Current Situation of Protective Effect of Lycium Barbarum Polysaccharide on Cardiac

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Abstract: Lycium barbarum is a kind of traditional Chinese medicine. Lycium barbarum tastes sweet and juicy with many benefits such as nourishing liver and kidney, improving eyesight, delaying aging, etc. Lycium barbarum polysaccharide (LBP) is the main active ingredient of Lycium barbarum which has been widely used in the treatment of cardiovascular diseases in China. It has many biological activities such as anti-oxidation, anti-aging, relieving body fatigue, regulating blood lipid and blood glucose. Recent studies on LBP have shown that LBP is involved in cardiac protection through various mechanisms such as blocking l-type calcium channel, antioxidant reaction, improving myocardial fibrosis, inhibiting apoptosis, and anti-cytotoxicity. In this paper, the relevant research contents are summarized in order to provide reference for clinical research.

Keywords: Lycium barbarum polysaccharide, Cardiomyocytes, Cardiac protection, Apoptosis, Fibrosis, Signaling pathways

1. Introduction

Lycium Barbarum, also known as Lycium Barbarum, is a very hard, prickly, shrubby vine belonging to solanaceae [1]. Lycium Barbarum has a history of more than 2000 years in China as a major medicinal material for both food and medicine [2]. The chemical components of Lycium barbarum polysaccharide mainly included Lycium barbarum polysaccharide, flavonoids, carotenoids, betaine, brain glycosides, β-sterols, amino acids, vitamins, trace elements, etc. [1-3], in which Lycium barbarum polysaccharide was the main chemical component of Lycium barbarum polysaccharide. It is also the main active ingredient of Wolfberry, with a variety of biological activities such as anti-aging [4], anti-oxidation [5], hypoglycemic [6], anti-tumor [7], neuroprotection [8] and immune regulation [9]. Among many pharmacological effects, the protective effect on the heart is very important, mainly manifested in improving the function of vascular endothelial cells, protecting myocardial ischemia, inhibiting myocardial apoptosis and inhibiting myocardial fibrosis. This paper reviews the protective effect and mechanism of LBP on heart.

2. Protective effect of Lycium barbarum Polysaccharide on hypoxia heart

Li et al. [10] treated H9c2 cardiomyocytes with LYcium barbarum polysaccharide (300μg/mL) for 24 h under hypoxia, evaluated the changes of cell viability, migration and apoptosis, established an animal model of myocardial infarction (MI), and further studied the effects of LYcium barbarum polysaccharide in vivo. The results showed that lycium barbarum polysaccharide increased cell viability and improved migration. It inhibited the apoptosis of hypoxia-damaged H9c2 cardiomyocytes, reduced the size of myocardial infarction and improved cardiac function in rats, possibly by down-regulating mir-122 pathway in vitro and in vivo. Studies have shown that “calcium overload” caused by accumulation of calcium ions in cells caused by various injuries may be the final pathway leading to cell damage and death [11-12]. Xu Shunlin et al. [13] cultured myocardial cells of SD Suckling rats two or three days old to establish myocardial hypoxia model, and pretreated with 50 mg/L LBP. By observing cell activity, morphology and [Ca2+] I fluorescence density, the results showed that LBP had protective effect on hypoxia myocardial cells. The mechanism may be related to the reduction of intracellular calcium overload by LBP. Liu Miao et al. [14], based on the results of previous experiments, further recorded calcium channel currents by using single rat cardiomyocytes and standard whole-cell patch clamp technique, and showed that LBP inhibited L-type calcium channels in a concentration-dependent manner.
mainly affecting the activation and recovery of calcium channels. It can not only reduce intracellular calcium ion concentration, reduce the occurrence of calcium overload, reduce the activation and release of degradation enzymes caused by myocardial ischemia and hypoxia injury; It can also shorten the action potential duration (APD), reduce the early and late depolarization caused by excitatory reentry, and reduce the occurrence of arrhythmias. These studies indicate that LBP has a certain protective effect on hypoxia heart, and LBP may achieve the protective effect on hypoxia heart through different mechanisms. The literatures can be summarized as Table 1.

Table 1: Protective effect and mechanism of Lycium barbarum Polysaccharide on hypoxic.

<table>
<thead>
<tr>
<th>Cardioprotective effect</th>
<th>mechanism</th>
<th>dose</th>
<th>The experimental model</th>
<th>The experimental type</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase cell viability, improve migration, inhibit apoptosis and reduce infarct area</td>
<td>Down-regulation of mir-122 pathway</td>
<td>300µg/mL</td>
<td>Cells, rats</td>
<td>In vitro and in vivo</td>
<td>10</td>
</tr>
<tr>
<td>Increase cell vitality and improve cell hypoxia morphology</td>
<td>Reduce calcium overload</td>
<td>25, 50, 100µg/L</td>
<td>cells</td>
<td>In vitro</td>
<td>13</td>
</tr>
<tr>
<td>Regulate cell excitation and contraction, reduce arrhythmia</td>
<td>Inhibits L-type calcium channels</td>
<td>25, 50, 100µg/L</td>
<td>cells</td>
<td>In vitro</td>
<td>14</td>
</tr>
</tbody>
</table>

3. Protective effect of Lycium barbarum Polysaccharide on heart after ischemia/reperfusion (I/R)

Zhou Xin et al. [15] established myocardial infarction rat model by coronary ligation, and gave lycium barbarum polysaccharide (100 mg/kg) intragastric administration for 4 consecutive weeks. Cardiac structural parameters of each group were collected at 3d, 1, 3 and 4 weeks after operation, respectively. The results showed that LBP can significantly improve myocardial ischemia injury in rats after myocardial infarction. The mechanism may be related to activating endothelial cell function, promoting neovascularization and blood perfusion by increasing the expression of CD133 and VEGFR2 proteins. Lu et al. [16] observed the effects of LBP on myocardial cell injury in rats with myocardial I/R injury, and the results showed that LBP could significantly reduce the LD level of I/R rats and improve the activities of Na+ -K+ -ATpase and Ca2+ -ATpase. In addition, LBP could significantly down-regulate Bax level and inhibit apoptosis. In addition, the expression level of Bcl-2 increased in a dose-dependent manner, which was consistent with the experimental conclusion of Hou et al. [17]. Wang Yucai et al. [18] also used myocardial I/R animal model to prove the protective effect of LBP on rat myocardial I/R, and its mechanism was related to the reduction of SOD content, promotion of Bcl-2 expression and inhibition of Fas protein expression by LBP after scavenging oxygen free radicals in serum after I/R. This experimental conclusion is consistent with that of Li Lifang et al. [19]. Pan H et al. [20] reported that LBP can also activate Nrf2 by inhibiting autophagy, thus exerting its protective effect on I/R-induced heart injury.

Table 2: Protective effect and mechanism of Lycium barbarum polysaccharide on myocardial

<table>
<thead>
<tr>
<th>Cardioprotective effect</th>
<th>mechanism</th>
<th>dose</th>
<th>The experimental model</th>
<th>The experimental type</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase EF, FS and decrease myocardial cell damage</td>
<td>Increased CD133 and VEGFR2 protein expression</td>
<td>100mg/kg</td>
<td>The rat</td>
<td>In the body</td>
<td>15</td>
</tr>
<tr>
<td>Decreased LD level and increased Na+ -K+ - atpase and Ca2+ - atpase activity</td>
<td>Bax level was down-regulated and bcl-2 expression level was increased</td>
<td>150, 300mg/kg</td>
<td>The rat</td>
<td>In the body</td>
<td>16 or 17</td>
</tr>
<tr>
<td>Inhibit apoptosis and oxidative stress</td>
<td>Promote bcl-2 expression and inhibit Fas expression</td>
<td>1mg/kg</td>
<td>The rat</td>
<td>In the body</td>
<td>18th and 19th</td>
</tr>
<tr>
<td>Increase cell viability, inhibit apoptosis, inflammation, oxidative stress</td>
<td>Nrf2 expression was activated and autophagy was inhibited</td>
<td>15, 30, 60µg/ml</td>
<td>cells</td>
<td>In vitro</td>
<td>20</td>
</tr>
</tbody>
</table>

In addition, Chinese wolfberry polysaccharides can also sympathetic nerve plays a protective role of ischemic myocardium, can maintain the stability of the cardiac electrophysiology, reduce the incidence of arrhythmia after myocardial infarction, its mechanism may be related to LBP effectively reduce inflammatory factor levels in the body, reduce the excitability of infarction myocardial tissue, inhibiting sympathetic nerve regeneration after myocardial infarction (mi). Reduction of NGF release is related[21].
In addition, Qi G X et al. [22] found that LBP has a protective effect on myocardium during endoplasmic reticulum stress (ERS) in homocysteine (Hcy) mediated apoptosis of APOE mouse and H9C2 rat myocardium, and its mechanism may be related to reducing ERS and decreasing Hcy-mediated apoptosis of myocardium. The literatures can be summarized as Table 2.

4. Lycium barbarum polysaccharide (LBP) inhibits myocardial fibrosis and protects the heart from heart failure

Meng Lili [23] established rat models of chronic heart failure (CHF) by abdominal aortic constriction method (ACC), and treated with LBP. The results showed that LBP could significantly improve cardiac systolic and diastolic functions, reduce myocardial cell damage, and improve ventricular structural changes and progression of myocardial fibrosis in CHF rats. The mechanism may be related to the down-regulation of TGFβ1/Smad3 signaling pathway and the reduction of collagen fiber deposition in myocardial tissue. Liu Xinyan et al. [24] established isO-induced heart failure rats as models and administered LBP for 30 d, and found that LBP could significantly reduce heart weight/body weight in heart failure rats (P<0.01), decreased serum CTN-I, improved cardiac function, increased SOD level in serum and myocardium, and decreased MDA content, suggesting that LBP has protective effect on myocardium hypertrophy and heart failure induced by ISO in rats. The mechanism may be related to increasing antioxidant enzyme activity and decreasing lipid peroxides. Pop C et al. [25] also proved the anti-inflammatory and antioxidant effects of LBP in HF animal models, improving heart failure and thus protecting the heart. Zang R et al. [26] found that LBP improved abnormal electrocardiogram and cardiac function indicators, restored sarcomere assembly, disc and intervertebral disc junction morphological changes, and reversed the decrease of CaM and cMLCK (Mir-1-targeted proteins) in PV ring detection of Mir-1-overexpressed transgenic (Tg) mice. The results showed that LBP restored adverse structural remodeling and improved cardiac systolic dysfunction, which may be related to down-regulation of Mir-1 expression. In addition, LBP can also reduce the level of oxidative stress in the heart of diabetic rats, which has a protective effect on diabetic cardiomyopathy rats. The mechanism may be related to the inhibition of calpain-1 activity and NF-κB activation [27]. The literatures can be summarized as Table 3.

Table 3: Protective effect and mechanism of Lycium barbarum polysaccharide on myocardial fibrosis and heart failure

<table>
<thead>
<tr>
<th>Cardioprotective effect</th>
<th>The experimental model</th>
<th>The experimental type</th>
<th>dose</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improve cardiac systolic and diastolic function, improve ventricular structure change and myocardial fibrosis progression</td>
<td>TGF beta 1 / Smad 3 Signal pathway</td>
<td>The rat</td>
<td>100mg/kg</td>
<td>23</td>
</tr>
<tr>
<td>Reduce cardiac hypertrophy and improve cardiac function</td>
<td>Increase antioxidant enzyme activity and decrease lipid peroxides</td>
<td>The rat</td>
<td>50, 100, 200mg/kg</td>
<td>24</td>
</tr>
<tr>
<td>Improve myocardial systolic function</td>
<td>Anti-inflammatory and antioxidant</td>
<td>The rat</td>
<td>100, 200mg/kg</td>
<td>25</td>
</tr>
<tr>
<td>Restore adverse structural remodeling and improve cardiac systolic function</td>
<td>Down-regulation of Mir-1 expression</td>
<td>The rat</td>
<td>200mg/kg/d</td>
<td>26</td>
</tr>
</tbody>
</table>

5. Protective effect of Lycium barbarum Polysaccharide on cardiac injury induced by Doxorubicin

Zhou Guoliang et al. [28] detected the survival rate, SOD activity and MDA content of H9c2 cells damaged by DOxorubicin (DOX) by adjusting the concentration of Lycium barbarum polysaccharide. The results showed that the survival rate of H9c2 cells reached the maximum when the concentration of Lycium barbarum polysaccharide reached 1.85μg/mL. At the same time, DOX induced decreased SOD activity and increased MDA concentration in myocardial cells, and the protective mechanism may be related to LBP alleviating oxidative stress injury. Xin YF et al. [29] also confirmed the typical protective effect of LBP on DOX induced acute cardiotoxicity by inhibiting oxidative stress in rats. On this basis, Xin Y et al. [30] treated male beagles with Lycium barbarum polysaccharide (20mg/kg, orally) for 7 days.
The protective effect of *Lycium barbarum* polysaccharide (LBP) on DOX-induced acute cardiotoxicity in beagle dogs was then investigated by intravenous injection of DOX (1.5 mg/kg). It was found that pretreatment with LBP effectively alleviated DOX-related conduction abnormalities and increased serum CK and AST. Confirm and extend previous observations on the efficacy of LBP against DOX-induced cardiomyopathy in rats. The literatures can be summarized as Table 4.

### Table 4: Protective effect and mechanism of *Lycium barbarum* Polysaccharide on cardiac injury induced by Doxorubicin

<table>
<thead>
<tr>
<th>Cardioprotective effect</th>
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<th>dose</th>
<th>The experimental model</th>
<th>The experimental type</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce cardiotoxicity and increase cell viability</td>
<td>Reduce oxidative stress damage</td>
<td>1.85 μM/g/mL</td>
<td>cells</td>
<td>In vitro</td>
<td>28</td>
</tr>
<tr>
<td>Reduce cardiotoxicity and increase cell viability</td>
<td>Reduce oxidative stress damage</td>
<td>200 mg/kg</td>
<td>The rat</td>
<td>In the body</td>
<td>29</td>
</tr>
<tr>
<td>Alleviates conduction abnormalities and reduces CK and AST</td>
<td>Reduce oxidative stress damage</td>
<td>20 mg/kg</td>
<td>beagle</td>
<td>In the body</td>
<td>30</td>
</tr>
</tbody>
</table>

6. Protective effect of *Lycium barbarum* polysaccharide on ovariectomized rat myocardium

Yu NING et al. [31] used ovariectomized SD rats and administered *lycium barbarum* polysaccharide (250, 125 mg/kg) orally for 12 weeks continuously. The results showed that LBP high-dose group increased serum estradiol content, increased myocardial H2S content, GSH-Px activity, eNOS protein and Akt phosphorylation levels, decreased myocardial ROS activity and MDA content, decreased serum LDH and CK activities, and improved the changes of myocardial morphology. These results indicate that LBP has protective effect on myocardium of ovariectomized rats, and its mechanism may be related to the regulation of PI3K/Akt/eNOS pathway. Yu N et al. [32] also used ovariectomized SD rats as a model to prove that LBP can improve the heart injury of ovariectomized rats caused by oxidative stress, and the mechanism may be that the improvement of antioxidiant status is related to the Akt signaling pathway in the ovariectomized rats. It provides a new therapeutic idea for the treatment of postmenopausal cardiovascular disease. Table 5.

### Table 5: Protective effect of *Lycium barbarum* Polysaccharide on ovariectomized rat myocardium

<table>
<thead>
<tr>
<th>Cardioprotective effect</th>
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<th>The experimental type</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improve oxidative stress damage</td>
<td>Regulation of PI3K/Akt/eNOS pathway</td>
<td>250, 125 mg/kg</td>
<td>The rat</td>
<td>In the body</td>
<td>31</td>
</tr>
<tr>
<td>Improve oxidative stress damage</td>
<td>Activation of Akt signaling pathway</td>
<td>125, 300 mg/kg</td>
<td>The rat</td>
<td>In the body</td>
<td>32</td>
</tr>
</tbody>
</table>

7. Conclusion

In conclusion, LBP has a certain protective effect on the heart, but the mechanism is not completely clear.

*Lycium barbarum* polysaccharides (LBP) may protect the heart through multiple pathways, which may be due to its simultaneous action on multiple targets. As these studies continue to deepen, the results will provide more references for clinical work and provide a reliable theoretical basis for screening more effective drugs to treat heart disease.

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