling tumor cell immunity. Notably, natural product polysaccharides have been identified as possessing great potential in inhibiting gastric cancer cells. Therefore, this review aims to provide researchers with insights into designing and developing the efficacy of natural product polysaccharides against gastric cancer.

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Data availability statement

Data will not be required for this article.

CRediT authorship contribution statement

Xinze Liu: Writing – original draft, Software, Resources, Data curation. **Kaijing Sun:** Writing – original draft, Formal analysis, Data curation. **Xin Jin:** Writing – review & editing, Project administration. **Xinmin Wu:** Methodology. **Mingjie Xia:** Methodology, Formal analysis. **Ying Sun:** Software, Resources. **Lin Feng:** Resources, Data curation. **Guangzhe Li:** Software, Resources. **Xilin Wan:** Writing – review & editing, Supervision, Project administration, Funding acquisition. **Changbao Chen:** Visualization, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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