

Bioactivity Applications of Lycium Barbarum Polysaccharide In Regulating Human Health

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Abstract. For approximately 2,000 years, Lycium barbarum was regarded as a traditional medicine, and was believed that Wolfberry can nourish the liver, eyes, and kidneys. The fruit of Goji berries can also be eaten as food, and these berries have various biological importance, its anti-inflammatory, antioxidant, anti-tumor, hypoglycemic, hypolipidemic and anti-aging effects were discovered. Among those bioactive components, the most important one is Lycium Barbarum polysaccharide (LBP). LBP main structures include β -(1 $\rightarrow$ 3)-galp, α -(1 $\rightarrow$ 4)-galA, α -(1 $\rightarrow$ 6)-glc, β -(1 $\rightarrow$ 6)-galp, β -(1 $\rightarrow$ 4)-galp, and α -(1 $\rightarrow$ 5)-ara. There are various ways in which LBP is extracted. Various studies have demonstrated that LBP possess various biological activities. The main activities of LBP are anti-oxidation, anti-cancer and metabolic regulation. It can also be used in nerve damage repair, liver protection and eye protection. In this article, the structure of LBP and its medicinal value will be summarized as a reference for its further applications.

Keywords: Lycium Barbarum, Polysaccharides, Natural Products

1. Introduction

Lycium is a perennial shrub with more than 80 species found in North America, Asia, and Europe. The most important of these is Lycium barbarum (LB) which is a perennial shrub-bearing fruit known as goji berries, Ningxia Gouqi or Wolfberry. Those fruits are red-colored and have a sweet taste. In China, wolfberry was regarded as a traditional medicine for nearly 20 centuries, and has been included in the National Pharmacopoeia, and according to China's ethnopharmacological experience, they have different nourishing effects on different parts of the body, Chinese believe that Wolfberry can nourish the liver, eyes, and kidneys. This fruit is also gained popularity among Western countries.

The fruit of Gouqi berries can also be eaten as food, and these berries have various biological importance, its anti-inflammatory, antioxidant, anti-tumor, hypoglycemic, hypolipidemic and anti-aging effects were discovered (Figure 1). The berries are also rich in different nutritional and natural products such as betaine, LBP, and flavone as well as different vitamins. Among those bioactive components, the most important one is LBP (Lycium Barbarum polysaccharide). In one dried Wolfberry, around 8% of the LBP will be found. LBP is a compound of six monosaccharides, namely, arabinose, glucose, mannose, arabinose, xylose, and rhamnose [1]. Owing to the extensive purported health benefits, LBP is popularly known as a "superfood". LBP is known to modulate the microbiota of the gut, thus improving health and nutrient utilization.

In this article, the structure of LBP and its medicinal value will be summarized as a reference for its further applications.

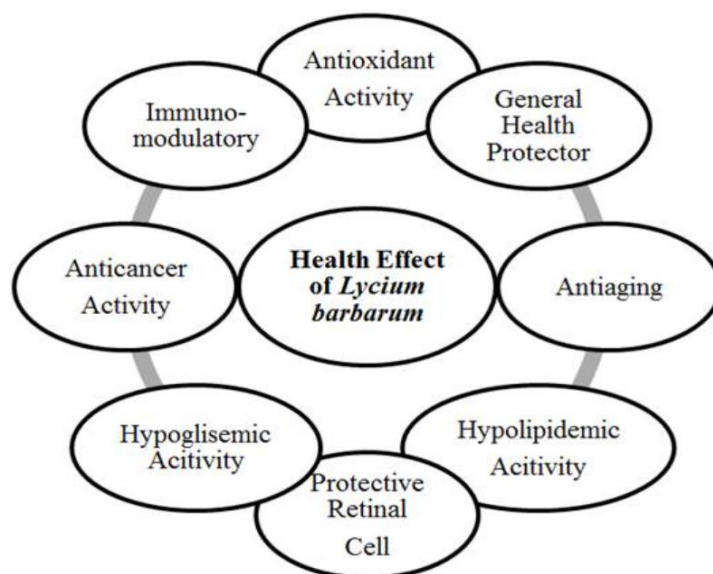


Figure 1. Health effects of Lycium barbarum

2. Structure of LBP and its identification

Lycium barbarum polysaccharides structure is determined by the extraction method that is used as well as the type of solution used to prepare the solution (Figure 2, Figure 3). The cell wall structure will vary depending on the different extraction methods used. There are different structural and separation methods of the LBPs that have been developed over time. There are several main ways of characterizing the main performance and application techniques of the LBP function. HPGPC is primarily used to estimate macromolecules' weights. HPTLC is a typical tool for estimating the monosaccharide content of LBP and mapping the glycoconjugates glycidic components. FT-IR is the spectral analysis that permits pyranose or furanose ring identification from β or α anomeric configurations that occurs within the residues of monosaccharides. ^1H and ^{13}C NMR is the spectroscopy that is used to assign present monosaccharides and anomeric bond ratios. GC-MS is used to determine what we call linkage positions. There exist different studies that have explored both the composition and structure of LBPs. The molecular weight of these LBPs ranges from 10 to 2300 kDa [2]. Different extraction methods of LBPs include gel-permeation chromatography, DEAE ion-exchange cellulose, as well as HPLC (high-performance liquid chromatography). Various studies have shown that the structure of LBPs includes side chains and branching sites, as well as glycoconjugates.

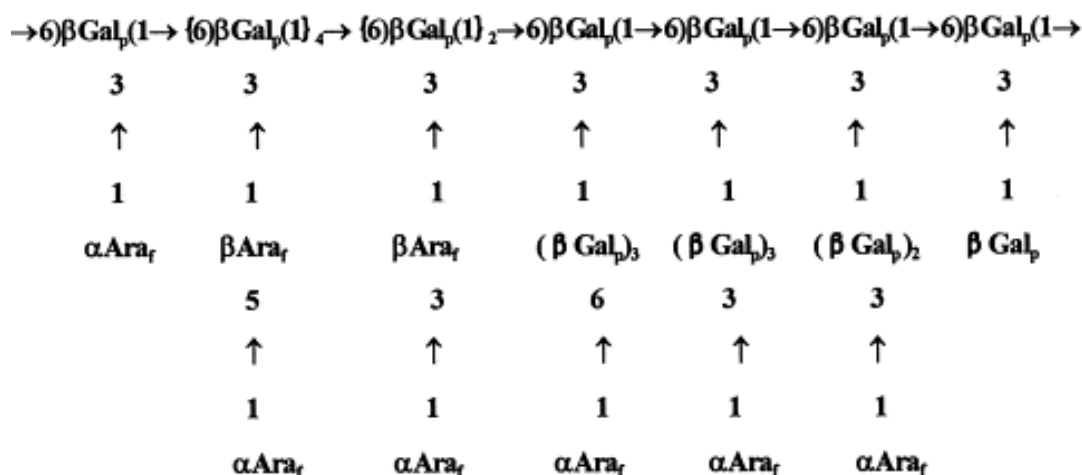


Figure 2. Structural fragment of L. barbarum polysaccharides with immunomodulatory activity

Number	Name	Mw (kDa)	Molar Ratio	Structure
1	LbGp2	68,200	Ara: Gal = 4:5	(1→6)- β-Gal. (1→3)- β-Ara and (1→3)- β- (1 → 3)/(1→5)- α-Ara.
2	LbGp4	214,800	Ara:Gal:Rha:Glc = 1.5:2.5:0.43:0.23	f (1→4)- β-Gal (backbone). x (1→3)- β-Gal (branches) (1→3)- α-Ara and (1→3)- β-Rha.
3	LbGp3	92,500	Ara:Gal = 1:1	of (1→4)- β-Gal. (1→3)- β-Ara,(1→3)- α-Gal, (1 → 3)/(1→5)- α-Ara.
4	LBPA3	66,000	Ara:Gal = 1.2:1	(1→4), (1→6).
5	WSP	n/a	Rha:Fuc:Ara:Xyl:Man:Gal:Glc = 1.6:0.2:51.4:4.8:1.2:25.9:7.3	(1 → 2)-linked-Rha, (1→4)-linked-Gal, (1→5)-linked-Ara, (1→4)-linked-Xyl

Figure 3. The molecular weight, structure, and analysis techniques used in those *L. barbarum* polysaccharides [2]

3. Bioactivity of LBP

Various studies have demonstrated that LBP possess various biological activities including immunomodulation, antioxidation, antitumor, radioprotection, neuroprotection, hepatoprotection, anti-diabetes, antifatigue as well as anti-osteoporosis. Those bioactivity attributes are discussed below.

3.1. Antioxidant

As a bioactive compound, the *Lycium barbarum* polysaccharides contain substantial antioxidant properties [3]. The antioxidant property is attributed to the presence of flavonoids, polyphenols, and derivatives [3]. The LBP biological functions possess a variety of potential functions which are relative to the antioxidant activity of various tissues. The antioxidant activity of LBP and its mechanism have been explored in several studies (Table 1). Various studies have been conducted to investigate LBPs' antioxidant activities that can be extracted with hot water as well as LBP's protective effects against TOI (tissue oxidation injury). The results show that LBPs have a good antioxidant effect as well as a protective effect against injuries from skin oxidation. Vivo model is used to extract those LBPs antioxidant effects extracted by hot water. The result shows that serum levels of both GSH-Px and SOD can increased by LBP treatment, as well as decreasing MDA content [4]. LBPs can increase cell viability that could have been decreased by LPS and also lower the oxidative stress that could be hindering the activation of ROS levels and caspase-3 in vitro. A study by Liu et al., which investigated LBP's impacts on stressed cells has shown that LBPs significantly lower the ROS levels through free radical scavenging [5].

Table 1. The LBPs' antioxidant mechanism and activity [5].

Antioxidant Activity	Mechanisms	Dosage	Model
oxidative stress reduction	Regulating f MDA, GSH, and SOD.	100, 200, 400 mg/kg	Rat Model
hypoxia-induced injury (against)	miR-122 downregulation	300 mu g/mL	Cells Model
hyperoxic acute reduction	Nrf2 Activation induction	100 mg/kg	Mice Model
diabetic testicular dysfunction attenuation	Akt and PI3K expression upregulated	40 mg/kg	Mice Model
Enzymes activity reduction	antioxidative enzymes activity increase	200–400 mg/kg	Rats Model

3.2. Anti-Tumor/Cancer

There are various data on plants-source natural products' antitumor activity. In the various studies, it has been seen that over 100 polysaccharides exhibit anticancer activities. Those studies have been done via Vivo animal models and Vitro studies. LBP as a natural product exhibits potential antitumor activity. This anticancer activity is exhibited due to the LBP's effects on cancer cells and cancer tissues (Table 2). A 24 hours exposure to *Lycium barbarum* hot water extracts made 15.31% hepatocellular cell viability reduction according to a previous study [6]. For colorectal cancer, results have shown that LBP treatment (5000 mg/L) is capable of decreasing SW480, and Caco-02 cell viability by 10% after about 5 days of treatment. The study also showed that there was LBP treatment that resulted in to increase in dose-dependent within the distribution cells [7]. This happens in G0/G1 phase. A dosage of LBPs can reduce cell growth as well as stop cell cycles in gastric cancer cells. This happens in G0/G1 phase. This suggests that LBP is an anticancer candidate agent.

Research has also explored the LBPs inhibitory attributes on glioma growth in rats. LBP inhibitory mechanism might be related to blood-brain barrier as well as the encouragement of CD 8+ T lymphocytes to penetrate the brain [8]. Another study was done to check the LBP effects on apoptosis as well as viability of hepatoma cells in humans. The findings reveal that LBPs can restrict cell development while also lowering apoptosis, and arresting the cell-cycle, especially in the S phase. This suggests that there is LBPs antiproliferative activity which is initiated through cell-cycle induction and elevated intracellular Ca [9].

The above examples show that LBP exhibits anticancer activity mainly through arresting the cell cycle, inhibiting cell growth as well as inducing cell apoptosis. The LBP antitumor activity displayed on different cancer cells can be seen on the table below.

Table 2. LBPs' Antitumor activities and mechanisms [10]

Activity Type	Mechanism	Model	In vivo/in vitro
Cell Viability Reduction	Tumor growth inhibition	MCF-7, T47D, DU145	Vitro Model
Apoptosis Reduction	Apoptosis Induction	BIU87, MCF-7	Vitro Model

Cell Cycle Regulation	Cells Arrest	Caco-2, SW480	Vitro Model
Immune Regulation	Immunity Enhancement	Mice Model	Vivo Model

3.3. Metabolism regulation

Studies show that consumption of LBP significantly regulates the serum TG (triglyceride), increasing the glucose level in the blood as well as lowering the HDL concentration ($p < 0.05$) [11]. LBP does not increase the cholesterol concentration in the body. The extract of LBP is rich in xylose, rhamnose, glucose, galactose, and arabinose which are used to give the body the required energy. The LBP produces lactic acid via the EMP pathway. There are various enzymes produced that aid in carbohydrate metabolism. Those enzymes include KE, PK, PFK, LDH, and β -GAL. Generally, the LDH and β -GAL play a vital role during the metabolic processes. There are also Bifidobacterium-specific enzymes that are used in sugar metabolism which are enhanced by the consumption of LBP. The increase in carbohydrate metabolism significantly increases the synthesis of secondary metabolites in the gut microbiota.

4. Other LBP Effects

The consumption of LBP also brings neuroprotective effects on the ischemic injury. This is done mostly through pathway signaling of NR2A inhibition and activation of NR2B [12]. This has a significant effect on the treatment of ischemic stroke. An experiment (mouse model experiment) on LBP neuroprotective attributes shows that LBP can prevent neurodegenerative diseases [12]. In the current society, there is significant health damage brought by blindness and visual impairments. However, the use of LBP in treatment can lower such injuries [13].

There are also other biological activities of LBP in the body. Those are minor and can only be discussed as combined. They include preventing hepatotoxicity in the liver, anti-diabetic effect, preventing dry-eye disease, preventing UV-induced damages, increasing cell morphological impairment, etc.

5. Conclusion

The medicinal value of wolfberry fruit is simply sorted out in this article. Previous studies have shown that LBP has multiple pharmacological activities in our bodies. Lycium barbarum fruit extracts are complex mixtures of glycoconjugates with molecular weights ranging from 10 to 2300 kDa, containing carbohydrates ($\geq 90\%$), water-soluble, and containing various polysaccharides. LBP main structures include β -(1 $\rightarrow$ 3)-galp, α -(1 $\rightarrow$ 4)-galA, α -(1 $\rightarrow$ 6)-glc, β -(1 $\rightarrow$ 6)-galp, β -(1 $\rightarrow$ 4)-galp, and α -(1 $\rightarrow$ 5)-ara. There are different LBP biological functions such as immunomodulation, antioxidant, neuroprotection, antitumor, and hepatoprotection.

Currently, LBP is only extracted from that Wolfberry. Given that the shrub takes one year to produce those berries, it means that the production is always low. There are also other aspects such as pests and diseases and climate change which have negatively affected the production of Goji berries. Goji berries also have a high level of perishability when fresh. It limits LBP acquisition. As a result, the current acquisition of LBP from goji berries cannot meet the current commercial demands of LBP. That is why different pharmaceutical companies should come up with other sustainable ways of acquiring this precious product. The best example is the use of yeast synthetic biology where different types of yeasts are converted to LBP in those cell factories. One advantage of this procedure is the fact that this production is that it does not depend on regions and seasons. The best yeast, in

this case, is known as *S. cerevisiae* which has been an ideal microbial host that helps in LBP production. The introduction of biosynthetic LBP proves to be the future.

Various models have been used in the study of LBP, but the biological activity and higher-order structure of LBP still cannot be thoroughly explored. Future studies need to use new omics techniques, such as metabolomics, proteomics, and genomics, to conduct effective LBP biological function studies to elucidate the relationship between its biological activity and structure. This will help us better understand the functional effects of LBP.

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