Translational Surgery

Review

Structural Characterization and Bioactivity of *Lycium Barbarum* Polysaccharides

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ABSTRACT

Lycium barbarum polysaccharides (LBPs), the major bioactive compounds of *L. barbarum* berries, exhibit several different pharmacological actions. The physicochemical characteristics of polysaccharides are intimately related to their bioactivities. Therefore, to thoroughly understand the extraction process as well as the structural and biological activities of LBPs, the extraction methods and structural characterization of LBPs were examined. The biological functions and related mechanisms of LBPs including antioxidant function, neuroprotection, immunomodulatory function, and antitumor activity were reviewed. This review offers an overview of LBPs as well as a theoretical framework for further investigation and expansion of LBPs' applications in the realms of food and medicine.

Keywords: Lycium barbarum polysaccharides; extraction methods; structural characterization; antioxidant function; neuroprotective effects; immune regulating function; antitumor activity

INTRODUCTION

Lycium Barbarum L., a member of the Solanaceae family, is widely cultivated in China. The fruit of *L. barbarum*, also known as goji berry, has been utilized in traditional Chinese medicine as a common medicinal plant and functional food for more than 2,300 years.[1] A well-known Chinese herbalist named Ni Zhu-Mo claimed in his "Convergent Speech on the Materia Medica" that the Goji berry could provide energy and blood, balance Yin and Yang and reduce internal heat.[2] It is mentioned in the "Compendium of Materia Medica" because of its ability to nourish the liver and kidneys and brighten the eyes. Additionally, it helps in the treatment of migraines, lethargy, infertility, foggy eyesight, and stomach pain.[3] *L. barbarum* polysaccharides (LBPs),

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flavonoids, alkaloids, Lycium colors, amino acids, and other active substances can be found in Goji berries. Polysaccharides, weighing between 10 and 2300 kDa, are also the most prominent active ingredients in Goji berries, about 5% – 8% of the dry fruit (4). LBPs are made up of six monosaccharides.[5] The activities of different LBP fractions vary, and one important factor affecting these activities is the galacturonic acid content. The biological effects of LBPs include antioxidant, neuroprotective, immunomodulatory, anticancer, radiation protection, antidiabetic, hepatoprotective, and anti-osteoporosis activities.[6] As a result, LBPs play a crucial biological role that safeguards human health. The main topics of this review are the structural characterization and bioactivity of LBPs.

STRUCTURAL CHARACTERIZATION

Extraction Methods

The chemical structure of polysaccharides is related directly to the extraction method. The principle of LBPs extraction is to extract polysaccharides by breaking and dissociating cell walls under mild circumstances without affecting the nature of the polysaccharides.[7] The withdrawal rate and bioactivity of LBPs are the main considerations when choosing the extraction method.[8] Before the extraction of LBPs, Goji berries are usually dried and ground into powder, added with chloroform: methanol (2:1) to degrease at reflux, and then soaked and stirred with 80% ethanol to remove small-molecule impurities, such as oligosaccharides and pigments.[9] Another method is to reflux the ground wolfberry mixed in petroleum ether at 80°C to remove lipids, oligosaccharides, and small-molecule pigments.[10] A water-soluble crude polysaccharide mixture is then extracted after filtering and drying. The post-harvest period of LBPs is affected by the ambient temperature and the endogenous enzyme metabolism, which in turn affects the chemical structure of LBPs. In consequence, the above process is usually followed to prepare LBPs regardless of the extraction technique used. The main extraction methods of LBPs include the traditional aqueous extraction method, the new ultrasound-assisted extraction method (UAE), the microwave-assisted extraction method (MAE), the enzyme-assisted extraction method (EAE), and other combined methods, which all have advantages and disadvantages.[11] The best solvent for extraction is water. The yield of the hot water extraction (HWE) method is 7.46%-7.63% with a liquid-solid ratio of 70:1, pH 10, 65ºC, and 3.5 h soaking.[12] With the technology development in recent years, new auxiliary methods with high extraction rates and short time consumption have been developed based on the HWE under the ideal extraction circumstances. Compared with the HWE, the best extraction process parameters are an extraction time of 30 min, an extraction temperature of 60 °C, a material-to-liquid ratio of 20 g/600 mL, a power density of 300 W/L, and an ultrasonic frequency of 28 kHz. This results in an increase in crude polysaccharide yield by dual-frequency ultrasound of 73.41%.[12] The optimal process parameters for dynamic MAE are a water-to-material ratio of 31.5 mL/g, an extraction period of 25.8 min, and a microwave power of 544.0 W. The LBPs extracted by this green, rapid, and efficient technique are a new type of natural antioxidant, which have the potential to be developed and applied in functional food and medicine.[13] The EAE with mild conditions has low investment cost and low energy consumption. Moreover, the UAE is an effective method with a simple and time-saving extraction process. The maximum yield of LBPs extracted by the ultrasound-assisted enzymatic method is 6.81±0.10% under the cellulose concentration of 2.0%, papain concentration of 1.0%, period of 91 minutes, the temperature of 59.7° C, and pH of 5.0 by orthogonal test and response surface test design.[14] The optimal process of ultrasound-enhanced subcritical water extraction (UESWE) at 100 °C, 53 min of extraction time, 26 mL/g of liquid, and 160 W of ultrasonic power can combine the environmental-friendly subcritical water with vigorous ultrasonic vibration.[15] Therefore, the UESWE can achieve a higher efficiency to meet the needs of modern industrialization with little effect on the medicinal properties of LBPs and retains significant antioxidant activity. Under otherwise identical conditions, different methods have an important impact on the nature and composition of LBPs. When hot water extraction was carried out in 100 °C boiling water, to prepare the fruit-water mixture for ultrasonic extraction, a 360 W ultrasonic homogenizer was used at room temperature. When subcritical water extraction (SWE) was carried out at 110°C and 5 MPa, the combination was once sonicated with an ultrasonic processor (160 W) at 110°C and 5 MPa in ultrasound-enhanced SWE (USWE). A comparison of the above methods concludes that USWE has the highest rate (14%), with significant antioxidant activity and immunoreactivity, and temperature and ultrasound are the main elements influencing the extraction rate, chemical composition, and bioactivity of LBPs.[16] Different methods are available for extracting different target activities. In general, the HWE is suitable for extracting total sugars and acidic polysaccharides; the MAE is appropriate for extracting glycoprotein complexes; the LBPs extracted by pressurized extraction, UUAE, and HWE have better immunomodulatory activity.[17] However, most of the current studies on LBPs extraction focus on improving the extraction rate, but the various extraction techniques have a decisive effect on the chemical structure, molecular weight, and conformation of LBPs, which in turn affect their

bioactivity.[18] Consequently, an in-depth investigation of the chemical structure of LBPs is necessary and important. Figure 1 shows the extraction, purification, and identification of LBPs.

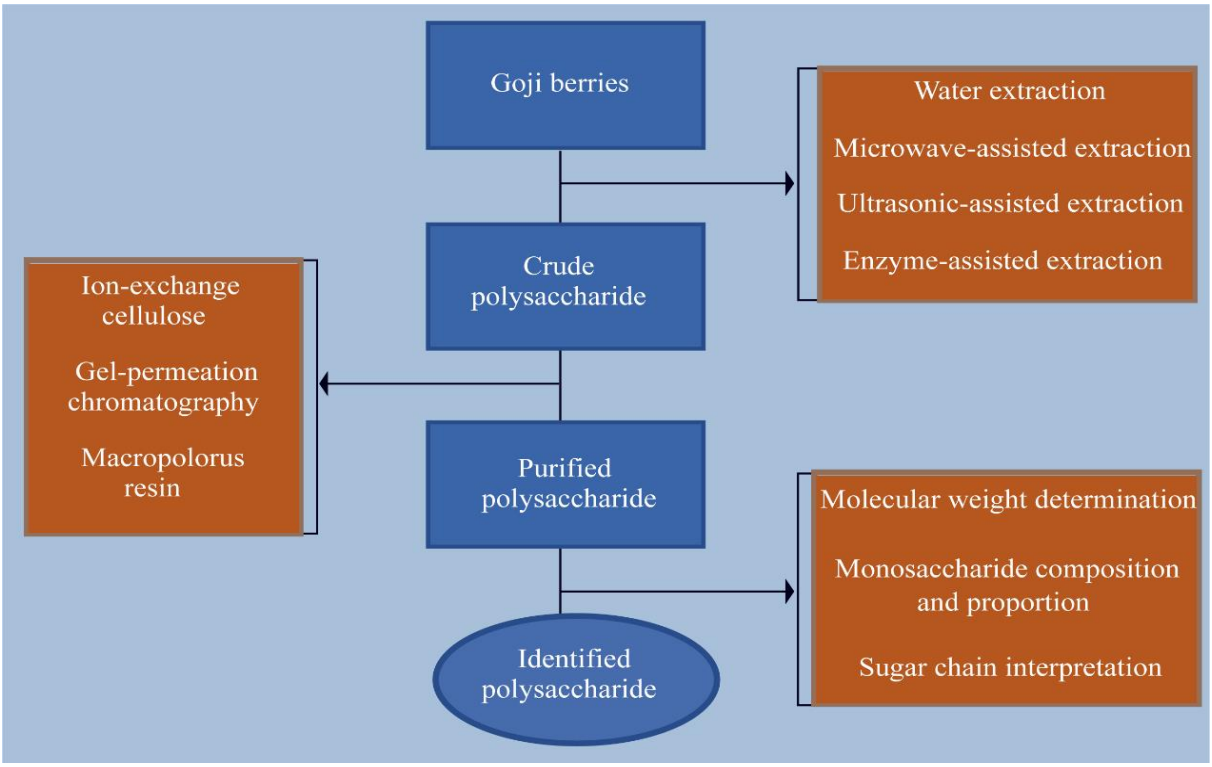

Figure 1. *Extraction, purification, and identification of LBPs*

Purification & Identification

So far, 33 polysaccharides; some of which are acidic heteropolysaccharides, polypeptides, or parts of proteins have been identified as LBPs. The glycoconjugates consist of monosaccharides and amino acid residues that are mainly composed of glycopeptide bonds.[19-21] Before being used in the purification and fractionation methods, the crude LBP extraction is deproteinized by using the zymolysis process, savage method, or aqueous two-phase extraction with the triblock copolymer, salt, and dialysis membrane separation. Anion-exchange chromatography, gel permeation chromatography, and macroporous resin extraction are the most common methods to separate and purify LBPs from Goji berries. Suitable chromatographic columns can be used for different properties and molecular weights of LBPs.

High-performance size-exclusion chromatography (HPSEC) is a common tool for determining the LBPs' molecular weight and purity of LBPs. Firstly, polysaccharide samples are separated on a gel exclusion column and then detected with a differential refractive index detector or evaporative light scattering detector. Lastly, the polysaccharide's molecular weights are calculated by using different molecular weights of standard dextran and plotting the dextran exclusion curve. SEC can be combined with multi-angle laser light scattering (MALLS) to independently determine the light scattering properties of polymers in solution and their absolute molecular weights. SEC-MALLS is recognized as one of the most potent macromolecular investigative approaches and is used to ascertain the pure polysaccharides (p-LBP) from *L. barbarum's* absolute molecular mass.[22] Over 7 times as much p-LBP's absolute molecular weight as dextran standards were used to test it by HPSEC. These findings reveal that SEC-MALLS-RID is more accurate. Gas chromatography (GC), liquid chromatography (LC), and high-performance LC (HPLC) are commonly used to resolve the composition and ratio of monosaccharides. As the large molecular weight and complex structure of polysaccharides, chemical techniques such as partial acid hydrolysis, methylation, pre-column derivatization, and Smith degradation are required before detection. Hydrochloric acid concentrated sulfuric acid, and trifluoroacetic acid are commonly used in acid hydrolysis, with trifluoroacetic acid being the most frequently used. With regard to GC of monosaccharide composition, hydroxylamine hydrochloride, and pyridine are usually added to react with acetic anhydride for 30 minutes at 100° C to produce a sugar alcohol acetate derivative.[22,23] Adding trifluoroacetic acid during monosaccharide composition is resolved by HPLC, and then 1-phenyl-3-methyl-5-pyrazolone (PMP) is used as the monosaccharide derivatization reagent.[24] Infrared spectroscopy is used to ascertain the chain conformation in the structure of

polysaccharides and can identify the pyranose or furanose rings and their terminal configurations in monosaccharides as well as the glycosidic bond conformation and functional groups in polysaccharides. For example, LBP3b with a 4.92 kDa molecular weight was detected as an asymmetric structure.[25] Although many methods are used to analyze LBPs, it is difficult to elucidate their specific structures, which poses a challenge to exploring the conformational relationships and bioactivity mechanisms. Table 1 summarizes LBPs in terms of structural characterization and corresponding bioactivities.

Table 1. *Structure characterization and bioactivities of LBPs*

Compound name	Molecular weight (kDa)	Monosaccharide composition	Structures	Pharmacological properties	References
LBP-s-1	1.92×103	Ara,Rha,Xyl, Man, Glc, Gla, GlacUA in the ratio of 8.34 : 1.00:1.25:1.26:1.91: 7.05: 15.28	α-and-β-isomeric furanand pyran rings	Anti-diabetes	(26)
LBPA	470	Ara:Gla:Rha:GlcUA in the ratio of 9.2: 6.6: 0.9: 1.0	β-D-(1→6)-galactan as the main chain of Ara		(22)
p-LBP	64	Fuc: Rha: Ara: Gla: Xyl:GlaU:GlcUA in the ratio of 1.00: 6.44:54.84:22.98: 4.05: 2.95: 136.98: 3.35	repeated,1,4-α-GalpA structure		(23)
LBP1B-S-2	80	Rha:Ara:Gla:GlcUA in the ratio of 3.13: 53.55: 39.37: 3.95	1,3-β-D-Galp, 1, 6-β-D-Galp	Anti-angiogenic activity	(24)
LbGp1	49.1	Ara:Gla in the ratio of 5.6:1	→6) Galp (1→		(27)
LBP3b	4.92	Man:Rha:Glc: Gla: Xyl in the ratio of 5.52: 5.11:28.06:1.00:1.70	Furan and pyran rings, α and β end group conformations	Hypoglycemic activity	(28)
LbGp3, 4, 5	50-60		(1→3)-linked β-d-galactosyl residues		(29)
LBP-a4	10.2	Fuc:Rha:Xyl:Glc:Man:Gla :Ara in the ratio of 3: 19.6: N: 8.2: 10.7: 15.1: 46.9:17.1		Anti-tumor activity	(29)
LBLP5-A	113,300	Rha:Ara:Gla in the ratio of 3 0.5: 1.9: 1.0	(1->3)-linked Gal, (1-> 4)	Anti-oxidant activity	(30)
LBP-3	67.4	Ara:Gla in the ratio of 31.00: 1.56		Hypoglycemic activity	(31)
LICP009-3F-2a	13.72	Rha:Ara:Gla:Glc: GlaUA:GlcUA in the ratio of 39.1: 7.4: 22.5: 8.3: 13.7: 4.0	→2)-α-L-Rha-(1→2, 4)-α-L-Rha-(1→4)-α	Anti-oxidant activity	(32)
LBP-W	112.97	Ara:GlcUA:Rha in the ratio of 55.6: 35.5: 8.0	α-Araf, β-Galp and α-Rhap	Anti-obesity	(33)

BIOACTIVITY OF LBPS

Anti-oxidant activity

When the body is subjected to various harmful external stimuli, the free radicals and reactive oxygen species in the body lose their dynamic balance, which leads to oxidative stress, further destroying the equilibrium state of the oxidative and anti-oxidative systems, thus causing tissue damage to the body. LBPs are pure natural antioxidants and have an obvious scavenging effect on hydroxyl radicals and superoxide anion radicals compared with other flavonoids and carotenoids.[34] Ultraviolet B irradiation is an important factor in skin damage, as it causes oxidative and inflammatory damage. LBPs have significant protective effects on photogenic damage, which may be related to the upregulation of antioxidant genes Nrf2 and TrxR1, indicating that LBPs can scavenge oxygen radicals and reduce mitochondrial oxidative stress.[35] Furthermore, LBPs can protect human skin fibroblast cells from UV-induced harm (due to the activation of oxidative reactions), hyperoxia-induced acute lung injury, ischemia/reperfusion-induced myocardial injury, and severe kidney damage by activating the Nrf2 antioxidant signaling pathway to modulate oxidative markers.[36-39] The antioxidant function of LBPs can prevent the increase of oxidative product levels after cyclophosphamide injection and thus treat ovarian damage by enabling the Nrf2/ARE signaling pathway to reduce oxidative stress.[40] As for H_2O_2-induced skin cell injury, LBPs may restrain apoptosis by the Nrf2/Ho-1

signaling pathway being activated to enhance antioxidant enzymes.[41] LBPs also inhibit PM2.5-induced injury, which reduces apoptosis and autophagy through oxidative stress and the endoplasmic reticulum.[42] In the exhaustive exercise rat model and endothelial cells, LBPs increase the antioxidant stress signaling system Keap1/Nrf2 expression, reducing oxidative stress and inflammatory response.[43] Additionally, LBPs reduce the inflammatory response and propylene glycol levels in a rat model of heart failure brought on by pressure overload, indicating that LBPs have cardioprotective effects.[44] Based on the above reports, it can be inferred that the antioxidant activity of LBPs mainly activates the Nrf2 signaling pathway and other antioxidant signaling pathways, increasing the antioxidant enzyme activity and reducing oxidative stress.

Neuroprotective activity

The nervous system plays a leading role in regulating physiological functions in the body, and neurons located throughout the body respond to changes in the internal and external environments so that the body maintains normal life activities. LBPs have neuroprotective effects both *in vitro* and *in vivo*, but their mechanism of action has not been fully elucidated. Neuronal diseases (e.g., retinal problems, stroke, Alzheimer's disease (AD), spinal cord injury) affects a huge number of people globally and incur high societal and financial costs. In the nervous system, LBPs prevent neuronal damage induced by glucose/hypoxia reperfusion, beta-amyloid, glutamate,2,4-dichlorophenoxyacetic acid, 1-methyl-4- phenyl-1,2,3,6-tetrahydropyridin (MPTP), and estrogen level reduction-induced cognitive impairment. LBPs, via PI3K/Akt/mTOR signaling pathway activation, inhibit hypoglycemic/hypoxic reperfusion-induced lactate dehydrogenase (LDH) leakage and improve antioxidant stress, apoptosis, and autophagic cell death, indicating LBPs have a protective effect on primary hippocampal neuronal injury.[45] In addition to a significant reduction in aβ42/aβ40 levels in N2a/APP695 cells, LBPs can label multiple targets in animal AD models, including synaptic plasticity, αβ pathology, and neuropathology, indicating that LBPs play a major role in the management of AD.[46,47] For glutamate-induced neurotoxicity, LBPs reduce the neurotoxic effects on PC12 cells by inhibiting reactive oxygen species accumulation, LDH release, and Ca^{2+} overload (48). In the neurological injury induced by 2,4-dichlorophenoxyacetic acid, LBPs play a neuroprotective role by reducing the inflammatory response and the release of mitochondrial reactive oxygen species, inhibiting the activation of NLRP3 inflammatory vesicles, and upregulating autophagy in the organism.[49] In the effects of MPTP-induced behavioral deficits and abnormal α-synuclein aggregation in mice with Parkinson's disease, relatively short-term treatment with LBPs can upregulate the levels of oxidative stress factors (SOD2, CAT, GPX1) and PTEN/AKT/mTOR phosphorylation, thus serving as a potential adjuvant therapeutic agent for Parkinson's disease.[50] For cognitive impairment caused by reduced estrogen levels, oral LBP treatment may reduce neuroinflammation and hippocampal neuronal damage by the TLR4/NF-κB signaling pathway, which may serve as a potential agent to prevent memory impairment caused by estrogen deficiency.[51] The connection between vision and the nervous system is close and involves multiple nerves in the formation, processing, and transmission of visual images in the eyes. LBPs can treat retina-alleviated ischemia-induced retinal dysfunction by enhancing the immunoreactivity of protein kinase Cα, attenuating the expression of the glial fibrillary acid protein, and reducing associated neuronal death and glial activation.[52] Acute and chronic hypertension *in vivo* models show that the neuroprotective effects of LBPs may promote blood-retinal barrier maintenance and revitalize neuronal cells by inhibiting neuronal degeneration after treatment and preservation of retinal Ganglion cell density and retinal function. And may modulate amyloid production and expression of late glycosylation end-product receptors and mediated retinal glial cell activity.[53,54] The above studies indicate that LBPs can potentially preserve retinal neurons and prevent or reduce the progression of illnesses. In conclusion, LBPs are highly likely to be natural pharmaceutical agents in the adjuvant treatment of neurological disorders through their relevant mechanisms.

Immunomodulatory activity

Many studies show that LBPs modulate changes in immune system components. For example, they can regulate immune cells like lymphocytes, erythrocytes, and natural killer cells. T cells are lymphocytes produced from the thymus and play a crucial part in the development and modulation of the immune response to protein antigens in adapted immunity. LBPs maintain large numbers of T cells in external blood, drainage lymph nodes of tumors, and tumor tissues, and block the rise of regulatory T cells and serum TGF-1 and IL-10 production. Furthermore, they can encourage $CD8^+$ T cell infiltration in tumor tissues while inhibiting the expansion of Tregs.[55] The most functional antigen presenting cells are dendritic cells (DCs) in the immune system. LBPs can stimulate DC phenotypic and functional maturation by raising the expressions of MHCII, CD80, and CD86 via the Notch or TLR4-Erk1/2-Blimp1 signaling pathways. This enhances the cytotoxicity of cytotoxic T lymphocytes mediated by DCs.[56,57] The production of cytokines is a crucial process in the induction and regulation of an immune

response. LBPs activate or stimulate immune cells to secrete cellular factors, which are directly involved in the pathological processes of the body. For instance, LBPs protect the body from cyclophosphamide damage by primarily increasing relevant immune cytokines, such as improving the interleukin (IL-2, IL-12), and tumor necrosis factor concentrations in serum with impaired reproductive systems in mice,[58] and preventing hepatotoxicity in mice.[59] Receptors for various plant polysaccharides exist on the surface of DCs and macrophages, some of which are receptors for the action of LBPs, suggesting that the immunomodulatory function of LBPs may be exerted through DCs and macrophages.

Antitumor activity

Current cancer treatment includes surgery, radiotherapy, immunotherapy, etc. These modes of treatment can have serious side effects and are resistant to drugs. Therefore, there is a pressing need to identify safe and effective anti-cancer compounds from natural resources. As a natural product, LBPs have a bioactivity of tumor growth inhibition *in vitro* and *in vivo*. LBPs inhibit the growth of SGC-790 and Caco-2 cells by inhibiting the G0/G1 and S cell cycle stages [60,61]and inhibit SMMC-7721 cells by increasing intracellular Ca^{2+} concentration.[30,62] Furthermore, LBPs induce apoptosis through the mitochondrial pathway in addition to inhibiting HeLa cell growth and cell cycle arrest.[63] In addition, LBPs restrained the proliferation of BIU87 cells and HemECs by activating the PI3K/AKT signaling pathway,[64,65] and induced apoptosis in T47D and MCF-7 cells by activating the ERK signaling pathway.[66,67] LBPs also induced apoptosis in A431 cells through autophagy.[68] Besides, LBPs can be used as adjuvant drugs to enhance drug effects or reduce adverse drug reactions. For example, In RCC cells, LBPs and interferon-a2b work together to synergistically reduce the expression of cyclinD1, c-My, and Bcl-2 and increase the manifestation of Bax. This means that they reduce Renca cell proliferation, slow down the cell cycle, and induce death.[69] LBPs also inhibit tumors through immunomodulatory effects. For example, LBPs can promote dendritic cell maturation through Notch signaling and increase the cytotoxicity of dendritic-cell-mediated T lymphocytes against colon cancer cells.[70] In glioma, LBPs also inhibit glioma growth by promoting improved immune function.[71] LBPs exhibit antitumor effects mainly through induction of apoptosis, blockade of cell cycle and related signaling pathways, and immunomodulation, thus exhibiting inhibitory activity against many types of cancer cells.

Other Bioactivities

LBPs contribute to reducing diabetes complications. In mice with diabetic nephropathy brought on by a high-fat diet and streptozotocin, LBPs in the experimental group lowered blood glucose levels and improved insulin resistance and renal insufficiency by inhibiting NF-κB activation compared to controls.[72] LBPs also decreased diabetic cataracts by increasing Sirt1 and Bcl-2 proteins while decreasing cell death-related genes.[73] In a model of cardiac hypertrophy in diabetic rats, administration of LBPs inhibited calmodulin-1 expression and NF-κB activation and reduced reactive oxygen species.[74] In diabetic rat testicular cells, LBPs could regulate the expression of SIRT1/HIF-1α, inhibit apoptosis, and protect against diabetic spermatogenic function.[75] The above results suggest that LBPs act in the treatment of diabetic complications mainly through the inhibition of NF-κB activation, inflammation, and apoptosis. The reduction in the activation of the inflammatory transcription factor NF-B is one potential mechanism for the anti-inflammatory impact of LBPs. For example, LBPs inhibit TLR4 and NF-κB inflammatory sites, reduce the production of NO and cytokine, and improve behavioral scores *in vitro* and *in vivo* in mice with peritonitis.[76] For hepatoprotection, LBPs exert a protective effect by restraining the NLRP3/6 inflammasome pathway in a mouse model of nonalcoholic steatohepatitis.[77] For ethanol and CCl_4-induced liver injury or liver fibrosis, LBPs inhibit the TLRs4/NF-κB signaling pathway, apoptosis, and oxidative stress, down-regulate the levels of inflammatory factors,[78-81] and restore intestinal flora.[82] Clinically, the hepatoprotective effect of LBPs was also studied in a randomized, double-blind and placebo-controlled study *in vivo*. LBPs were shown to be a potential probiotic with safety and efficacy in regulating the gut microbiota of persons with non-alcoholic fatty liver disease,[83] promoting the growth of beneficial bacteria *in vitro*, balancing intestinal microbial composition, and improving intestinal flora concentration and immunity in mice.[84]

SUMMARY AND OUTLOOK

In China, *Lycium barbarum* is a conventional herb that has been used for thousands of years to treat diseases and enhance the functions of the liver, kidneys, and lungs. Extraction methods such as aqueous, enzymatic, microwave, and ultrasonic extraction have various consequences on the yield and bioactivity of LBPs. About 90% of the carbohydrates in LBPs are highly branched polysaccharides. In addition to the main sugar chain structure, LBPs have other minimally representative α-(1→5)-ara and β-(1→4)-galp and various branch and end positions, which are the basis for the broad range of drug activity.

As the most important water-soluble components of

traditional medicine, LBPs have extensive bioactivities, safety, low toxicity, and high efficiency. Due to the complex and irregular structure of LBPs and the different molecular weights obtained by other extraction and purification techniques, there are differences in identifying their monosaccharide composition and sugar chain linkage, for which their conformational effect relationship remains unclear. Therefore, future research shall be carried out at the molecular level to explain the advanced structure and related bioactivity by using a more plausible mechanism and to find the effective targets and mechanisms of their structural effects. LBPs with the roles in antioxidants, immunomodulation, and increasing resistance can be regarded as food and health products for further development. According to a few reports, the combination of LBPs with other drugs will enhance the bioactivity of drug efficacy, such as anti-tumor efficacy and hepatoprotective efficacy. LBPs can be used as an adjunct to the development of pharmaceutical products to treat diseases. With the development of a significant health industry, functional food and health products are the future development trend of LBPs, which is because LBPs are a medicinal food source with excellent research value. This review presents the extraction methods, purification, identification, bioactivities, and action mechanism of LBPs, and gives reference guidance and significance for future LBP research and applications in food and medicine.

AUTHOR CONTRIBUTIONS:

Jinhua Q, Hangping Chen and Huaqing Lin conceived the idea; Jinhua Q, Hangping Chen and Huaqing Lin wrote the draft; Hongyuan Che and Wen Rui edited the manuscript; all authors read and approved the final manuscript.

CONFLICTS OF INTEREST:

The author(s) declare that they have no conflicts of interest to disclose.

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REFERENCES

1. Qian D, Zhao Y, Yang G, Huang L. Systematic Review of Chemical Constituents in the Genus Lycium (Solanaceae). Molecules. 2017;22(6). Epub 2017/06/21. doi: 10.3390/molecules22060911. PubMed PMID: 28629116; PubMed Central PMCID: PMCPMC6152755.

2. Amagase H, Farnsworth NR. A review of botanical characteristics, phytochemistry, clinical relevance in efficacy and safety of Lycium barbarum fruit (Goji). Food Research International. 2011;44(7):1702-17.

3. Yanjie G, Yifo W, Yuqing W, Fang G, Zhigang C. Lycium Barbarum: A Traditional Chinese Herb and A Promising Anti-Aging Agent. Aging & Disease. 2017;8(6):778-91.

4. Ni J, Au M, Kong H, Wang X, Wen C. Lycium barbarum polysaccharides in ageing and its potential use for prevention and treatment of osteoarthritis: a systematic review. BMC complementary medicine and therapies.21(1):212.

5. Tian X, Liang T, Liu Y, Ding G, Zhang F, Ma Z. Extraction, Structural Characterization, and Biological Functions of Lycium Barbarum Polysaccharides: A Review. Biomolecules. 2019;9(9). Epub 2019/08/24. doi: 10.3390/biom9090389. PubMed PMID: 31438522; PubMed Central PMCID: PMCPMC6770593.

6. Bin, Liang, Minglin, Jin, Hongbo, Liu. Water-soluble polysaccharide from dried Lycium barbarum fruits: Isolation, structural features and antioxidant activity. Carbohydrate Polymers. 2011;83(4):1947-51.

7. Zhang M, Cui SW, Cheung PC, Wang Q. Antitumor polysaccharides from mushrooms: a review on their isolation process, structural characteristics and antitumor activity. TRENDS IN FOOD SCIENCE AND TECHNOLOGY. 2007.

8. Ling Y. Lycium barbarum polysaccharides (LBP) extraction technology and its antioxidation activity. African Journal of Pharmacy & Pharmacology. 2013;7(19):1175-8.

9. Dong JZ, Wang ZC, Wang Y. RAPID EXTRACTION OF POLYSACCHARIDES FROM FRUITS OF LYCIUM BARBARUM L. Journal of Food Biochemistry. 2011.

10. Qin X, Yamauchi R, Aizawa K, Inakuma T, Kato K. Isolation and Characterization of Arabinogalactan-protein from the Fruit of Lycium chinense Mill. The Japanese Society of Applied Glycoscience. 2000(2).

11. Masci A, Carradori S, Casadei MA, Paolicelli P, Petralito S, Ragno R, et al. Lycium barbarum polysaccharides: Extraction, purification, structural characterisation and evidence about hypoglycaemic and hypolipidaemic effects. A review. Food Chem. 2018;254:377-89. Epub 2018/03/20. doi: 10.1016/j.foodchem.2018.01.176. PubMed PMID: 29548467.

12. Muatasim R, Haile MA, Yang X. Effect of multimode ultrasound assisted extraction on the yield of crude polysaccharides from Lycium Barbarum (Goji). Ciência e Tecnologia de Alimentos. 2018;38(7).

13. Liu Z, Dang J, Wang Q, Yu M, Jiang L, Mei L, et al. Optimization of polysaccharides from Lycium ruthenicum fruit using RSM and its anti-oxidant activity. Int J Biol Macromol. 2013;61:127-34. Epub 2013/07/09. doi:

10.1016/j.ijbiomac.2013.06.042. PubMed PMID: 23831533.

14. Jiao Z, Jia S, Yong L, Wu S, Ran J. Optimization of enzyme-assisted extraction of the Lycium barbarum polysaccharides using response surface methodology. Carbohydrate Polymers. 2011;86(2):1089-92.

15. Zhao CA, Yang R, Qiu T. Ultrasound-enhanced subcritical water extraction of polysaccharides from Lycium barbarum L. Separation and Purification Technology. 2013;120:141-7.

16. Yang RF, Zhao C, Chen X, Chan SW, Wu JY. Chemical properties and bioactivities of Goji (Lycium barbarum) polysaccharides extracted by different methods. Journal of Functional Foods. 2015;17:903-9.

17. Wei HB, Sfw B, Jing Z, Spl B. Effects of extraction methods on immunology activity and chemical profiles of Lycium barbarum polysaccharides - ScienceDirect. Journal of Pharmaceutical and Biomedical Analysis.185.

18. Peng J, Wang L, Wang M, Du R, Qin S, Jin CY, et al. Yeast Synthetic Biology for the Production of Lycium barbarum Polysaccharides. Molecules. 2021;26(6). Epub 2021/04/04. doi: 10.3390/molecules26061641. PubMed PMID: 33804230; PubMed Central PMCID: PMCPMC8000229.

19. Huang LJ, Tian GY, Ji GZ. Structure Elucidation of Glycan of Glycoconjugate LbGp3 Isolated from the Fruit of Lycium barbarum L. Journal of Asian Natural Products Research. 1999;1(4):259-67.

20. Peng XM, Huang LJ, Qi CH, Zhang YX, Tian GY. Studies on chemistry and immuno- modulating mechanism of a glycoconjugate from Lycium barbarum L. &dagger: Chinese Journal of Chemistry; 2001.

21. Chunjiu Z, Rongzhi LI, Yunqing HE, Guohui C. STUDIES ON THE CHEMISTRY OF GOUQI POLYSACCHARIDES. JOURNAL OF BEIJING MEDICAL UNIVERSITY. 1997.

22. Yuan Y, Wang YB, Jiang Y, Prasad KN, Yang J, Qu H, et al. Structure identification of a polysaccharide purified from Lycium barbarium fruit. International Journal of Biological Macromolecules. 2015:696.

23. Wei L, Liu Y, Rui Z, Yu J, Gaoa X. Structure characterization, chemical and enzymatic degradation, and chain conformation of an acidic polysaccharide from Lycium barbarum L. Carbohydrate Polymers. 2016;147:114-24.

24. Zhou, Lishuang, Huang, Lulin, Yue, Han, et al. Structure analysis of a heteropolysaccharide from fruits of Lycium barbarum L. and anti-angiogenic activity of its sulfated derivative. International Journal of Biological Macromolecules: Structure, Function and Interactions. 2018;108:47-55.

25. Chen, Sun, Gui-Ju, Wang, Shao-Kang, Tang, et al. Biochemical analysis and hypoglycemic activity of a polysaccharide isolated from the fruit of Lycium barbarum L. International Journal of Biological Macromolecules: Structure, Function and Interactions. 2015.

26. Zhu J, Liu W, Yu J, Zou S, Wang J, Yao W, et al. Characterization and hypoglycemic effect of a polysaccharide extracted from the fruit of Lycium barbarum L. Carbohydrate Polymers. 2013;98(1):8-16.

27. Wang Z, Yang L, Sun Y, Mou Q, Bo W, Ying Z, et al. Structural characterization of LbGp1 from the fruits of Lycium barbarum L. Food Chemistry. 2014;159(sep.15):137-42.

28. Biochemical analysis and hypoglycemic activity of a polysaccharide isolated from the fruit of Lycium barbarum L. International Journal of Biological Macromolecules. 2015;77:235-42.

29. Redgwell RJ, Curti D, Wang J, Dobruchowska JM, Gerwig GJ, Kamerling JP, et al. Cell wall polysaccharides of Chinese Wolfberry (Lycium barbarum): Part 2. Characterisation of arabinogalactan-proteins. Carbohydrate Polymers. 2011;84(3):1075-83.

30. Gong G, Fan J, Sun Y, Wu Y, Liu Y, Sun W, et al. Isolation, structural characterization, and antioxidativity of polysaccharide LBLP5-A from Lycium barbarum leaves. PROCESS BIOCHEMISTRY. 2016;51(2):314-24.

31. Wu J, Chen T, Wan F, Wang J, Li X, Li W, et al. Structural characterization of a polysaccharide from Lycium barbarum and its neuroprotective effect against β-amyloid peptide neurotoxicity. Int J Biol Macromol. 2021;176:352-63. Epub 2021/02/08. doi: 10.1016/j.ijbiomac.2021.02.016. PubMed PMID: 33549666.

32. Liu J, Li Y, Pu Q, Qiu H, Di D, Cao Y. A polysaccharide from Lycium barbarum L.: Structure and protective effects against oxidative stress and high-glucose-induced apoptosis in ARPE-19 cells. Int J Biol Macromol. 2022;201:111-20. Epub 2021/12/31. doi: 10.1016/j.ijbiomac.2021.12.139. PubMed PMID: 34968548.

33. Yang Y, Chang Y, Wu Y, Liu H, Liu Q, Kang Z, et al. A homogeneous polysaccharide from Lycium barbarum: Structural characterizations, anti-obesity effects and impacts on gut microbiota. Int J Biol Macromol. 2021;183:2074-87. Epub 2021/06/08. doi: 10.1016/j.ijbiomac.2021.05.209. PubMed PMID: 34097961.

34. Wang CC, Chang SC, Inbaraj BS, Chen BH. Isolation of carotenoids, flavonoids and polysaccharides from Lycium barbarum L. and evaluation of antioxidant activity. food chemistry. 2010;120(1):184-92.

35. Tang L, Bao S, Du Y, Jiang Z, Ma H. Antioxidant effects of Lycium barbarum polysaccharides on photoreceptor degeneration in the light-exposed mouse retina. Biomedicine

& pharmacotherapy = Biomedecine & pharmacotherapie. 2018;103:829-37.

36. Liang B, Peng L, Li R, Li H, Mo Z, Dai X, et al. Lycium barbarum polysaccharide protects HSF cells against ultraviolet-induced damage through the activation of Nrf2. Cellular & Molecular Biology Letters. 2018;23(1):18.

37. Zheng G, Ren H, Li H, Li X, Li Y. Lycium barbarum polysaccharide reduces hyperoxic acute lung injury in mice through Nrf2 pathway. Biomedicine & Pharmacotherapy. 2019;111:733-9.

38. Liu JJ, Zhao GX, He LL, Wang Z, Lu Y. Lycium barbarum polysaccharides inhibit ischemia/reperfusion-induced myocardial injury via the Nrf2 antioxidant pathway. Toxicology Reports. 2021;8(9973).

39. Xie W, Huang Y, Chen H, Zhou X. Study on the Efficacy and Mechanism ofLycium barbarumPolysaccharide against Lead-Induced Renal Injury in Mice. Nutrients. 2021;13(9).

40. Yang DM, Zhang JQ, Fei YF. Lycium barbarum polysaccharide attenuates chemotherapy-induced ovarian injury by reducing oxidative stress. J Obstet Gynaecol Res. 2017.

41. Liang R, Zhao Q, Zhu Q, He X, Gao M, Wang Y. Lycium barbarum polysaccharide protects ARPE19 cells against H 2 O 2induced oxidative stress via the Nrf2/HO1 pathway. Spandidos Publications. 2021(5).

42. Molagoda IMN, Kavinda MHD, Choi YH, Lee H, Kang CH, Lee MH, et al. Fisetin Protects HaCaT Human Keratinocytes from Fine Particulate Matter (PM2.5)-Induced Oxidative Stress and Apoptosis by Inhibiting the Endoplasmic Reticulum Stress Response. Antioxidants. 2021;10(9):1492-.

43. Wu Q, Liu LT, Wang XY, Lang ZF, Wang HW. Lycium barbarum polysaccharides attenuate kidney injury in septic rats by regulating Keap1-Nrf2/ARE pathway. Life Sciences. 2019;242:117240.

44. Pop C, Berce C, Ghibu S, Scurtu I, Mogoan C. Effects of Lycium barbarum L. Polysaccharides on Inflammation and Oxidative Stress Markers in a Pressure Overload-Induced Heart Failure Rat Model. Molecules. 2020;25(3).

45. B YYA, A XW, A JP, A PL, C WM, A JW, et al. Lycium barbarum polysaccharide protects against oxygen glucose deprivation/reoxygenation-induced apoptosis and autophagic cell death via the PI3K/Akt/mTOR signaling pathway in primary cultured hippocampal neurons. Biochemical and Biophysical Research Communications. 2018;495(1):1187-94.

46. Wu J, Chen T, Wan F, Wang J, Ma L. Structural characterization of a polysaccharide from Lycium barbarum and its neuroprotective effect against β-amyloid peptide neurotoxicity. International Journal of Biological Macromolecules. 2021(8).

47. Zhou Y, Duan Y, Huang S, Zhou X, Pei G. Polysaccharides from Lycium barbarum ameliorate amyloid pathology and cognitive functions in APP/PS1 transgenic mice. International Journal of Biological Macromolecules. 2019;144.

48. Zhu Y, Zhao Q, Gao H, Peng X, Wen Y, Dai G. Lycium barbarum polysaccharides attenuates N-methy-N-nitrosourea-induced photoreceptor cell apoptosis in rats through regulation of poly (ADP-ribose) polymerase and caspase expression. Journal of Ethnopharmacology. 2016:125-34.

49. Zhou J, Wang F, Jia L, Chai R, Wang H, Wang X, et al. 2,4dichlorophenoxyacetic acid induces ROS activation in NLRP3 inflammatory bodyinduced autophagy disorder in microglia and the protective effect of Lycium barbarum polysaccharide. Environmental Toxicology. 2022;37.

50. Wang X, Pang L, Zhang Y, Xu J, Ding D, Yang T, et al. Lycium barbarum Polysaccharide Promotes Nigrostriatal Dopamine Function by Modulating PTEN/AKT/mTOR Pathway in a Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) Murine Model of Parkinson's Disease. Neurochem Res. 2018;43(4):938-47. Epub 2018/03/30. doi: 10.1007/s11064-018-2499-6. PubMed PMID: 29594732.

51. Zheng X, Wang J, Bi F, Li Y, Xiao J, Chai Z, et al. Protective effects of Lycium barbarum polysaccharide on ovariectomy-induced cognition reduction in aging mice. Int J Mol Med. 2021;48(1). Epub 2021/05/07. doi: 10.3892/ijmm.2021.4954. PubMed PMID: 33955518; PubMed Central PMCID: PMCPMC8121556.

52. Yang D, So KF, Lo AC. Lycium barbarum polysaccharide extracts preserve retinal function and attenuate inner retinal neuronal damage in a mouse model of transient retinal ischaemia. Clin Exp Ophthalmol. 2017;45(7):717-29. Epub 2017/03/30. doi: 10.1111/ceo.12950. PubMed PMID: 28349587.

53. Lakshmanan Y, Wong FSY, Zuo B, So KF, Bui BV, Chan HH. Posttreatment Intervention With Lycium Barbarum Polysaccharides is Neuroprotective in a Rat Model of Chronic Ocular Hypertension. Invest Ophthalmol Vis Sci. 2019;60(14):4606-18. Epub 2019/11/23. doi: 10.1167/iovs.19-27886. PubMed PMID: 31756254.

54. Mi XS, Feng Q, Lo ACY, Chang RC, Chung SK, So KF. Lycium barbarum polysaccharides related RAGE and Aβ levels in the retina of mice with acute ocular hypertension and promote maintenance of blood retinal barrier. Neural Regen Res. 2020;15(12):2344-52. Epub 2020/07/01. doi: 10.4103/1673-5374.284998. PubMed PMID: 32594059; PubMed Central PMCID: PMCPMC7749484.

55. Deng X, Luo S, Luo X, Hu M, Ma F, Wang Y, et al. Polysaccharides from Chinese Herbal Lycium barbarum Induced Systemic and Local Immune Responses in H22

Tumor-Bearing Mice. J Immunol Res. 2018;2018:3431782. Epub 2018/07/04. doi: 10.1155/2018/3431782. PubMed PMID: 29967800; PubMed Central PMCID: PMCPMC6008830.

56. Wang W, Liu M, Wang Y, Yang T, Li D, Ding F, et al. Lycium barbarum Polysaccharide Promotes Maturation of Dendritic Cell via Notch Signaling and Strengthens Dendritic Cell Mediated T Lymphocyte Cytotoxicity on Colon Cancer Cell CT26-WT. Evid Based Complement Alternat Med. 2018;2018:2305683. Epub 2018/04/06. doi: 10.1155/2018/2305683. PubMed PMID: 29619065; PubMed Central PMCID: PMCPMC5829330.

57. Duan X, Lan Y, Zhang X, Hou S, Chen J, Ma B, et al. Lycium barbarum Polysaccharides Promote Maturity of Murine Dendritic Cells through Toll-Like Receptor 4-Erk1/2-Blimp1 Signaling Pathway. J Immunol Res. 2020;2020:1751793. Epub 2020/12/22. doi: 10.1155/2020/1751793. PubMed PMID: 33344654; PubMed Central PMCID: PMCPMC7725586.

58. Ding Y, Yan Y, Chen D, Ran L, Mi J, Lu L, et al. Modulating effects of polysaccharides from the fruits of Lycium barbarum on the immune response and gut microbiota in cyclophosphamide-treated mice. Food Funct. 2019;10(6):3671-83. Epub 2019/06/07. doi: 10.1039/c9fo00638a. PubMed PMID: 31168539.

59. Miao Y, Xiao B, Jiang Z, Guo Y, Mao F, Zhao J, et al. Growth inhibition and cell-cycle arrest of human gastric cancer cells by Lycium barbarum polysaccharide. Med Oncol. 2010;27(3):785-90. Epub 2009/08/12. doi: 10.1007/s12032-009-9286-9. PubMed PMID: 19669955.

60. Mao F, Xiao B, Jiang Z, Zhao J, Huang X, Guo J. Anticancer effect of Lycium barbarum polysaccharides on colon cancer cells involves G0/G1 phase arrest. Med Oncol. 2011;28(1):121-6. Epub 2010/01/13. doi: 10.1007/s12032-009-9415-5. PubMed PMID: 20066520.

61. Zhang XJ, Yu HY, Cai YJ, Ke M. Lycium barbarum polysaccharides inhibit proliferation and migration of bladder cancer cell lines BIU87 by suppressing Pi3K/AKT pathway. Oncotarget. 2017;8(4):5936-42. Epub 2016/12/20. doi: 10.18632/oncotarget.13963. PubMed PMID: 27992374; PubMed Central PMCID: PMCPMC5351602.

62. Zhang Q, Lv X, Wu T, Ma Q, Zhang M. Composition of Lycium barbarum polysaccharides and their apoptosis-inducing effect on human hepatoma SMMC-7721 cells. Food & Nutrition Research. 2015;59.

63. Zhu CP, Zhang SH. Lycium barbarum polysaccharide inhibits the proliferation of HeLa cells by inducing apoptosis. Journal of the Science of Food & Agriculture. 2012;93(1):149-56.

64. Zhang XJ, Yu HY, Cai YJ, Ke M. Lycium barbarum polysaccharides inhibit proliferation and migration of bladder cancer cell lines BIU87 by suppressing Pi3K/AKT pathway. Oncotarget. 2016;8(4):5936-42.

65. Lou L, Chen G, Zhong B, Liu F. Lycium barbarum Polysaccharide Induced Apoptosis and Inhibited Proliferation in Infantile Hemangioma Endothelial Cells via Down-regulation of PI3K/AKT Signaling Pathway. Bioscience Reports. 2019;39(8):BSR20191182.

66. Wawruszak A, Czerwonka A, Oka K, Rzeski W. Anticancer effect of ethanol Lycium barbarum (Goji berry) extract on human breast cancer T47D cell line. Natural Product Research. 2015:1.

67. Shen L, Du G. Lycium barbarum polysaccharide stimulates proliferation of MCF-7 cells by the ERK pathway. Life Sciences. 2012;91(9-10).

68. Zeng M, Kong Q, Liu F, Chen J, Sang H. The Anticancer Activity of Lycium barbarum Polysaccharide by Inhibiting Autophagy in Human Skin Squamous Cell Carcinoma Cells In Vitro and In Vivo. International Journal of Polymer Science. 2019;2019:1-8.

69. Chen S, Liang L, Wang Y, Diao J, Zhao C, Chen G, et al. Synergistic immunotherapeutic effects of Lycium barbarum polysaccharide and interferon-α2b on the murine Renca renal cell carcinoma cell line in vitro and in vivo. Molecular Medicine Reports. 2015.

70. Qian L. Modulation of cytokine level and sperm quality of mice by Lycium barbarum polysaccharides. International Journal of Biological Macromolecules. 2018;126:475-7.

71. Wang J, Zou Y, Li Y, Wu Q, Shen B. Lycium barbarum polysaccharide inhibits the growth of rat glioma by regulating the blood-brain barrier. Tumor. 2018;38(2):102-10.

72. Wan F, Ma F, Wu J, Qiao X, Chen M, Li W, et al. Effect of Lycium barbarum Polysaccharide on Decreasing Serum Amyloid A3 Expression through Inhibiting NF-κB Activation in a Mouse Model of Diabetic Nephropathy. Anal Cell Pathol (Amst). 2022;2022:7847135. Epub 2022/02/09. doi: 10.1155/2022/7847135. PubMed PMID: 35132370; PubMed Central PMCID: PMCPMC8817866 publication of this paper.

73. Yao Q, Zhou Y, Yang Y, Cai L, Xu L, Han X, et al. Activation of Sirtuin1 by lyceum barbarum polysaccharides in protection against diabetic cataract. J Ethnopharmacol. 2020;261:113165. Epub 2020/07/31. doi: 10.1016/j.jep.2020.113165. PubMed PMID: 32730875.

74. Liu Q, Han Q, Lu M, Wang H, Tang F. Lycium barbarum polysaccharide attenuates cardiac hypertrophy, inhibits calpain-1 expression and inhibits NF-κB activation in streptozotocin-induced diabetic rats. Exp Ther Med. 2019;18(1):509-16. Epub 2019/07/02. doi: 10.3892/etm.2019.7612. PubMed PMID: 31258688; PubMed Central PMCID: PMCPMC6566019.

75. Lei X, Huo P, Wang Y, Xie Y, Shi Q, Tu H, et al. Lycium barbarum Polysaccharides Improve Testicular Spermatogenic Function in Streptozotocin-Induced Diabetic Rats. Front Endocrinol (Lausanne). 2020;11:164. Epub 2020/05/05. doi: 10.3389/fendo.2020.00164. PubMed PMID: 32362869; PubMed Central PMCID: PMCPMC7181356.

76. Liu ZC, Yu WW, Zhou HC, Lan ZC, Wu T, Xiong SM, et al. Lycium barbarum polysaccharides ameliorate LPS-induced inflammation of RAW264.7 cells and modify the behavioral score of peritonitis mice. Journal of Food Biochemistry.

77. Xiao J, Wang F, Liong EC, So KF, Tipoe GL. Lycium barbarum polysaccharides improve hepatic injury through NFkappa-B and NLRP3/6 pathways in a methionine choline deficient diet steatohepatitis mouse model. Int J Biol Macromol. 2018;120(Pt B):1480-9. Epub 2018/09/30. doi: 10.1016/j.ijbiomac.2018.09.151. PubMed PMID: 30266645.

78. Liu RJ, He YJ, Liu H, Zheng DD, Huang SW, Liu CH. Protective effect of Lycium barbarum polysaccharide on di-(2-ethylhexyl) phthalate-induced toxicity in rat liver. Environ Sci Pollut Res Int. 2021;28(18):23501-9. Epub 2021/01/16. doi: 10.1007/s11356-020-11990-8. PubMed PMID: 33449321.

79. Wang H, Li Y, Liu J, Di D, Liu Y, Wei J. Hepatoprotective effect of crude polysaccharide isolated from Lycium barbarum L. against alcohol-induced oxidative damage involves Nrf2 signaling. Food Sci Nutr. 2020;8(12):6528-38. Epub 2020/12/15. doi: 10.1002/fsn3.1942. PubMed PMID: 33312537; PubMed Central PMCID: PMCPMC7723211.

80. Yun-Yun C, Chao CJ. Olive oil combined with Lycium barbarum polysaccharides attenuates liver apoptosis and inflammation induced by carbon tetrachloride in rats. Journal of Functional Foods. 2018;48:329-36.

81. Gan F, Liu Q, Liu Y, Huang D, Pan C, Song S, et al. Lycium barbarum polysaccharides improve CCl(4)-induced liver fibrosis, inflammatory response and TLRs/NF-kB signaling pathway expression in wistar rats. Life Sci. 2018;192:205-12. Epub 2017/12/03. doi: 10.1016/j.lfs.2017.11.047. PubMed PMID: 29196051.

82. Gao LL, Ma JM, Fan YN, Zhang YN, Ge R, Tao XJ, et al. Lycium barbarum polysaccharide combined with aerobic exercise ameliorated nonalcoholic fatty liver disease through restoring gut microbiota, intestinal barrier and inhibiting hepatic inflammation. Int J Biol Macromol. 2021;183:1379-92. Epub 2021/05/17. doi: 10.1016/j.ijbiomac.2021.05.066. PubMed PMID: 33992651.

83. Gao LL, Li YX, Ma JM, Guo YQ, Li L, Gao QH, et al. Effect of Lycium barbarum polysaccharide supplementation in non-alcoholic fatty liver disease patients: study protocol for a randomized controlled trial. Trials. 2021;22(1):566. Epub 2021/09/16. doi: 10.1186/s13063-021-05529-6. PubMed PMID: 34521466; PubMed Central PMCID: PMCPMC8439032.

84. Zhu W, Zhou S, Liu J, McLean RJC, Chu W. Prebiotic, immuno-stimulating and gut microbiota-modulating effects of Lycium barbarum polysaccharide. Biomed Pharmacother. 2020;121:109591. Epub 2019/11/17. doi: 10.1016/j.biopha.2019.109591. PubMed PMID: 31733576.