Immunomodulating fungal and plant polysaccharides; Biochemistry, immunologic activity and clinical application

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The polysaccharide (PS) fractions isolated from fungi and higher plants have been shown as potent biological response modifiers exhibiting immunostimulating and antitumor activities through the functions involving activation of macrophages, cell-mediated immunity and cytokine induction. The primary structure of these PSs exhibits \( \beta (1\rightarrow3) \), \( \beta (1\rightarrow4) \)-linkage glycans as the common form of main chain, while the side chains involve \( \beta (1\rightarrow3) \), \( \beta (1\rightarrow4) \), \( \beta (1\rightarrow6) \) or \( \alpha (1\rightarrow4) \) linkages. The hydrogen bond, tertiary structure of triple helix, and high molecular weight contribute to the stability and biological activities of the PSs. The degree of substitution on the backbone chain and the length of the side chains are important for the conformation of structure and their immunologic activity. Here we review the biochemical characterization, immunomodulating activities, and clinical application of important PSs isolated from fungi including Lentinus, Ganoderma, Hoeien, Polyporus, and Ascomyces and higher plants such as Radix Astragali, Angelica, Ginseng, and others. Immunomodulating PSs thus far have been used to prevent disease and promote restoration of the body's homeostasis, and current evaluations focus on treatment of pathogenic factors. Development of these polysaccharides into drugs for therapeutic use needs research on structure-activity relationship and quality assurance for polysaccharide molecules and final products.

Key words  activation of macrophage, cell-mediated immunity, cytokine induction, fungal and plant polysaccharides, immunostimulating and antitumor activities, structure-activity relationship.

I. Introduction

Many Western medicines contain natural products or their extracts. Recently, there has been a resurgence of interest in these products, and, in particular, the Oriental medicines. Herbs including traditional Chinese medicines and Kampo drugs have been used for centuries in Asian countries to prevent a variety of ailments, and thus indirectly reducing treatment costs through disease prevention. The World Health Organization (WHO) urges member nations to develop new medicines that combine the ancient arts of herbs with modern science. Oriental medicines are a widely accepted means of healing even in high-technology societies in Asia. However, to most Westerners, herb medicines are a mystery because the active components are often poorly characterized and the mechanism of action frequently misunderstood.

Immunomodulating and antitumor activities have been observed in the polysaccharide (PS) fractions of fungi and higher plants. These PSs have been tested in animal models and in clinical studies to treat select tumors. PSs have been evaluated as a single therapy, as an adjunct therapy combined with chemotherapeutic agents, and as conjugates bound to antibodies. The mechanisms of the immunostimulating and antitumor activities of these PSs are thought to involve the functions related to amplification of phagocytosis, activation of macrophages, T-lymphocytes and complement, and enhancement of cytokine production and cell-mediated immune response.1)

The immunity of the body decreases with age, which is thought to be associated with a consequent decreased recognition of antigens, and perhaps an increased frequency of diseases such as arthritis, diabetes, and cancer in the elderly. Since immunomodulating PSs can stimulate the immune response, PSs may potentially help to prevent these types of diseases. As a result, overall quality of life, and ultimately the survival rate, of the elderly population might also improve.

II. Immunostimulating PSs from fungi

In the practice of traditional Oriental medicine, different kinds of fungi belonging to basidiomycetes have been used for treatment of cancer. Following this idea, in 1969, a polysaccharide with a marked antitumor activity was isolated from the edible mushroom Lentinus edodes (Hsiang-Ku) and termed Lentinan.2) Likewise, Ganoderma (Lingzhi, Ling-chih), a medicinal fungus, is recognized historically as a valuable tonic remedy in China. In Shen Non's Material Medica, the first folk pharmacopoeia published in the second century B.C., Ganoderma was classified as a drug of "high grade", which was defined as an herb of good medical value and without toxicity. Commercial products that include Ganoderma as an ingredient, such as health foods, have been widely used in Asian countries. Recently, such health foods are becoming popular in the U.S. The main immunostimulating fungal polysaccharides are shown in Table 1.

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<table>
<thead>
<tr>
<th>Product</th>
<th>Scientific name</th>
<th>Molecular Weight (kDa)</th>
<th>Active component(s):</th>
<th>Structure</th>
<th>Major activity</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lentinus (Hsiang-ku)</td>
<td>Lentinus edodes</td>
<td>$10^6$</td>
<td>PS (Lentinan)</td>
<td>$\beta(1\rightarrow3)G$ $\beta(1\rightarrow6)G$</td>
<td>Enhances immune functions. Antitumor activity.</td>
<td>2-16, 18-26, 95</td>
</tr>
<tr>
<td>Coriolus (Coriolus, Kawaratake, protein bound glucan)</td>
<td>2 x $10^6$</td>
<td>PSK (Krestin)</td>
<td>$\beta(1\rightarrow4)G$ $\beta(1\rightarrow6)G$</td>
<td>Stimulates cytokine production CSF, IL-1, TNF-α, antitumor activity</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Ganoderma (Lingzhi, Ling-chih)</td>
<td>Ganoderma lucidum</td>
<td>$4 \times 10^4$</td>
<td>GL-1</td>
<td>$\beta(1\rightarrow3)G(Ara)$ $\alpha(1\rightarrow4)G$ $\beta(1\rightarrow6)G$ $\beta(1\rightarrow6)G$ (Xyl)</td>
<td>Increases cellular immunity. Inhibits tumor cell growth</td>
<td>27-35, 60</td>
</tr>
<tr>
<td>(Spores)</td>
<td></td>
<td></td>
<td>PSG1 to PSG7</td>
<td>$\beta(1\rightarrow3)G$ $\beta(1\rightarrow6)G$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>#(M), $7.4 \times 10^3$</td>
<td>Ganoderan B</td>
<td>$\beta(1\rightarrow3)G$ $\beta(1\rightarrow6)G$</td>
<td>Hypoglycemic activity</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(M, $5.8 \times 10^3$)</td>
<td>Ganoderan C</td>
<td>$\beta(1\rightarrow3)G$ $\alpha(1\rightarrow3)G$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G. japonicum</td>
<td>G-A</td>
<td>$\beta(1\rightarrow3)G$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoelen</td>
<td>Poria cocos</td>
<td>$1.8 \times 10^5$</td>
<td>PS Pachymaran</td>
<td>$\beta(1\rightarrow3)G$</td>
<td>Antitumor activity. Enhances phagocytic activity, production of TCGF</td>
<td>36, 37, 96</td>
</tr>
<tr>
<td>Polyporus (Chu-ling)</td>
<td>Polyporus umbellatus (Grifola umbellata)</td>
<td>$75 \times 10^6$</td>
<td>GU-2</td>
<td>$\beta(1\rightarrow6)G$ $\beta(1\rightarrow3)G$</td>
<td>Regulates and stimulates immune system, transforms cancer cells into normal cells. Stimulates phagocytic activity, increases CAMP in sarcoma 180 cells, improves lung cancer survival rate</td>
<td>38-40, 97, 98</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GU-3</td>
<td>$\beta(1\rightarrow3)G$ $\beta(1\rightarrow6)G$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GU-4</td>
<td>$\beta(1\rightarrow3)G$ $\beta(1\rightarrow6)G$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$1.2 \times 10^6$</td>
<td>$\beta(1\rightarrow3)G$ $\beta(1\rightarrow6)G$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascomycetes (Tung-chung-hsia-tsao)</td>
<td>Cordyceps ophioglossoides</td>
<td>$6.32 \times 10^5$</td>
<td>CO-1 (Galactomannan)</td>
<td>$\beta(1\rightarrow3)G$ $\beta(1\rightarrow6)G$</td>
<td>Inhibits tumor cell growth</td>
<td>99-101</td>
</tr>
<tr>
<td>C. cicadae (Chun-hua)</td>
<td>C-3 (Galactomannan)</td>
<td>$2.7 \times 10^4$</td>
<td>$\alpha(1\rightarrow2)G$ $\alpha(1\rightarrow6)G$</td>
<td>Antitumor activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricholomataceae (Shuh-hua)</td>
<td>Schizophyllum commune</td>
<td></td>
<td>Schizophylin</td>
<td>$\beta(1\rightarrow3)G$ $\beta(1\rightarrow6)G$</td>
<td>Antitumor activity. Stimulates IL-2 production</td>
<td>5</td>
</tr>
<tr>
<td>(Lui-wan)</td>
<td>Omphalina lepidescens</td>
<td>OL-2</td>
<td>$\beta(1\rightarrow3)G$</td>
<td>Vermifuge</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Zhu-sun (Kimugatake)</td>
<td>Dictyophora indusiata</td>
<td>T-4 (glucan)</td>
<td>$\beta(1\rightarrow3)G$ $\beta(1\rightarrow6)G$</td>
<td>Antitumor activity</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>T-5 (glucan)</td>
<td>$\beta(1\rightarrow3)G$ $\beta(1\rightarrow6)G$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

# GL-1 structure contains $\beta(1\rightarrow3)G$ in both main and side chains. Ms: Molecular mass, similar to molecular weight.

Abbreviations: G, glucose; CSF, colony stimulating factor; IL, interleukin; TNF, tumor necrosis factor; Ara, arabinose; Xyl, xylose; G-A, arabinogalactan; TCGF, T-cell growth factor (IL-2); cAMP, cyclic adenosine monophosphate.
(A). **Lentinus (Hsiang-ku, Shiitake)**

(A-1). Lentinan

Lentinan, isolated from *Lentinus edodes*, is one of the most thoroughly studied fungal PSs. The structure of Lentinan which consists of a glucan is comprised of repeating units of five β(1→3) glucopyranoside linkages, two β(1→6)-glucopyranoside branchings that exist mainly as a right-handed triple-helical structures in solid state, and possible hydrogen bonds between adjacent glucose units. Lentinan has a molecular weight of up to 10^6 kDa. Fig. 1 lists the primary structure of Lentinan.

Lentinan is relatively non-toxic. The LD₅₀ values of Lentinan combination with Tegafur (600 mg/day, oral) in mice and rats are estimated to be 250-500 mg/kg by i.v. administration and greater than 2,500 mg/kg by i.p., s.c. and oral route. Lentinan exhibits marked immunostimulating and antitumor activities in animal experiments. Augmentation of helper T cell-mediated cytotoxic activity, NK cell activity and humoral immune responses were observed. In addition, Lentinan activated non-specific cytotoxicity of macrophages in vitro and in vivo. In mouse peritoneal cells and splenocytes, mRNA levels, expressed from genes that produce the cytokines IL-1α, IL-1β, TNF-α, IFN-γ and macrophage colony-stimulating factor, were markedly induced by Lentinan. Combined use of Lentinan and IL-2 was found to result in synergistic antitumor and antitemetastic effects in mice against spontaneously metastatic 3-methylcholanthrene-induced fibrosarcoma. Likewise, the enzyme pyrimidine nucleoside phosphorylase (PyNPase), which converts 5'-deoxy-5-fluorouridine (5'-DFUR) to 5-fluorouracil (5-FU), is induced by various cytokines in tumor cells. A combination of 5'-DFUR and Lentinan has been used to verify antitumor effects, the induction of cytokines, and PyNPase activity against AH66 ascites hepatoma cells in rats. It was demonstrated that PyNPase activity in the tumor was induced by Lentinan. In addition, levels of TNF-α and TGF-β production in the tumor were significantly lower in the 5'-DFUR + Lentinan group compared to the 5'-DFUR control group. A multicenter clinical study of Lentinan used in combination with cytostatic agents was evaluated in patients with advanced, unresectable and recurrent gastric cancer. Participants receiving chemotherapy and Lentinan were observed to have a prolonged in survival rate (297 days vs. 199 days) and improved quality of life. Lentinan, at a daily i.v. dosage of

![Chemical structure of Lentinan isolated from Lentinus edodes.](image)

**Fig. 1.** Chemical structure of Lentinan isolated from *Lentinus edodes*. There are hydrogen bonds between adjacent glucose units of the β(1→6) glucopyranoside branches for every five β(1→3) glucopyranoside linear linkages.
2 mg per patient, combined with tegafur was effectively used for postoperative therapy of gastric cancer. An increase of more than 50% IL-1β production in the peripheral blood of gastric cancer patients associated with Lentinan treatment was observed, as well as an enhanced induction of lymphokine-activated NK cell activity. In Japan, Lentinan has been used (2 mg/wk iv injection in adults) in combination with Tegaful (600 mg/day, oral administration) for gastric cancer patients. However, its effectiveness for single use has not been established.

(A-2). PSK (Polysaccharide K, Krestin) and PSP

The mushroom Coriolus versicolor has been used in traditional Chinese medicine for centuries and recorded in the *Compendium of Materia Medica* by Li Shi Zhen during the Ming Dynasty in China as being beneficial to health. Various substances have been isolated from this mushroom including PSK and PSP. PSK, a protein-bound β-glucan containing approximately 25% protein, and PSP, a polysaccharide peptide, were isolated from the CM-101 strain and COV-1 strain, respectively, of *Coriolus versicolor*. PSK has a molecular weight of approximately 100 kDa, contains a number of glutamic acid and asparatic acid, and in its polypeptide component, as well as the neutral amino acids leucine and valine. The structure of the main glycoside portion is β-glucan, which includes α-1,4 and β-1,3 glucosidic linkages, and branched chains including 1→3, 1→4 and 1→6 bonds. Also, branches at 3- and 6-positions occur in a ratio of one per several 1→4 linkages. The primary monomer of the polysaccharide portion is glucose with decreasing percentages of mannose, xylose, galactose and fructose. The presence of fructose in PSK, and rhamnose and arabinose in PSP, distinguishes the two protein-bound PSs, which are otherwise chemically similar. Figure 2 shows the primary structure of carbohydrate moiety in PSK.

PSK is a promising potential adjuvant cancer therapy agent. PSK is thought to contribute to prolonging the five-year survival of patients with cancers of the stomach, colon, rectum, esophagus, nasopharynx, lung, and in breast. Although the exact mechanism of action of PSK is not well defined, PSK is thought to increase leukocyte activation and induction of cytokines. Natural killer (NK) and lymphocyte-activated killer (LAK) cell activation has been demonstrated *in vivo* and *in vitro*. It exhibits antioxidant capability, which may play a role as a tissue chemotherapeutic and/or radiotherapy, in the treatment of cancer. PSK may inhibit carcinogenesis by direct inhibition of various carcinogens on vulnerable cell lines. Proposed mechanism on immunomodulatory and antitumor activities is described in Figure 3.

In addition to being a potential chemotherapeutic adjuvant, PSK has been reported to enhance glutathione peroxidase (GST) activity, and to increase selenium-dependent glutathione peroxidase and GST-P mRNA expression in mouse peritoneal macrophages. It also enhances manganese superoxide dismutase activity and its mRNA expression. Furthermore, it induces nitric oxide synthetase (iNOS) gene expression and nitric oxide production in mouse peritoneal polymorphonuclear leukocytes. The stimulated production of nitric oxide in combination with IFN-γ may regulate the immune system *in vivo*.

PSK activated the transcription of TNF gene in tumor cell lines, indicating that PSK exerted an immunostimulatory effect on the defensive cells. Both mouse lymphocytes and macrophages were activated by preparations of PS from cultured mycelia and culture medium of *C. versicolor*. It induced the production of IFN-α, IFN-γ, IL-2, and T-cell proliferation. PSK counteracted the depressive effect of cyclophosphamide on leukocyte count, IL-2 production and delayed hypersensitivity reaction. A small peptide with a molecular weight of 16-18 kDa, which originated from PSK, has been shown to exhibit antiproliferative and antitumor activities. PSP, when evaluated in clinical Phase II and Phase III double-blind trials in China, extended the five-year survival time of patients with esophageal cancer. In addition, PSP substantial pain relief, and enhanced immune status was reported in 70-97% of patients with cancers of the stomach, esophagus, lung, ovary, and cervix. PSK and PSP have demonstrated favorable responses in initial studies on treatment of various cancers. However, more clinical trials are needed to confirm the previous observations. Further clinical data and evidences on efficacy and safety for these products are important and necessary for their therapeutic application.

(B). Ganoderma (Lingzhi, Ling-chih, Rheishi)

Lingzhi (*Ganoderma*) has been used in China as an herbal drug for thousands of years, as reported in *Shen Nong's Materia Medica*. It has been classified into six types according to their different colors. However, only the red and purple Lingzhi have been recognized as *Ganoderma lucidum* and *Ganoderma sinense*, respectively. Traditionally,
Lingzhi has been used for Fu-cheng Ku-pen (Fuzheng Guben: supporting the vital force and securing the root). Its major components with pharmacological activities include triterpenses and polysaccharides. *Ganoderma lucidum* polysaccharide (GL-PS) has been reported to exhibit remarkable activities in modulating immune functions and inhibiting tumor growth.\(^\text{5,20}\) Extensive immunomodulating effects, including promoting the function of mononuclear phagocytes, and humoral, as well as cellular immunity, have been observed. The active site of GL-PS is thought to be exposed during immune precursor cells proliferation and differentiation to effector cells. The combination of GI-PS with antitumor drugs, such as mitomycin or etoposide, could antagonize the inhibitory effects of these drugs on mixed lymphocyte culture (MLC).\(^\text{20}\)

A water-soluble, antitumor polysaccharide, GL-1, which has a molecular weight of 40 kDa, was isolated from the fruit bodies of *Ganoderma lucidum*. GL-1 is a D-glucopyranosyl \(\alpha\) and \(\beta(1\rightarrow4), \beta(1\rightarrow6),\) and \(\beta(1\rightarrow3)\) linkages. Arabinose is present as a part of the non-reducing terminal residues, and xylose may be present as a part of the side-chain. The nondialyzable fraction, GL-2, having molecular weight of 38 kDa, exhibits only glucose on acid hydrolysis. GL-3 has a molecular weight of 37 kDa. Similar inhibitory activity (95.6-98.5\%) to growth of Sarcoma 180 tumor cell was observed in GL-1, GL-2 and GL-3 when injected i.p. 20 mg/kg for 10 days.\(^\text{30}\) Seven polysaccharides, PSG1 to PSG7, have been isolated from *G. lucidum* spores. All PSs exist naturally as a glucan, but each glucan has a different sugar chain structure, which contributes to a unique glycosyl linkage and sugar chain conformation. Purified PS fractions of PSG2, PSG4, PSG5 and PSG6 have been shown to exhibit immunostimulating activity, while PSG3 and PSG7 have no obvious effect on T and B lymphocyte proliferation. PSG2 and PSG5 contain a structure of \(\beta(1\rightarrow3)\) linked glucan backbone. However, PSG2 contains a single-helical conformation, while PSG5 exists in a highly-ordered structure of triple-helix. The primary structures of PSG2 and PSG5 are depicted in Figures 4-A and 4-B. Results from structure-function relationship studies indicate that \(\beta(1\rightarrow3)\) linked backbone, a relatively short side chain, substitution, and a highly organized helical structure are important features that account for the immunostimulating activities of Lingzhi PSs.\(^\text{31}\)

Ganoderans B and C, isolated from the fruit bodies of *Ganoderma lucidum* are shown to be peptidoglycans with molecular masses (\(M_r\)) of 7400 and 5800, respectively. The backbone and side chains of ganoderan B contain D-glucopyranosyl \(\beta(1\rightarrow3)\) and \(\beta(1\rightarrow6)\) linkages, while those of ganoderan C contain D-glucopyranosyl \(\beta(1\rightarrow3)\) and \(\alpha(1\rightarrow3)\) linkages and a D-galactopyranosyl \(\alpha(1\rightarrow6)\) linkage. They induce hypoglycemic activity.\(^\text{21}\) Figures 5-A and 5-B show the structures of ganoderans B and C.

GL-PS can increase the co-expression of bone marrow-derived dendritic cells and cell surface phenotype of the I-A/I-E (MHC II) molecule, which is a marker of dendritic cell maturation. GL-PS also increases mRNA expression, IL-12 p40 secretion, and, enhances lymphocyte proliferation in mixed lymphocyte culture (MLC).\(^\text{31}\) In addition, GL-PS isolated from boiling water extract of wood-cultured G. (anol. wt., 5.84 x 10\(^5\)) promotes the effect of dendritic cell-induced cytotoxic T-lymphocytes. The mechanism of cytotoxicity is considered to be via the IFN-\(\gamma\) and granzynme B pathways.\(^\text{34}\)

Treatment of advanced-stage cancer patients with Ganopoly, a *G. lucidum* polysaccharide extract, at an oral dosage of 1800 mg three times daily for 12 weeks increased the plasma concentration of IL-2, IL-6 and IFN-\(\gamma\), and NK

Figure 3. Proposed mechanism on immunomodulatory and antitumor activities for herbal polysaccharides. Polysaccharides (PSs), such as Lentimian, PSK, activate the C3 alternative pathway to induce splitting of C3 into C3a and C3b. PS opsonized with C3b binds to CR1 or CR3 on antigen presentation cells (APCs), e.g. macrophages, dendritic cells. It may also bind these cells through \(\beta\)-glucan receptors. Tumor antigen binds to APCs and interact with MHC (major histocompatibility) class I or II molecule. After such processing, the complexes are displayed on the cell surface and bind to Th cells, inducing various cytokines. The activation of Th cell helps to elicit humoral (antibody-type) and cellular (cytotoxicity) immune response to destroy tumor cells. Immunomodulatory PSs may also exert direct antitumor effects.

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**Cellular immune response**

**Humoral immune response**

*Abbreviation:* Th1 and Th2, T helper type 1 and 2 cells; NK, natural killer; IL, interleukins; TNF-\(\alpha\), tumor necrosis factor; IFN, interferon; C, complement; Ag, antigen; Ab, antibody.
Immunomodulating herb polysaccharides

(4-A) PSG2

\[ \beta-D-GlcP(1 \rightarrow 3)\beta-D-GlcP(1 \rightarrow 3)\beta-D-GlcP(1 \rightarrow 3)\beta-D-GlcP(1 \rightarrow 3) \]

(4-B) PSG5

\[ \beta-D-GlcP(1 \rightarrow 3)\beta-D-GlcP(1 \rightarrow 3)\beta-D-GlcP(1 \rightarrow 3)\beta-D-GlcP(1 \rightarrow 3) \]

\[ n = 0, 1, 2 \]

Note: three of the four branching chains are terminal glucosidic residues.

(5-A). Ganoderan B

\[ \beta-D-Glp \]

(5-B). Ganoderan C

\[ \beta-D-Glp \]

Figure 4. Chemical structure of polysaccharides isolated from *Ganoderma lucidum* spores.

PSG2 and PSG5 shared a structural feature of having a β(1->3)-linked glucan backbone. However, the sugar chain conformation of PSG2 is much different from those of PSG5. PSG2 contains a single-helical conformation, while PSG5 exists in a highly-ordered structure of triple-helix.

cell activity. Also, IL-1 and TNF-α levels were decreased.\(^5\)

(C). Hoelen (Fuling), Polyporus (Chu-ling, Zhuling), and Ascomyces (Tung-chung-hsia-tsao).

Hoelen is used to treat gastric disease in Oriental traditional medicine. Administration of Hoelen into the rat duodenum resulted in increased efferent gastric vagus nerve activity. Since both fractions containing polysaccharide and triterpenoid significantly increased such activity in an experimental animal model, Hoelen could perhaps be clinically useful to treat gastric disease.\(^6\) Polysaccharide isolated from Hoelen contains galactose, glucose, mannose and galacturonic acid. Mice injected with Hoelen PS, 0.2-1.0 mg/dose, i.p., followed by administration of pneumococcal type 9V PS-protein conjugate, 5 μg/dose, i.p., produced higher serum levels of 9V PS IgG and IgM antibodies than the non-treated control group. Mice treated with Hoelen PS exhibit more rapid bacterial clearance from blood after challenge with virulent type 19F pneumococci. In addition, in mice immunized with type 9V PS glycoconjugate the treatment of Hoelen PS induces TNF-α 2.4 to 4.7 fold higher than the control group. Moreover, in Hoelen PS-immunized group, a level of 2.1 fold higher INF-γ was induced. IL-2 and IL-4 production were also significantly higher, compared with non-immunized controls. These results indicate that the stimulating effects of fungal PS might contribute to the protective effects of a bacterial glycoconjugate through the enhancing activities of cytokines and immune response.\(^7\)

Pachyman, obtained from *Poria cocos*, has a structure of β(1->6) linear glucan, and is completely devoid of antitumor activity. However, when it is converted into a Lentinan-like β(1->3) linear glucan (derivatives II and III), it exhibits a strong antitumor activity.\(^8\)

A water-soluble glucan, GU-1, isolated from *Grifola umbellata* has been reported to exhibit marked inhibition on the growth of Sarcoma 180 tumor cells in mice. Furthermore, other antitumor glucan GU-2 contains a backbone involving β(1->6) and β(1->3) linkages, and two kinds of branches involving β(1->6) and α(1->4) linkages. GU-3 has a β(1->3) linked backbone and branches involving β(1->6) linkages or α(1->4) and β(1->6) linkages. GU-4 also contains a β(1->3) glucan backbone and a small number of β(1->6) linked branches. The antitumor effect against Sarcoma 180 tumor cells indicates that the complete regressions induced by GU-2, GU-3, and GU-4 are 7/10 (1 mg/kg), 9/10 (1 mg/kg), and 6/10 (5 mg/kg) respectively.\(^9\)

CO-1, also a water-soluble extracellular glucan, was isolated from the precipitate of the culture filtrate of *Cordyceps ophioglossoides*. The backbone of CO-1 is comprised of β(1->3)linked glucopyranosyl. CO-1 strongly inhibits the growth of Sarcoma 180 tumor. CO-1 polyalcohol, prepared by Smith degradation of CO-1, exhibits more potent antitumor activity than CO-1. In addition, a water-soluble galactomannan, C-3, isolated from *C. cicadae*, has a molecular weight of 27 kDa. The PS is composed of D-mannose and D-galactose in the molar ratio of 4:3, and highly branched structure containing α(1->2) and α(1->6) linked mannopyranosyl residues in the core; some of these residues are substituted at O-6 and O-2 terminal β-D-
galactofuranosyl and α-D-mannopyranosyl groups, and with short chains of β(1->2) linked D-galactofuranosyl units.\(^{39,40}\)

Other fungal PSs with immunostimulating and antitumor activities have been isolated from *Auricularia auricula*,\(^{41}\) *Armillaria tabescens*,\(^{42}\) *Tricholomataceae*, and *Zhu-sun*.\(^{43,44}\)

### III. Immunostimulating PSs from higher plants.

In general, PSs from higher plants are complex heteroglycans. Many antitumor PSs are soluble D-glucans that are not quickly hydrolyzed by D-glucanases\(^{45,46}\). Many of these herbs are frequently used in combination to promote longevity in traditional Chinese medicine. These preparations have been used in humans for many generations. Since their actions are mild, prolonged use may be necessary to achieve the desired effects. There are no major side effects if these preparations are used properly.

**(A). Radix Astragali (Huangqi)**

The root of *Astragalus membranaceus*, var. *mongholicus*, or *Astragalus membranaceus* has been used as a general tonic in traditional Chinese medicine for generations.\(^{47}\)* A series of PSs including Astragalans I-III, AG-I, AG-II, AH-II, Amem-P and Amon-S are isolated from the roots of Astragali. Astragalan I is composed of D-glucose, D-galactose, and L-arabinose in addition to trace amounts of pentose with an average molecular weight of 36.3 kDa. The sugar component in both astragalans II and III is D-glucose (Mol. Wts., 12.3 kDa and 34.6 kDa respectively). These two PSs consist mainly of α(1->4) glucopyranose and a small amount of α(1->6) glucopyranose residues. AG-I is a glucan with α(1->4) and α(1->6) linkages, while AG-2 is an α(1->4) glucan. The sugar components in AH-1 are identified as galacturonic acid, glucuronic acid, glucose, rhamnose, and arabinose, whereas those in AH-2 contain glucose and arabinose. Amon-S is composed of L-arabinose, D-galactose, D-galacturonic acid and D-glucuronic acid, in addition to small amounts of O-acetyl groups and a peptide moiety.\(^{47-49}\)

An extract of the root of *A. membranaceus* is reported to enhance the activity of IL-2, B cell growth factor, and IL-6 *in vitro*, and proliferation of T lymphocytes in patients with IgG subclass deficiency.\(^{50}\)

Administration of a polysaccharide fraction of *A. membranaceus*, which consists of mainly astragalins I and II, to mice stimulated humoral immune functions and restored immunosuppression caused by prednisolone and cyclophosphamide.\(^{51}\)

Astragalans enhances the secretion of TNF from human peripheral blood mononuclear cells *in vitro*.\(^{52}\)

It is suggested that *A. membranaceus* may exert its antitumor effect through augmentation of phagocyte and lymphokine-activated NK cell activities.\(^{53}\)

Furthermore, *Astragalus membranaceus* and *Oldenlandia diffusa* markedly stimulate murine spleen cells to proliferate. These results suggest that Chinese medicinal herbs have immunomodulating activity *in vitro* and this activity can be used clinically for the modulation of immune responses.\(^{54}\)

**(B). Angelica (Tang-kuei, Dansgui)**

Angelica, the root of *Angelica sinensis*, is one of the most widely used Chinese medicines among other of the same family, e.g. *A. gigas* and *A. acutiloba* for its anti-ulcer activity. The polysaccharide fraction from *Angelica* (AP) prevents gastric mucosal damage, and its preventive effect is dose-dependent. Simultaneous administration of AP and prostaglandin E2 reduce mucosal myeloperoxidase activity. AP pretreatment also prevents ethanol- or indomethacin-induced gastrointestinal damage and promotes ulcer healing. It has a direct stimulating effect on gastric epithelial cells for wound healing. The PS also stimulates DNA synthesis and increases epithelial growth factor (EGF) mRNA expression. Angiogenesis is inhibited by the PS treatment. These findings suggest that PS from *Angelica* exhibits an anti-inflammatory activity, by inhibiting neutrophil infiltration within the gastrointestinal mucosa.\(^{55-57}\)

A PS, isolated from *Angelica acutiloba* (Tang-kuei), has been reported to induce interferon, stimulate B-lymphocytes, mediate antitumor activity against Ehrlich ascites, and activate polyclonal B cells and complement. PS subcomponents have been isolated and their immunologic activities examined. The major PS is identified as a pectin, which consists of sugar components, including rhamnose, arabinose, xylose, galactose, and galacturonic acid; it also contains a large amount of amylopectin-like glycan. The crude PS extract, designated AR-1, from Tang-kuei was purified by cetylton precipitation. The resultant fraction was termed AR-2, and is an acidic PS. The supernatant fraction from AR-2 was treated with 1% boric acid and 2N sodium hydroxide, and adjusted to a pH of 8.8. The resultant precipitation fraction obtained was termed AR-3, and the supernatant fraction, further precipitated by ethanol, was termed AR-4, respectively. AR-1 elicits strong mitogenic activity, whereas AR-4 exhibits strong complement activation, interferon-inducing, and antitumor activities. AR-4 was fractionated further, by DEAE-Sephardex chromatography, into fraction I (nonabsorbed) and fraction II (absorbed, including IIIa, IIIb, and IIc). Fraction I largely contains amylopectin-like glycans. In contrast, fractions IIIa and IIIb contain arabinogalactan, and show strong complement activation (IIa). Fraction IIc induces interferon. This AR-4 fraction exhibits antitumor and interferon-inducing activities, suggesting that activation of both biological functions may be associated with the same AR-4 fraction. The results also reveal that specific immunologic functions can be attributed to specific PS subcomponents.

The immunomodulating activity of the Tang-kuei extract is postulated to be due to both polysaccharide and protein components. The side chain structure of nonreducing terminal molecules, sugar composition, and linkage of the PSs influence resultant immunologic and pharmacologic properties. Although functional activity is not dependent on a specific structural confirmation, the polarity of ionic and amino sugars, conformation of the β(1->3) glycan, and triple-helix structures are factors that appear to contribute to the immunomodulating properties of PSs.\(^{58-60}\)

AP prevents liver toxicity in mice induced by
acetaminophen, which is associated with the glutathione deple-tion and nitric oxide synthetase activation in the liver. It normalized the rises of serum alanine transferase (ALT) and hepatic nitric oxide synthetase (NOS) activities and the de-crease of glutathione level in the liver.61) Angelan, having a molecular weight of 10 kDa, is a polysaccharide isolated from the root and cell culture of *angelica gigia*. Angelan elicits cytokine production from monocytes.62,63) Both angelan and LPS stimulate murine macrophage to produce inductible nitric oxide synthetase (iNOS) and mediating nitric oxide (NO), and nuclear factor for immunoglobulin k chain in B cells (NF-kB/Rel) activation. Although angelan and LPS utilize the same membrane receptor CD14 and complement receptor type 3 (CR3), the mechanism for receptor activation is different for signaling NF-kB/Rel activation, compared with NO production.64,65)

(C). Ginseng

The root of *Panax ginseng* is one of the most popular natural tonics used in Asia. The water extracts of ginseng is thought to contribute to antitumor activity against several mouse tumors and, in some cases, reduce the incidence of human cancers.66,67) An acidic polysaccharide with a molecular weight of 150 kDa, has been isolated from ginseng, and termed ginsan.68,69) Ginsan induces cytokine production from LAK cells, exhibits cytotoxic activity against B16 melanoma cells, influences phagocytic activity in macrophages, and metastasis of tumor cells. In addition, ginsan increases TNF-α, IL-1β, IL-6, IL-12 and IFN-γ levels, increases CD14 and 1-A expression on the surface of murine peritoneal macrophages, and enhances the production of reactive oxygen/nitrogen components, e.g. nitric oxide and hydrogen peroxide.70,71)

IL-6 expression has been implicated as one of the cytokidal factors in the antitumor action of activated macrophages. IL-12 produced by macrophages enhances T-cell responses by producing IFN-γ, and is an immunomodulating cytokine that has been shown to generate Th1 and NK response, thereby overcoming tumor-induced immunosupression. Moreover, nitric oxide is formed by the inducible enzyme nitric oxide synthetase (iNOS), which is a central molecule in the regulation of the immune response to tumors. TNF-α and IL-1β can induce the expression of iNOS in tumor cell lines. iNOS also plays a key role in host defense against infectious agents, e.g. viruses. Treatment of murine peritoneal macrophages with ginsan induces mRNA of cytokines, e.g. TNF-α, IL-1β, IL-6 and IL-12. It also induces the mRNA expression of iNOS. The tumoricidal activity of macrophage is enhanced with ginsan treatment. These results indicate that ginsan exerts an effective immunomodulator and enhances antitumor activity of macrophages.72,73) In addition, PS from ginseng exhibits a potent anti-septicemic activity to *Staphylococcus aureus* through the production of nitric oxide, IL-1 and IL-6 in macrophages. Combined treatment with PS and vancomycin results in 100% survival of the animals, whereas only 67% or 50% of the animals survived respectively, when treated with PS or vancomycin alone.74)

PS fractions have been obtained from other higher plants, many of which show the antitumor and immunostimulating activities in animals. The possible mechanisms of action of PSs from higher plants include: lymphoproliferation, increased colony-stimulating factors and interferon production, stimulation of NK cells, T-cells, B-cells and macrophages, and complement system. These higher plants include *Cnidium rhizoma* (Chuan-kung), *Lycium barbarum* (Gouqizi), *Codonopsis pilosula* (Dangshen), and *Acanthopanax chiosqensis* (A. senticosus (Ciwu-jia).75,46)

IV. Issues regarding research and development of herbal PSs and related products.

There are a number of potential immunostimulating and immunomodulating polysaccharides in herbs and fungi that are yet to be developed for market approval. Before, however, clinical development of any PS can begin, scientific investigations to immunochemically characterize the active component of a PS is essential. Also, a thorough understanding of structure-activity relationship is important for targeting possible medical applications. Lastly, improved quality assurance, via regulation, provides greater assurance of a stable, high quality, safe and effective drug. Further details of each issue are discussed in the subsequent sections:

(A). Structure-activity relationship

Although herbal and fungal products have been used for centuries, these products are not widely accepted as drugs. Recognition of herbal and fungal PSs as active drug components is likewise limited due to an inability to purely isolate and identify the active PS component. Inability to study the biochemical structure, as it relates to pharmacological activity, hence hinders the critical basis to confidently determine the specific targets with clinically applicable, immunological properties. Characteristics of fungal PSs that are thus far recognized to be important for immunologic function are listed below,75 and perhaps might also be applicable to the characterization of herbal PSs:

1. The primary structure of the PSs, β(1→3), β(1→4)-linkages appear to be the most common structure for the main chain, while the side chains involve β(1→3), β(1→4), β(1→6) or α(1→4) linkages.
2. The secondary structure involving H-bond of the neighboring sugar units,-OH···O, will contribute to the stability of these compounds.
3. The tertiary structure of the polysaccharide, e.g. a right-handed helical structure in Lentinian, has been found in the solid state. A triple helix of the branched glucan, e.g. Lentinian, is important for its biological activity.
4. Significant correlation exists between the molecular weight of PS and its immunologic activities. Branched β(1→3) glucans have been found in many fungal and plant polysaccharides that exert immunomodulating and antitumor activities. Various chemical modification studies have been performed to elucidate their structure-activity relationships. A PS isolated from spores of the
fungus, *Ganoderma lucidum*, has a backbone of β(1→3)-linked D-glucopyranosyl residues with branches of mono-, di- and oligosaccharide side chains substituting at the C-6 of the glucosyl residues in the main chain (SP or PSG2 in Figure 4-A). The degraded glucan SP1 has a more linear structure and more ordered conformation than those of the native glucan SP. It has been observed that the native SP enhances the lymphocyte proliferation and antibody production. In contrast, SP-1 shows a remarkable effect on complement activation. Thus, the degree of substitution on the backbone chain and the length of the side chains are important in the conformation of structure and their immunologic activity.76 Although there is no accepted mechanism or agreement on the critical parameters which affect the immunopharmacological activities, it is observed that the introduction of ionic or nonionic groups can significantly influence the physical chemical properties and immunomodulating activities of α or β(1→3) glucans. The nature of functional groups and degree of substitution would cause the changes of physico-chemical characterization and the immunomodulating activity of the parent PS structure. For studying the effects of chemical modifications on immunologic activity, six different derivatives of the α(1→3) glucan, isolated from spores of *Ganoderma lucidum*, are synthesized, including aminopropylated, hydroxymethylated, sulfated, carboxymethylated, carboxymethylated and sulfated, and benzylamidated-carboxymethylated derivatives with varying degrees of substitution. In general, the structural and physicochemical properties, and lymphocyte proliferation activity of all derivatives transform to different characteristics, when the PS was introduced with various functional groups and the degree of substitution. Some modified derivatives, such as introducing carboxymethyl or hydroxethyl group with low degree of substitution exhibit potent stimulating effects on lymphocyte proliferation and antibody production.77

(B). Medical application

For thousands of years Fuzheng (supporting the vital force) and Chi-She (getting rid of the abnormal) herbs have been used in cancer therapy and treatment of various diseases. Many of the Fuzheng herbs including polysaccharides isolated from fungi and higher plants have shown to stimulate cellular immunity functions. Fuzheng principle in traditional Chinese medicine describes that homeostasis is the premise of body health. When the homeostasis is interfered by pathogenic factors, the person will become ill. If the body has capability to modulate the interfered factors and recover homeostasis, the body will gain health.78 Based on this principle, immunomodulating PSs may exert their therapeutic effects by (a) inhibiting the responses of body to the adverse effect of pathogenic factors and thus reducing the degree of damage to homeostasis; (b) enhancing the modulating and repairing functions of important organs to facilitate the restoration of homeostasis; or the combination of these two responses. Fungal and plant PSs have shown the following biologic activities79, 80, 81:

(1) Modulating the immunologic functions and alleviate the allergic reaction.

(2) Reducing the body damage caused by pathogenic factors, such as hypoxia, chemical agents, irradiation, thus raising the disease-resisting capability of the body.

(3) Enhancing the DNA, RNA and protein synthesis to promote the production of bioactive substances, such as enzymes, hormones, cytokines and neurotransmitters. Through these activities, they repair the tissue injuries caused by pathogenic factors.

(4) Improving the heart function to ensure the homeostasis of circulatory system.

(5) Protecting the liver and stomach from injury by chemicals and reinforcing their functions including detoxification.

(6) Enhancing the protective inhibitory mechanisms of the central nervous system and modulating the function of autonomic nervous system. Clinical application of immunomodulating PSs has emphasized the preventive effects to diseases and restoration of body's homeostasis, rather than direct attack or treatment of the pathogenic factors. Precaution should be taken on therapeutic application of these PSs and other herbal products. For example, in treatment of various kinds of cancer, the first or primary choice for treatment includes surgery, radiation and chemotherapy. The use of immunostimulating PSs as supplement to combine with the primary therapy has been proposed and investigated.

Therapeutic indications of these PSs have been applied to various diseases including (a) chronic bronchitis and asthma, (b) cardiovascular disease and hypercholesterolemia, (c) hypertension, (d) neurosis, (e) hepatitis, (f) leukocytosis, and (g) tumors.79-84 Promising clinical results on prolongation of survival and improvement of quality of life have been reported in a randomized control study of Lentinan in patients with advanced and recurrent stomach and colorectal cancer.82, 83

(C). Regulatory issues

Herbal products are mainly recognized as health supplements, which are intended to promote the overall well being, rather than a specific health condition or treatment of diseases. In the U.S., an herbal product is not considered a drug, and thus is not subject to the same regulations as a pharmaceutical or biologic product. If, however, promotion and advertisement of the same herbal product is intended for treatment or prevention of a particular disease, then, by law, the same requirements for pre-clinical and clinical studies, and quality assurance would be needed as for any other drug. Currently, a system to evaluate the safety, stability, and manufacturing consistency for herbal products has not yet been established. Also, a proven therapeutic or preventive effect would need to be demonstrated in a well-controlled clinical trial. In many cases, the therapeutic indications listed on the label of an herb medicine are based not on acceptable scientific methods of biochemical analyses, animal studies, and clinical trials, but on limited subjective observations and anecdotal experiences.85

The evaluation of immunomodulating PSs and herbal
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products can be approached in a manner similar to drug development, with emphasis on characterization of purified active component, well-controlled clinical trials, and greater quality control\textsuperscript{[86-88]}:

\textbf{(I). Manufacturing process}

The first essential step in manufacturing an herbal product is preparation of the raw materials. Product development begins with purification, characterization and manufacture of the active moiety. If possible, the active component should be freshly isolated from the herb. Standard operating procedures (SOP) should be established to ensure consistent herbal growth and harvest conditions, as well as processes to maintain stability of the active component during prolonged storage. Characterization of the raw herbs further ensures that a uniform, stable product would be available for large-scale production of the herbal product. Likewise, quality control (QC) testing provides additional assurance that the active herbal component can be identified by morphological and chemical characteristics, and that the final product is free of microbial and chemical contamination.

The establishment of manufacturing facilities to produce the herbal drug on a large scale should be designed with the proper equipment and procedures to reduce potential contamination of one product by another product. The environmental air and water quality used during production should be carefully monitored throughout manufacturing process. In-process controls should be conducted during the operating procedures considered to be the most critical. Validation of these processes is also an important step in the quality assurance of a product. The principles and conditions similar to the regulatory guidance of current Good Manufacturing Practice (cGMP) should be established and enforced.

\textbf{(II). Clinical trials}

Although, historically, herbal products have been used for centuries, clear demonstration of safety and effectiveness via well-controlled trials has been critically lacking. More specifically, reports in the published literature frequently conclude that an herbal product is safe due to the absence of serious adverse events; however, adverse effects may not be recognized or reported since monitored safety parameters are often not prospectively defined. Safety information from case series hence offer limited supportive data. Secondly, the rationale for dose selection is often based on the anecdotal experience of other clinical investigators, rather than a demonstrated therapeutic effect, or toxic effect, in an animal model. Dose selection becomes particularly problematic when the rationale a dose and dosing regimen is based on previous human experience, but in different target population or for an alternative therapeutic indication. In essence, the safety profile should be evaluated in a stepwise fashion, starting from healthy adults and then in a target population with a specific disease condition.

Hence, in general, the initial approach to planned clinical trials for an herbal product would be similar to an evaluation of any chemical drug. If no adverse safety or toxic outcomes are observed in pre-clinical and toxicity studies, respectively, then Phase I studies to initially characterize the safety of an herbal product, if humans, could proceed.

In later studies, comparison to a control group is essential. Since herbal products would likely be used in combination with another drug, inclusion of a control group, who would receive an approved drug regimen alone, is critical towards demonstrating an adjunct therapeutic effect. Phase II studies results would further characterize the overall safety profile, and enable selection of an optimal dosing regimen for Phase III studies. Phase III studies results would provide the essential data needed to demonstrate drug effectiveness and safety. All trials should be conducted according to the current Good Clinical Practice (cGCP) regulations.

\textbf{(III). Quality control of products}

Quality control of herbal products historically has also been lacking. Detailed specifications on herbal active component, the final drug formulation, and extract products should be available, as well as the control test methods for assessing the product quality. Analytical testing of the completed lot of a final product should be performed before releasing the lot for use by the general public. Likewise, inspection controls should be performed for incoming raw materials and at various stages during the manufacturing process, such as during packaging, labeling, and lot-release testing.

A comprehensive process that could allow evaluation and production of well-characterized, high quality herbal products could serve as a basis for wider acceptance of therapeutic indications for these products by the Western medical community and regulatory agencies.

\textbf{V. Future prospectives}

There is currently increased interest in identifying polysaccharides from fungi and higher plants that have immunomodulating properties, and understanding the mechanisms responsible for these properties. Extensive studies have been conducted out to further characterize mechanism of actions, potential clinical application and the safety of herbal products. If increased public demand for herbal drugs were to occur, in turn, there may be more reliance on artificial cultivation for the herbal production to meet the market demand. Since artificial cultivation conditions may not be comparable to the natural environment, additional quality control testing may need to be established to ensure that selected species, and nutrients to enhance the growth would not alter the composition of the active herbal component. In addition, variations in extraction methods, manufacturing process, and storage conditions may affect the chemical characterization. Thus, it is important to have adequate reference standards that would reliably measure the amount of active ingredient. If there are multiple action targets, the multiple standards could be used. For example, in evaluating the quality of Lingzhi, polysaccharide fraction would be a useful indication of immunomodulatory activity, and the triterpene component could serve as marker for cardiovascular effect.\textsuperscript{[89]} While it may be difficult to isolate each compound separately from an herb, use of an
appropriate reference standard provides an alternative measure of quality control to predict biologic activity.

Various chemical analytical techniques, such as high performance liquid chromatography (HPLC), gas chromatography (GC), ultraviolet spectroscopy (UV), nuclear magnetic resonance (NMR), mass spectroscopy (MS), GC-MS, can be applied at different stages during the manufacturing process to identify and quantitatively analyze bioactive determinants in herbal products.\(^9,10\)

Most herbal products available in the market are prepared from the extraction with boiling water or hot solvent, and provided in the final forms as powders, capsules or granules. Since the macromolecules, including polysaccharides and proteins, are sensitive to heat, their biological activities might be damaged during the heating process. Furthermore, an herbal product, if given orally, may be inactivated by gastric acid and enzymes before the drug reaches a desired site. Efforts to develop alternative drug delivery systems would be beneficial.\(^9,12\)

Another issue for the commercialization of an herbal product as a drug is marketing competence. Appropriate establishment of valid indications for medical use and accurate advertisement are crucial for building credibility and public acceptance. Therapeutic claims without adequate supporting data from animal and clinical studies, and misleading advertisement would seriously undermine the reputation of the product, to the manufacturer, and to the pharmaceutical industry as a whole. Ultimately, sound scientific approaches towards research and regulation of herbal products strengthen the basis for the global acceptance of these products.\(^9,13\)

**Conclusion**

Polysaccharides isolated from fungal and plants have exhibited immunomodulating and antitumor activities through activation of immune system and cytokine induction. Elucidation of the role of polysaccharides may provide an important basis to evaluate the efficacy of formulated herbal products. The immunostimulating activity of a polysaccharide is related to specific primary structure and conformational feature. Research and development of immunomodulating polysaccharides into drugs for therapeutic use require the approaches of structure-activity relationship for rational drug design and quality assurance on the polysaccharide molecules and final products.

(The contents of this article is the authors' own opinion and does not represent the official positions of their respective institutions).

**References**

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