Application Progress of Bear Bile Powder and Ursodeoxycholic Acid in Liver Disease and its Mechanism of Action

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Abstract. Liver disease is a type of disease that threatens human life and health, including viral liver disease, cirrhosis, fatty liver, liver cancer and other liver diseases. Slowing or even blocking the progress of liver disease has great clinical significance. Today, western medicine lacks effective treatment for liver diseases, and Chinese medicine has achieved significant results in the treatment of liver diseases. This article reviews the application progress of ursin bile powder and ursodeoxycholic acid in liver disease, and hopes to advance the mechanism of ursin bile powder and ursodeoxycholic acid in the treatment of liver disease, which will help its clinical application and new drug development.

1. Introduction:
Liver disease is a general term for liver diseases, including viral hepatitis, alcoholic hepatitis, cirrhosis, fatty liver, liver cancer and other diseases, which seriously threaten human life and health. Bear bile powder is a precious traditional Chinese medicine. There are many related records in ancient Chinese medicine. It plays an irreplaceable role in the treatment of liver disease. Ursodeoxycholic acid is a hydrophilic bile acid and an important pharmacological component of bear bile powder \cite{1}. It is used in a variety of liver diseases with significant curative effects. This article reviews the mechanism of biliary bile powder and ursodeoxycholic acid in the treatment of liver disease.

2. Application of ursodeoxycholic acid in the treatment of liver disease and its mechanism of action

2.1. Fatty liver
The experimenter \cite{2} explored the effects of ursodeoxycholic acid on the biochemical indexes and the expression levels of NF-κB and TNF-α protein in tissues by constructing a NASH rat model to evaluate the efficacy of ursodeoxycholic acid treatment. The results show that ursodeoxycholic acid can effectively reduce various biochemical indicators of NASH and improve its tissue characteristics. This effect may be achieved by inhibiting hepatocyte steatosis and inflammatory cell infiltration, thereby reducing insulin resistance and reducing liver damage.

Ling Lin et al. \cite{3} research on the efficacy of probiotics combined with ursodeoxycholic acid in the treatment of non-alcoholic fatty liver disease found that ursodeoxycholic acid can significantly reduce...
total TC, TG, and low density lipoprotein. Biochemical indicators such as LDL-C, AST, ALT, and FBG have proved that ursodeoxycholic acid can reduce liver damage and improve lipid and blood glucose metabolism. Researchers [4] also observed the role of simvastatin combined with ursodeoxycholic acid in the treatment of non-alcoholic fatty liver with hyperlipidemia. Studies have found that the combination of ursodeoxycholic acid and simvastatin has a good clinical effect in the treatment of non-alcoholic fatty liver with hyperlipidemia, which has positive significance for reducing blood lipids, protecting liver function and improving prognosis.

2.2. Primary biliary cirrhosis

Ursodeoxycholic acid is a commonly used drug for hepatobiliary diseases. It can promote endogenous bile acid secretion, reduce bile acid reabsorption, promote bile metabolism, and dissolve cholesterol stones [5-7]. It is widely used in biliary diseases treatment. Zhang Xiaoyu et al. [8] studied the clinical effect of benzabate (BF) combined with ursodeoxycholic acid (UDCA) in the treatment of primary biliary cirrhosis and the effect of the IL-17 / Th17 ratio in its peripheral blood mononuclear cells. The experimental results prove that the IL-17 / Th17 ratio plays an important role in the pathogenesis of PBC. UDCA combined with BF treatment can more effectively suppress inflammatory cytokine levels and improve liver function and liver fibrosis in patients with PBC.

Xu Liqin et al. [9] studied the effect and mechanism of magnesium isoglycyrrhizinate combined with ursodeoxycholic acid in the treatment of primary biliary cirrhosis. The results showed that the serum levels of TBIL, GGT, TBA, and AST were lower than before. It is proved that the combination of magnesium isoglycyrrhizinate injection and ursodeoxycholic acid can protect the liver and reduce enzymes without the occurrence of adverse reactions.

2.3. Primary liver cancer

Ma Xueqin et al. [10] vaccinated and modeled 18 nude mice to form HepG2 nude mice liver cancer xenografts. They were randomly divided into three groups and given ursodeoxycholic acid derivatives by intraperitoneal injection to calculate the tumor suppression of the three groups Rate, and pathological analysis of liver tissue and expression analysis of liver cancer-derived growth factor (HDGF). The results showed that the dosage of ursodeoxycholic acid derivative was directly proportional to the tumor suppressive effect, which could improve liver pathological conditions, and its tumor suppressive effect might be related to its ability to inhibit HDGF gene expression. Researchers [11] studied the inhibitory effect and mechanism of ursodeoxycholic acid on rat primary liver cancer, and found that ursodeoxycholic acid can inhibit the primary by reducing hMTH1 mRNA expression and oxidative stress in rat liver Liver cancer, reduce serum ALT, AST content.

3. Application of bear bile powder in the treatment of liver disease

Li et al. [12] carried out an experimental study on the treatment of fatty liver rats with bear bile powder, and the results showed that bear bile powder has a positive therapeutic effect in controlling fatty liver rats' liver weight, liver weight, liver pathological status and liver biochemical indicators. Liu Jingjing et al. [13] observed the effect of bear bile powder on ethanol-induced oxidative damage in mouse liver cells, and found that the consumption of GSH, SOD and lipid peroxidation caused by ethanol was significantly reduced after treatment with bear bile powder. It can protect the liver from oxidative damage. When the concentration of bear bile powder was increased to 150 μg / ml, the recovery of GSH could be restored to normal level, and the effect of cell protection was significant. Analysis of its possible mechanism is that it can inhibit the protein kinase inhibitor LY294002 that blocks the signal transduction pathway of PI3K cells, increase the level of protein kinase B (Akt) phosphorylation, and then activate the PI3K pathway in cells, while promoting Nrf2, a key gene that is basically expressed by oxidative stress, enters the nucleus region to increase the glutamate-cysteine ligase (GCL) gene expression and induce GSH synthesis.
Researchers [14] observed the mechanism of action of bear bile powder on middle and advanced liver cancer in rats and found that the area and number of cancer lesions treated with bear bile powder (BBP) can be significantly inhibited, and cell proliferation activity is significantly reduced. To some extent, bear bile powder can delay the progression of liver cancer by inhibiting the value-added activity of cells. Zhao Jinyan et al. [15] observed the effect of bear bile powder on the STAT3 pathway in liver cancer transplanted mice, and found that bear bile powder has a significant effect in inhibiting tumor volume and tumor weight. Studies have shown that bear bile powder inhibits Bcl-2, CDK4, cyclinD1 mRNA, p-STAT3, PCNA, Bcl-2, CDK4, cyclinD1 and other regulatory pathways through promoting Bax expression to inhibit liver cancer cell proliferation and promote its apoptosis.

Quan Mingji et al. [16] observed the inhibitory effect of bear bile powder on dimethylnitrosamine-induced liver fibrosis in rats, and found that compared with the model group, the action of bear bile powder on liver fibrosis rats can reduce serum ALT and AST. Compared with the increase in liver-to-body mass ratio, the facial density of collagen fibers decreased significantly, and the pathological changes of liver tissue in bear bile group were lighter than those in model group. Studies have shown that bear bile powder can effectively inhibit DMN-induced liver fibrosis in rats. The mechanism may be related to inhibiting KC, reducing cytokine secretion, and then inhibiting HSC activation and transformation, and reducing collagen fiber synthesis and secretion. Zhou Jianyin et al. [17] observed the effect of bear bile on diethylnitrosamine-induced liver cancer in rats. The experiment showed that the degree of liver cirrhosis in the bear bile group was lighter, alanine aminotransferase and total bilirubin were significantly reduced, and expression of PCNA and α-SMA genes were significantly reduced. The results show that bear bile powder has a good inhibitory effect on diethylnitrosamine-induced liver cancer in rats.

Researchers [18] used human liver cancer HepG2 cells to establish a nude mouse transplantation tumor model. After subcutaneous transplantation tumor formation, the nude mice were randomly divided into a bear bile powder group and a saline saline gavage group, once a day for 21 consecutive days. Tumors were removed after 3 weeks. The mRNA expression of p21, CDK2, CyclinE, VEGF, and VEGFR2 was detected by RT-PCR. The protein expressions of p21, CDK2, CyclinE, VEGF, and VEGFR2 were detected by immunohistochemical techniques, and the microvessel density (MVD) was detected by CD31 expression. The experimental results show that bear bile powder can significantly inhibit the formation of microvessels in the body. It can also significantly promote the expression of p21 and inhibit the expression of CDK2, CyclinE, VEGF, and VEGFR2. It is proved that bear bile powder can achieve the purpose of treating liver cancer by inducing cancer cell cycle arrest and inhibiting angiogenesis of transplanted tumors.

4. Conclusion and Outlook

The role of bear bile powder and ursodeoxycholic acid in the treatment of liver diseases has been repeatedly confirmed by many experiments. A summary of the diseases and their target targets of bear bile powder and ursodeoxycholic acid in the literature in the past 5 years has been summarized and obtained table 1 and 2. It can be found that (1) Bear bile powder and ursodeoxycholic acid can improve the liver enzyme index and reduce the lipid in various liver diseases, which may lead to the extensive application of bear bile powder and ursodeoxycholic acid in liver diseases; (2) Although ursodeoxycholic acid is an important component of ursodeoxycholic acid in liver diseases, it has a slightly different disease spectrum. Ursodeoxycholic acid is widely used in a variety of liver diseases, while ursodeoxycholic acid is mainly used in cholestatic liver disease and non-alcoholic fatty liver disease; (3) The role of bear bile powder and ursodeoxycholic acid in different liver diseases almost overlap in biochemical indicators, indicating that bears The role of bile powder and ursodeoxycholic acid in liver disease is diverse and complex. The more important role targets and pathways need to be clarified.
Table 1. Summary of diseases and targets of bear bile powder in the literature

| Disease                      | Target                      |
|------------------------------|-----------------------------|
| Liver cancer                 | TNF-α, IL-6 and NF-κB p65   |
| Liver cancer                 | p21, CDK2, CyclinE, VEGF, VEGFR2 |
| Liver cancer                 | Bax, p-STAT3, PCNA, Bel-2, CDK4, cyclinD1 |
| Liver cancer                 | ALT, AST, TP, KC, HSC       |
| Liver cancer                 | PCNA, α-SMA                 |
| Alcoholic liver disease      | GSH, SOD, PI3K, Akt, Nrf2, GCL |
| Fatty liver                  | ALT , ALP, LDH, CHO         |
| Liver Fibrosis               | GPT , TBIL, ALT             |
| Liver Fibrosis               | CD4+, CD8+                  |
| Liver Fibrosis               | ALT, AST, T-CHO, MDA        |
| Alcoholic liver disease      | MDA, GSH, SOD               |
| Cholestatic liver disease    | ALT, AST, TBA               |

Table 2. Statistical table of diseases and targets of ursodeoxycholic acid in literature

| Disease                      | Target                      |
|------------------------------|-----------------------------|
| PBC                          | IL-17, IL-22, TGF-β, Th17, ALT, AST, GGT, ALP |
| PBC                          | TBIL, GGT, TBA, AST         |
| Non-alcoholic fatty liver    | AST , ALT, MDA, SOD, NF-κB, TNF-α |
| Non-alcoholic fatty liver    | TC, TG, LDL-C, AST, ALT, FBG |
| PBC                          | ALT, AST, ALP, TBIL, γ-GGT, IgG, IgA, IgM |
| Non-alcoholic fatty liver    | AST, ALT, TC, TG            |
| Cholestatic liver disease    | Cyp7a1, Cyp8b1, Fxr, Shp, Bsep, Ostβ |
| Non-alcoholic fatty liver    | ALT, GGT, TG                |
| PBC                          | CD41, CD61, PAIg G          |
| Liver cancer                 | ALT, AST, hMTH1mRNA        |

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