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Chinese FDA Approved Fungal Glycan-Based Drugs: An Overview of Structures, Mechanisms and Clinical Related Studies

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Abstract

Edible mushrooms have been used not only as food and nutraceuticals but also as important ingredients in traditional Chinese medicines for centuries. Pharmaceutical active components from different types of mushrooms have been extracted and studied by scientists all over the world during the past 50 years, and many biological functions, such as antitumor, immunomodulating, anti-oxidative, anti-inflammatory, and hypoglycemic activities, have been reported in peer reviewed English journals. Interestingly, the purified polysaccharides or glycans possess many reported functions of medicinal mushrooms, which make them potential drug candidates. However, glycans are a mixture of polysaccharides having variable numbers of monosaccharides, linkages, and molecular weight distributions as well as multiple biological functions that are hard to conceive as drugs by conventional standard in that a drug should have one structure and one function. On the other hand, multiple ingredients with multiple beneficial effects are essence of traditional Chinese medicines. Subsequently, glycans from different types of medicinal mushrooms are partially purified and trialed as oral and/or injectable drugs in China. Without serious safety concerns of mostly hot water extracted glycans from edible mushrooms and/or the cultured mycelium, eight of them are approved by Chinese Food and Drug Administration (SFDA) and used clinically in China since 1980s. This review article provides basic clinical information of the fungal glycan-based drugs in China and also summarizes structures, functions, and animal studies of fungal glycans conducted by scientists world-wide. Understanding glycan-based drugs at molecular biology level would be central for improving the clinical efficacy of current glycan-based drugs and for designing effective clinical trials of glycan-based drugs in future.

Keywords: Fungal glycan base; Chinese FDA; Mushrooms; Polysaccharides

Introduction

Polysaccharides or glycans are located at intracellular, cell membrane, and extracellular spaces serving energy storage, structure, signal transduction, and system regulatory purposes in all living organisms. Among them, animal glycans have been extensively studied at genetic levels. Knocking out a series genes responsible for biosynthesis or modifications of glycans in different animal model systems reveals that animal glycans are indispensable for cell division [1], for animal development [2], and for maintenance of proper immunity and homeostasis in adult animals [3]. For example, endothelial heparan sulfate deficiency impairs L-selectin- and chemokine-mediated neutrophil trafficking during inflammatory responses [4]. Moreover, life-saving drug heparin, one type of glycans purified from animal tissues, remains to be an un-replaceable anticoagulant drug in modern medicine after 78 years of clinical use [2]. Furthermore, 20 different kinds of animal glycan-based drugs have preceded through clinical trials and are used clinically world-wide not only as anticoagulant but also used together with other conventional drugs for cancer treatment with an annual sale over $7 billion dollars [5].These facts indicate glycan-based drugs are not different from other biological drugs either from views of modern molecular biology or from views of their clinical importance.

Like animal cells, fungi synthesize several different types of glycans located in intracellular, cell wall, and extracellular spaces. Moreover, fungi possess several unique glycans that are not made by animal cells, such as chitin, β - glucans, and heteroglycans. In addition, glycan-peptide, glycan-lipid, and glycan-protein complexes isolated from fungi also have potent biological activities. This review article provides basic information of eight fungal glycan-based drugs in China and also summarizes peer-reviewed literatures about structures and biological functions of the fungal glycans at cell- and animal levels along with clinical studies that have been conducted by scientists world-wide.

Eight Fungal Glycans-Based Drugs Approved By Chinese Food and Drug Administration (SFDA)

According to published reports, water-soluble glycans are the most active pharmacological components tested in over 300 kinds of glycans extracted from either plants or fungi [6]. Thus, all eight glycans-based drugs approved by SFDA are hot water extracted glycans either from edible mushrooms and/or from cultured mycelium. Table 1 summaries the basic information of the 8 drugs including imagine of the medicinal mushrooms, starting materials for glycans extraction, type of drugs approved, specified glycan contents, drug number granted by SFDA, clinical indications, and published clinical studies [7-65].

As shown in Table 1, glycan contents of the eight approved drugs range from 30% to 93%. There are no specifications about monosaccharide compositions, glycan structures, molecular weight, or biological activity for these approved drugs due to inherent structural diversity of glycans. Taking *Ganoderma lucidum* glycans as an example, 16 different types of glycans with different monosaccharide compositions, different glycan linkages, and different molecular weight have been purified and identified by applying additional purification schemes when hot water extracted glycans are used as starting materials (Table 2). Therefore, these drugs are not "pure" or a single type of glycans.

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Imagine	Specie	Source	Drug type	Glycan content	SFDA drug number	Clinical applications	Ref.
 Ref. [160]	*Ganoderma lucidum*	Spores	Injection	Ganoderma lucidum glycans no less than 90%	H20003510	Improving endurance of cyclists Dyslipidemia Facial paralysis	[7] [8] [9]
 Ref.[161]	*Ganoderma Sinensis*	Fruiting body	Tablet	*Ganoderma Sinensis* glycan no less than 83%	Z22022112	Mushroom poisoning Leukopenia	[10] [11]
 Ref.[160]	*Lentinus edodes*	Fruiting body	Capsule	Lentinan	Z20080579	Artificial urticaria	[12]
			Tablet	Lentinan no less than 40%	Z20026215	Gastrointestinal cancers Primary liver cancer Hepatitis Malignant pleural effusion HIV-positive	[13-18] [19] [20, 21] [22-27] [28]
			injection	Lentinan no less than 85%	H20067183		
 Ref.[161]	*Polyporus unbellatus*	Fruiting body	Capsule	no less than 40%	Z10970134	Hepatitis B Reduce the recurrence of bladder cancer	[29-33] [33]
			Injection	Polyporus glycan no less than 90%	Z32021229		
 Ref.[161]	*Polystictus Versicolor*	Culture of mycelium	Capsule	Krestin (PSK) glycans no less than 35%	H31022501	Acute nonlymphocytic leukemia Colorectal cancer Gastric cancer Lung cancer Primary liver cancer Hepatitis Hyperlipidemia	[34] [35, 36] [37-40] [41] [42-44] [45-50] [51]
			Dropping pills	Krestin(PSK) glycans no less than 38%	Z20090728		
 Ref.[161]	*Poria cocos*	Culture of Mycelium	Injection	Pachymaran no less than 84%	H20003510	Chronic pulmonary edema Insomnia Alopecia Schizophrenia	[52] [53] [54] [55]
 Ref.[160]	*Grifola frondosa*	Culture of mycelium	Capsule	Maitake glycans no less than 40%	B20020023	Antitumor Impaired Glucose Tolerance Polycystic ovary syndrome	[56, 162] [58] [59]
 Ref. [163]	*Tremella fuciformis Berk*	Fruiting body	Capsule	Tremella glycan no less than 60%	Z22022048	Mycoplasma pneumonia Chronic active hepatitis Antidiabetics Cancer patients with leukopenia	[60] [61] [62] [63-65]

Table1: Eight fungal glycan based-drugs.

Source	Extraction method	Backbone	Major monosaccharide	Mw	Ref.
Fruiting bodies	Hot-water extraction. Ethanol fractionation, DEAE-cellulose and gel chromatography	β-Arabinoxyloglucan, α-Arabinoxyloglucan	Glucose, xylose, arabinose	4×10^4	[164]
Fruiting bodies	Hot water and alkali extraction	Water-soluble heteroglycans	Glucose,Galactose, Mannose,Arabinose, Xylose, Fucose	–	[165]
		Water-insoluble β-glucan	Glucose	–	
Culture of mycelium	–	Branched β-glucan	Glucose	–	[165]
Fruiting bodies	Alkali-extraction at 25°C and 65°C.	Linear α-glucan	Glucose	–	[166]
Spores	Hot-water extraction. DEAE-cellulose and Sephacryl S-200HR	β-Glucan	Glucose	1×10^4	[130]
Fruiting bodies	Hot-water extraction. DEAE-cellulose and gel-filtration chromatography	α-Heteroglycans β-Heteroglycans	Glucose,Galactose, Rhamnose	8.3×10^3	[131]
		β-Glucan	Glucose	6.3×10^4	
		β-Heteroglycan	Glucose, Mannose	2.0×10^5	
Extracellular	DEAE-Sephacel and Sephadex G200	α-Galactose	Galactose,Mannose, Glucose,Arabinose, Rhamnose	2.2×10^4	[167]
Fruiting bodies	Hot-water extraction DEAE-Sepharose Fast-Flow and SephacrylS-300	α-Galactose, α-Glucose	Galactose, Glucose, Fucose	1.2×10^4	[168, 169]
Fruiting bodies	Ultra-filtration, DEAE- Sepharose Fast-Flowand Sephacryl S-300	α-Galactose, β-Glucose	Galactose,Glucose, Fucose	–	[170]
Fruiting bodies	Hot-water extraction DEAE-cellulose-32 and Sephacryl S-200h	β-Glucan	Glucose	5.2×10^3	[171]
		Heteroglycans	Glucose,Galactose, Mannose	1.54×10^4	
Fruiting bodies	Hot-water extraction DEAE Sepharose Fast-Flow and Sepharose CL-6B	α-Galactose,	Galactose,Glucose, Fucose	1.12×10^4	[172]
		β-Glucose			
Fruiting bodies	Ultrasound/microwave assisted extraction DEAE Sepharose Fast Flow and Sephacryl S-500	β-Glucose	Glucose, Galactose	2.5×10^6	[173]
Spores	Hot-water extraction, graded ethanol precipitation, DEAE-cellulose and Sephacryl S-300	β-Glucan	Glucose	10.3×10^4	[174]

Table 2: Different glycans isolated from *Ganoderma lucidum*.

B - Glucans are glycans that contain only glucose as structural components and are linked with β - glycosidic bonds. β - glucans are the simplest and the most studied fungal glycans. The biologically active fungal β - glucans are those comprising β (1,3) linked-glucose with side-chains of glucose with *β* (1,6) linkage. As shown in Table 2, the six β - glucans purified from *Ganoderma lucidum* are either water soluble or insoluble with molecular weight ranged from 5.2×10^3 to 1.0×10^5 Da. Therefore, β - glucans are not pure glycans. β -glucans can bind to six identified receptors on cell surface of immune cells (Figure 1) [66-73]. The β - glucan and receptor interactions can activate multiple signaling transduction pathways directly or indirectly through macrophages, monocytes, dendritic cells, natural killer cells, B-cells, T-cells and neutrophils. β -Glucans also stimulate the release of cytokines, such as tumor necrosis factor (TNF-α) and several interleukins.

Activating the immune cells explain the immunomodulating and antitumor activities of β - glucans. However, not only fungi but also bacteria, plants, and algae synthesize biological active β - glucans. Moreover when present in animal blood circulation, tissues, or organs, most foreign glycans are recognized as sign of bacterium or fungus invasions through a series of receptors on immune cells including those receptors that bind to β - glucans. Most of glycans also have anti-inflammatory properties that could not be explained by the glycan/receptor signal transduction mechanism. Moreover, anti-oxidative and hypoglycemic properties are also common to all biological active glycans. As shown in Table 1, the drug indications of the 8 fungal glycan-based drugs are very different, which suggests the unique glycan compositions, but not the β - glucans alone, might contribute to the observed pharmaceutical effects of the fungal glycan-based drugs. Being not pure might be a reasonable character for glycan-based drugs since glycans produced by nature are never pure even for the simplest β -glucans (see different characteristics of six β -glucans purified from *Ganoderma lucidum* listed in Table 2. We will briefly review the structure, function, clinical uses, and animal studies (summarized in Table 3) of the 8 fungal glycans and the glycan-based drugs in the next section.

Structural and Functional Studies of Fungal Glycans

Lentinan from *Lentinus edodes*

Lentinan is a name given to β - glucans purified from *Lentinus edodes*. The antitumor property of lentinan was first reported by Chihara et al in 1970 [74]. Sasaki and Takasuka demonstrated that the primary structure of lentinan has β - (1-3)-glucose backbone with many (1-6)- β - glucose branches [75].

Letinan-based drugs are available as capsules, tablets, and injections in China. The published clinical reports indicate that these drugs have been used for treating urticaria [12], gastrointestinal cancers [13-18], primary liver cancers [19], hepatitis [20, 21], malignant pleural effusion [22-27], and HIV [28].

In 1985, lentinan is approved as an adjuvant for stomach cancer therapy in Japan. The lentinan activates immune cells [76], promotes the T- and B-lymphocyte proliferation, and enhances the activities of NK cells. The lentinan also plays multiple roles in inducing α-interferon production and leukocyte infiltration into tumor tissues [77]. The biological activities of lentinan have been studied by using mouse-,

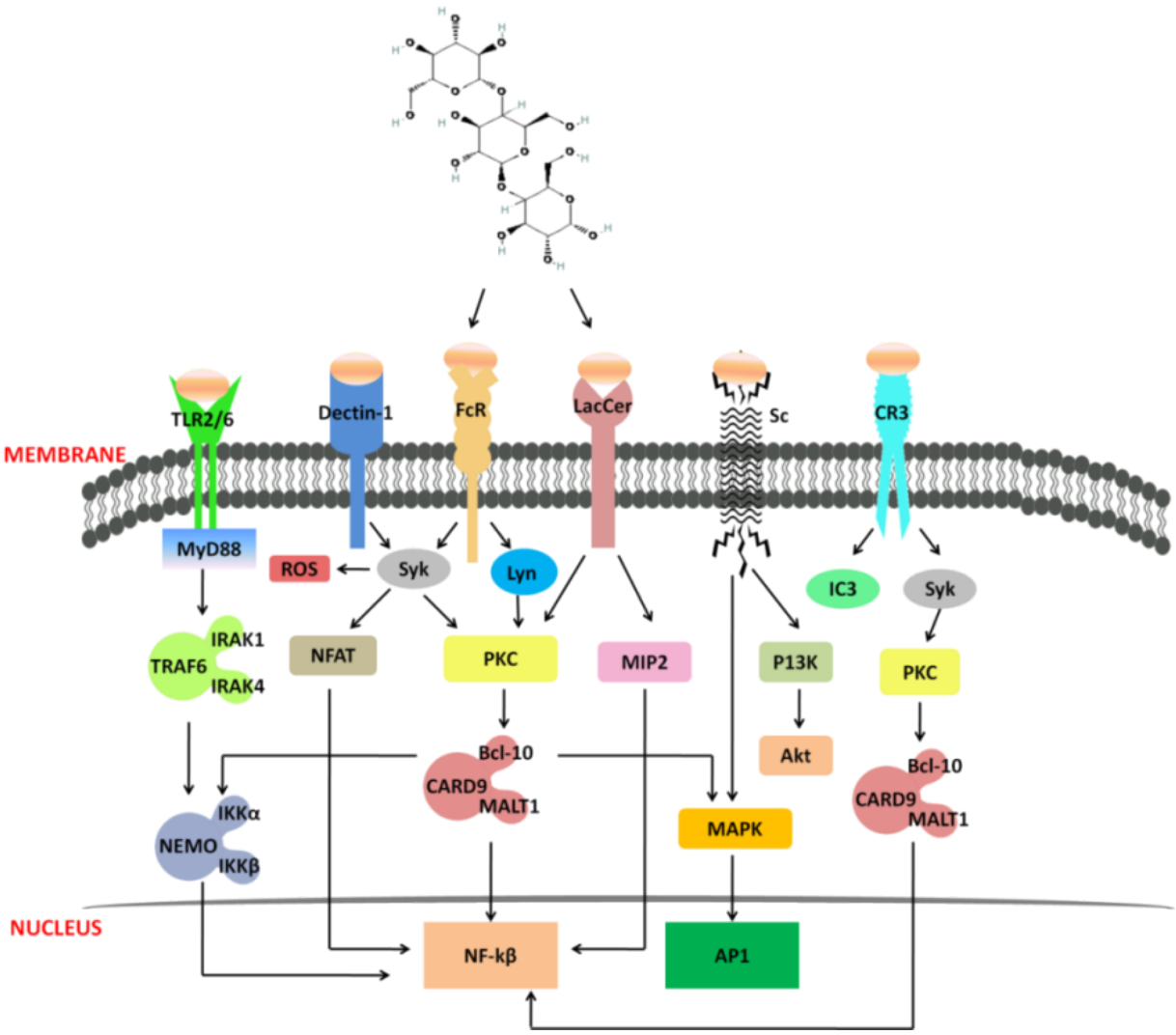

Figure 1: Receptors for β-glucans. β -glucans can bind to several membrane receptors on the immune cell surface, such as toll-like recepters 2/6 (TLR2/6), Dectin-1, Fc receptor (FcR), lactosylceramide (LacCer), scavenge receptor (Sc), and complement receptor 3 (CR3). Subsequently, multiple signaling pathways are activated and merged onto important immune regulatory pathways, such as NF- κ B.

rat-, chicken-, and pig-based animal models [76, 78-88]. These animal studies confirm that lentinan stimulate the productions of different cytokines and have antitumor and immunomodulating properties.

Polyporus glycan

Polyporus glycan is extracted from the sclerotium of *Polyporus umbellatus*. The major component of polyporus glycan is a β - glucan with a (1-3)- β -glucose backbone and (1-6)- β -glucose side chains with a molecular weight of approximately 1.6×10^5 Da [89].

Polyporus glycans have been commercially available as an immunomodulating drug since 1990. Based on published reports, the polyporus glycan-based capsules are effective in treating hepatitis B [29-33, 90,91] and the polyporus glycan-based injections reduce the recurrence of bladder cancer [33]. Polyporus glycan boosts the immune system and have anti-parasite properties [92, 93]. It is also used in treating leukemia and liver cancers [94,95]. Study has also shown that Polyporus glycans are effective in protecting liver from certain toxins [95]. Polyporus glycans are also used together with chemotherapy drugs to treat primary lung cancer, liver cancer, cervical cancer, nasopharyngeal carcinoma, esophageal cancer and leukemia.

Polysaccharide-K (PSK) or krestin

PSK or Krestin is a protein bound glycan isolated from cultured mycelium of *Polystictus Versicolor*. Glucose is the major monosaccharide found in PSK. PSK also contains arabinose, rhamnose, fucose, galactose, mannose, and xylose [96]. The glycans in PSK is highly branched. The molecular weight of PSK is around 1×10^5 Da and the protein component is covalently linked to the β-1,6 glucose side chain.

PSK-based drugs are available as capsules and dropping pills in China. The published clinical reports indicate that these drugs have been used for treating acute nonlymphocytic leukemia [34], colorectal cancers [35,36], gastric cancers [37-40], lung cancer [41], primary liver cancer [42-44], hepatitis[45-50], and hyperlipidemia [51].

PSK has increased the survival time of cancer patients in randomized, control studies, with stomach cancer (meta-analysis of 8,009 patients) [97], colorectal cancer (randomized, controlled study

Glycans	Models	Effects	Ref.
Ganoderma lucidum glycans	Mouse	Enhance phagocytosis and cytotoxicity of macrophages	[125]
	Mouse	Enhance Lymphokine-activated killer cells	[125]
	Mouse	Increase cytotoxic T lymphocyte cytotoxicity and NK activity	[134-136]
	Mouse	Stimulate spleen-cell proliferation and cytokine generation	[134, 137, 138]
	Mouse	Reduce tumor weight	[134]
	Mouse	Exert antitumor effect on solid tumor induced by Ehrlich's ascites carcinoma cells	[128]
	Nude Mouse	Reduce Human lung carcinoma xenograft size	[140]
	Mouse	Induce tumor apoptosis and enhance immunological effect	[141]
	Mouse	Enhance scavenging abilities on reactive oxygen species	[175]
	Rat	Reduce ROS production and increase the activity of Manganese superoxide dismutase (Mn-SOD)	[142]
	Mouse	Increase insulin levels and decrease blood glucose	[143, 144]
	Rat	Decrease total cholesterol (TC)	[143, 144]
	Mouse	Reduce serum triglyceride (TG)	[143]
	Mouse	NO production	[139]
Ganoderma sinensis glycan	Mouse	Enhance levels of IL-2, IL-3, IL-4, interferon γ, TNF α, and IL-2R	[112]
Lentinan	Mouse	Inhibite growth of Sarcoma	[78]
	Mouse	Increase production of cytokine in immune cells	[79, 80]
	Nude Mouse	Trigger delayed-type hypersensitivity response against tumor-associated antigens	[81]
	Chicken	Enhance serum antibody titer and promote lymphocyte proliferation	[82]
	Rat	Improve bactericidal ability of peritoneal and alveolar macrophages	[83]
	Mouse	Enhance sensitivity of colon 26 tumor to cis-diamminedichloroplatinum (II) and decrease glutataione transferase expression	[84]
	Pig	Induce high level of alveolar macrophage activation	[85]
	Mouse	Induce TNF-α secretion of murine macrophages	[86]
	Rat	Induce long-term potentiation in the rat dentate gyrus	[87]
	Mouse	Induction of cytotoxic peritoneal exudate cells	[176]
	Mouse	Stimulate the expression of cytokines	[88]
Polyporus glycan	Mouse	Enhance TNF- α , IL-1b, and NO production	[177]
	Rat	Prevente the progression of renal injury and the subsequent renal fibrosis in Aristolochic acid nephropathy	[178]
	Rat	Inhibit bladder carcinogenesis, which may be associated with upregulation of GSTPi and NQO1 in the bladder	[179]
	Rat	Down-regulate AQP2, and down-regulate AQP2 by down-regulating V(2)R	[180]
Krestin	Rat	Suppress metastasis induced by hepatic I/R	[100]
	Rat	Inhibit bone Metastasis of Breast Cancer	[101]
	Rat	Improve GALT inhibition caused by TPN	[102]
Pachymaran	Mouse	Increase thymus and spleen indices, lysozyme, catalase , superoxidase dismutase activities, and total antioxidant capacity. Decrease xanthine oxidase activity and malondialdehyde levels.	[118]
	Rat	Decrease MDA and increase GSH levels in serum cervical of rats with cervical cancer	[119]
	Rat	Increase SOD, CAT, GPx, and GR activities in serum and cervical of rats with cervical cancer	[119]
	Mouse	Enhance antitumor activities	[120]
	Mouse	Increase macrophage activities and PFC, SRFC, DTH, IL-2 , IFN-γ, TNF-α, TCGF levels	[121-123]
Maitake glycan	Mouse	Activate macrophage and induce of IL-1, IL-6 and TNF-a secretion	[181]
	Mouse	Lower plasma cholesterol level	[152]
	Mouse	Activate natural killer and dendritic cells and enhance antitumor immunity	[147]
	Mouse	Protective effect of pancreatic β-cells exerted by decreasing levels of oxidative stress and NO synthesis	[148]
	Mouse	Induce systemic tumor-antigen specific T cell response, increase infiltration of activated T cells into tumor and decrease number of tumor-caused immunosuppressive cells	[149]
	Rat	Significantly lower systolic blood pressure (SBP) in diabetic Sprague-Dawley rats	[150]
	Rat	Inhibite LPS-induced upregulation of NF-κB activation and the production of IL-1β, TNF-α, iNOS, ICAM-1, and COX-2	[151]
Tremella glycan	Mouse	Have radiation protection properties	[154]
	Mouse	Increase plasma insulin level and the activities of hepatic hexokinase and glucose-6-phosphatase dehydrogenase, and decrease hepatic glucose-6-phosphatase level	[155]
	Rat	Improve cognitive function via regulation of the CREB signaling pathway and cholinergic system in the hippocampus	[156, 157]
	Rat	Increase cholinergic activity	[158]
	Rat	Increase fecal neutral steroids, total bile acids excretion, and SCFA productions	[159]

Table 3: Animal studies of biological effects of Fungal glycans.

of 448 patients) [98], but PSK has produced mixed results with liver cancer [99]. Rat-based animal studies confirmed the anti-metastasis properties of PSK [100-102].

Three mechanisms are proposed to explain the clinical effectiveness of PSK in suppressing cancer relapse [103]. First, PSK improves host immune-competence by inhibiting the production and also by neutralizing immunosuppressive substances that are increased in cancer. Second, PSK activates immune cells such as lymphocytes, either directly or by regulating the production of various cytokines. Third, PSK acts directly on cancer cells. In addition, the effects of PSK on the production of various cytokines and nitric oxide (NO) have also been reported [104,105].

Ganoderma Sinensis glycans

Ganoderma sinensis glycans are purified from fruiting body of *Ganoderma Sinensis*. The major bioactive *Ganoderma sinensis* glycans are α/β -glucans, glycan-protein complex and water-soluble heteroglycans with different combinations of glucose, mannose, galactose, xylose, fucose as well as arabinose. The molecular weight of the glycans ranges from 10^3 to 10^6 Da [106].

Ganoderma sinensis glycan-based drugs are available as capsules. Published reports indicated the drug is used for neutralizing mushroom poisoning [10] and stimulate leukocytes productions in leukopenia patients [11] . Further studies showed that *Ganoderma sinensis* glycans enhance the immune responses in patients with advanced-stage cancer [107,108]. *Ganoderma sinensis* glycans also have potent antioxidant activities [109-111]. Mouse-based animal studies indicate that *Ganoderma sinensis* glycans enhance the levels of a variety of citokines [112].

Pachymaran

Pachymaran is a name giving to a heteroglycan isolated from *Poria Cocos*. Pachymaran consists of glucose, galactose, and mannose. It exhibits antitumor activities both *in vitro* and *in vivo* [113,114]. β-Glucan extracted from *Poria Cocos* is water-insoluble and has no antitumor activity, whereas its phosphorylated water soluble derivatives exhibits strong anti-S-180 tumor activities [115].

Pachymaran used for making the glycan-based injection drugs in China is isolated from mycelium of *Poria Cocos*. It is used for treating chronic pulmonary edema [52], insomnia [53], alopecia [54], and schizophrenia [55]. It prevents tumor metastasis through its immunomodulatory activities [116,117]. Mouse- and rat-based animal studies showed that pachymaran has potent antioxidative and antitumor activities [118-123].

Ganoderma Lucidum glycans

Ganoderma Lucidium glycans are composed of different variety of glycans as shown in *Table 2*. *Ganoderma Lucidium* glycan-based drugs are purified form spores and available as injections. Published reports indicated the drug improves endurance of cyclists [7] and helps patients with dyslipidemia conditions [8]. Interestingly, when combined with glucocorticoid, the drug cures facial paralysis in patients [9].

Mouse and rat-based animal studies showed *Ganoderma Lucidium* glycans activate different immune cells and stimulate chemokine and cytokine production [108, 124-139]. *Ganoderma Lucidium* glycans also have antitumor [128,140,141], anti-oxidative [124,142], antidiabetic [143,144], and hypolipidemic [143,144] activities.

Maitake glycans

Grifola Frondosa is also called maitake. A bioactive β - glucan fraction termed D-fraction was isolated from both mycelia and fruiting body of *Grifola Frondosa* by Japanes mycologists in 1984. Grifolanis of maitake glycans is a glycan-protein complex, which is called Wu Rong D-fraction in China. Its glycans mainly consist of glucose along with xylose, fucose, galactose, and mannose. The ratio of protein to glycan in Grifolanis is 7:3. The average molecular weight of Grifolanis is greater than 1x 10^6 Da. Only Wu Rong D-fraction have antitumor activities [145].

Grifola Frondosa glycans used for drug production is isolated from cultured mycelium. The glycan-based drugs are available as capsules. Published reports indicated the drug is used for cancer treatment [56,57], impaired glucose tolerance conditions [58], and for treating polycystic ovary syndrome [59]. *Grifola Frondosa* glycans have also been used for cosmetic and other biological purposes [146].

Mouse and rat-based animal studies showed *Grifola Frondosa* glycans activate different types of immune cells [147] and regulate chemokine and cytokine productions [147-151]. *Grifola Frondosa* glycans also have antitumor [147], anti-oxidative [148], hypo-cholesterol [152], and hypo-systolic blood pressure [150] activities.

Tremella glycan

Tremella glycans are isolated from fruiting body of *Tremella fuciformis*. The most representative glycans in *Tremella fuciformis* is acidic heteroglucan where α - mannan constituteits the backbone with β - (1,2) xylose, β - (1,2) glucuronic acid, and minor amount of fucose on the side chains. Other glycans include several neutral heteroglycans comprising of xylose, mannose, and galactose.

Tremella glycan-based drugs are available as capsules in China. The drug is used clinically in treating mycoplasma caused pneumonia [60], chronic active hepatitis [61], diabetic [62], leukopenia [63-65] conditions. The drug also promotes neural cell growth and improves memory [153].

Mouse-based animal studies showed tremella glycans have radiation protection properties [154]. Tremella glycans increase plasma insulin level and the activities of hepatic hexokinase and glucose-6-phosphatase dehydrogenase and decrease hepatic glucose-6-phosphatase level [155]. Interestingly, tremella glycans improve cognitive functions through multiple distinctive mechanisms in rats [156-159].

Future Perspectives

There are multiple issues needed to be addressed before fungal glycan-based drugs are accepted by governments and clinicians worldwide, such as how to comprehend the pharmacodynamics of fungal glycan-based drugs at molecular level, how to standardize quality, composition, purity of the highly dispersed glycan molecules, and how to perform reliable pharmacokinetic studies. Compared to conventional small molecule- and protein-based drugs, the advantages of glycan-based drugs are their broad spectrum of therapeutic properties, relatively low toxicity, less drug-resistant issues, and relatively low costs. The disadvantages of glycan-based drugs are the inherited heterogeneity of their structures and functions, lack of tools to do proper structure analyses, and difficulty in establishing structure and function relationships. Thus, developing reliable biological assays and novel structural characterization tools might be critical in understanding the information encoded in the fungal glycans and to perform reliable pharmacokinetic and pharmacodynamic studies.

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