

Traditional Medicine in Modern Use: Bupleurum in Treating Liver Fibrosis, Depression, Inflammatory and Endotoxin

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Abstract: Bupleurum is a common traditional Chinese medicine, which has been widely used in China since ancient times. It has antipyretic, analgesic and cholagogic effects. Chinese Bupleurum is a part of the species of Bupleurum belonging to the angiosperma, dicotyledonta, umbelliferae, umbelliferae, amirenae. Indications: wind-heat cold, whooping cough, liver depression and rib pain, rubella, sore nodules, etc. Main chemical constituents: Radix Bupleuri contains volatile oil, SAikosaponins (SS) A, C, D, S and polysaccharides, and flavonoids in stems and leaves. This passage talks about four uses for Bupleurum including treatment to the liver fibrosis, treatment to depression, anti-inflammatory and anti-endotoxin and some researches about them.

1. Introduction

Bupleurum is one of the most commonly used traditional Chinese medicines in China. It was first published in the "Shen Nong's Materia Medica". It has the functions of relieving the surface and relieving fever, soothing the liver and relieving depression, raising Yang Qi, and also anti-inflammatory, analgesic, liver protection or grooming. Liver Qi. Later, it was discovered that Bupleurum can enhance people's immunity, and it has anti-endotoxin activity. However, if it is taken for a long time or in an overdose, it will have toxic side effects to the human body and may cause liver damage.

Zhang Cunti's experience is recorded in "Principles of Famous Doctors": Treating epistaxis, Guo Pengnian Xuanhutaijiang during the Guangxu reign, there was a case of epistaxis due to hard reading day and night, sometimes full of bowls, long-term prescriptions, multiple treatments are not effective, Yan Guo Zhen, prescription of Bupleurum 250g, decoction as a tea frequently, a doctor said: "Bupleurum sex rises and activates the liver yin, how can you use half a catty?" The patient has tried other methods, right. After taking a dose, unexpectedly, the epistaxis stopped, and the exam was rushed as scheduled, and it turned out to be high school.

2. Bupleurum for liver disease

2.1 Treatment to liver fibrosis

Liver cancer is one of the most important causes of human death. It becomes the most fatal malignancy all over the world. As the initial phenomena are not obvious, most patients with liver cancer have entered the middle and late stages when diagnosed. The diffusion of cancer cells causes ineffective clinical treatment. Liver fibrosis is a wound-healing response to the cause of the damage of the liver. It is likely to be transferred to liver cirrhosis or liver cancer. Saikosaponin-d (SSd) is the extraction from Radix Bupleuri which is the dried root of Bupleurum falcatum L.

The levels of ALT and AST in the model group were 60.33 ± 13.72 IU/L and 105.00 ± 47.80 IU/L, and ALT was significantly increased compared with the normal group ($P < 0.01$), and AST also showed an increasing trend. ALT in the prevention group was significantly lower than that in the

model group ($P < 0.01$) ($33.83 \pm 8.68 \text{ IU/L}$), with a decreasing trend in AST, indicating that SSd had a certain effect on improving liver function (See Table 1).

Table.1. Changes of serum ALT and AST in each group

group	n	ALT	AST
Normal group	6	25.33 ± 4.97	89.33 ± 18.06
Model group	6	60.33 ± 13.72	105.00 ± 47.80
SSd prevention group	6	33.83 ± 8.68	80.50 ± 17.07

The model group was compared with normal control group, $P < 0.01$; SSd prevention group compared with model group, $P < 0.01$.

3. Bupleurum is an antidepressant

Depression is a common, chronic, and complex mental illness. It has high morbidity and mortality. According to epidemiological data, the prevalence of depression in China is 3.02%, and depression is accompanied by suicide. The mortality rate is 3.4%, and the worldwide disability rate from depression is about 3.4% to 16%. Chinese medicine believes that depression belongs to the category of depression syndrome, which is mainly caused by excessive anxiety and worry stagnation, liver loss, and drainage, leading to liver qi stagnation, ultimately resulting in an insufficient source of qi and blood biochemistry, and psychosis. Therefore, Chinese medicine's clinical treatment of depression is mainly based on regulating the liver, and reconciliation depression. These two experiments adopt forced swimming of mice and tail suspension of mice were two behaviors of despair mouse depression model. The anti-depression effect of bupleurum was studied. Units

3.1 Mousetail suspension experiment

Each group was carried out 30 minutes after the last administration. The tail end of the mice (2 cm from the tail tip) was pasted on a horizontal wooden stick with adhesive tape to make it in an inverted state, and the head was about 15cm away from the experimental table. Judgment criteria: During the passive suspension period, when the mouse has no activity, it is considered an immobile state. Observe 6 min, and compare the immobility time of each group in the last 4 min.

Table.2. Effect of Small Bupleurum decoction on the immovable time of mouse tail suspension ($n = 10$)

group	dose/g·kg - 1	Dead time/s
blank	-	110 ± 47
Fluoxetine hydrochloride	0.02	57 ± 32
Minor Radix Bupleuri Decoction	9	74 ± 22
	18	60 ± 32
	27	68 ± 18

Note: compared with blank group, $P < 0.01$, $P < 0.05$ (table 2).

Effect on immobile time of mouse tail suspension at 27, 18, and 9 g·kg⁻¹ xiao chai hu Decoction could significantly shorten the immobile time of mouse tail suspension, and the difference was significant compared with a blank group. See table 2.

3.2 Forced swimming experiment in mice

It was conducted 30 min after the last administration. The mice were placed in a water tank with a 20cm height, an 18cm diameter, a 10cm depth, and a water temperature of $(24 \pm 1)^{\circ}\text{C}$ for 6 min allowing the mice to adapt for 2 min. Accumulate immobile time within 4 min after recording (s). Determination of immobility time: the mouse floats on the water surface and does not try to climb out of the tank, but only makes some movements that must keep its head on the water surface.

The experimental results showed that 27, 18 and 9 g·kg⁻¹ of Xiaochaihu Decoction could significantly shorten the immobilization time of forced swimming in mice, and the difference was significant compared with the blank group. Are shown in table 3.

Table.3. Effect of Bupleurum decoction on immobile time of forced swimming in mice (n = 10)

group	dose/g·kg - 1	Dead time/s
blank	-	107 ± 28
Fluoxetine hydrochloride	0.02	74 ± 20
Minor Radix Bupleuri Decoction	9	82 ± 19
	18	79 ± 25
	27	86 ± 16

4. Bupleurum for anti-endotoxin

Scientists have made some progress in the treatment of liver fibrosis, tumors, inflammation and immune regulation with saikosaponins. Obtained by distillation, the Bupleurum injection made from the volatile oil of Bupleurum chinensis as the main active ingredient is clinically mainly used to treat fever caused by various inflammations such as influenza, tonsillitis, and respiratory tract infections, and has a definite effect. Later, when it was discovered that the use of saikosaponins for a long time or overdose would have toxic side effects on the human body, people began to study the toxic effects of Bupleurum (it was found that Bupleurum is the most toxic). The patient's main symptoms such as elevated transaminase, hepatitis, and jaundice are confirmed to be acute liver damage, but the liver function can return to normal after stopping the drug for a period of time. The main symptoms of poisoning are irritability, asynchrony, increased heart rate, shortness of breath, and continuous convulsions.

Studies have shown that the toxic components of Bupleurum volatile oil include α -spinach sterol, 7-stigmasterol, 22-sterol stigmasterol, stigmasterol, paramarigoldol, angelin and so on. Different doses of Bupleurum extract can cause different degrees of liver damage. In vitro anti-endotoxin experiments show that the concentration of Bupleurum spp. extract has a greater impact on the strength of anti-endotoxin. When the concentration of Bupleurum spp. extract is greater than 25% (dilution below 1: 4), it has obvious effects on bacterial endotoxins. Destructive effect; but when its concentration is diluted to below 12.5% (dilution above 1: 8), the anti-endotoxin effect is significantly weakened or disappeared.

Table.4. Comparison of anti-endotoxin effect of extracts from *Bupleurum chinensis* with different concentrations

Concentration	sample cell 1	sample cell 2	sample cell 3	sample cell 4	sample positive tube	sample negative tube
1: 1	-	-	-	-	+	-
1: 2	-	-	-	-	+	-
1: 4	-	-	-	+	+	-
1: 8	-	+	+	+	+	-
1: 16	+	+	+	+	+	-
1: 32	+	+	+	+	+	-
1: 64	+	+	+	+	+	-

In the data table, the sample tube is - will cause damage to the human body, and is + will not cause damage to the human body Use the two-fold dilution method to dilute the limulus reagent dissolved in water into a series of 1: 1, 1: 2, 1: 4, 1: 8, 1: 16, 1: 32, 1: 64 solutions, and take 0.5mL of each dilution, respectively Add 0.5mL of the pre-prepared bacterial endotoxin solution with a concentration of 20EU·mL, shake it well, and keep it in a water bath at (55±2)°C for 30 minutes. Take the above-mentioned endotoxin solution that has been reacted with the drug and 0.1ml (containing bacteria). Endotoxin solution 10EU·mL), add: 0.5EU·mL limulus reagent 0.1ml, 37°C incubate for 60min, make 4 tubes for each concentration at the same time, and make positive and negative controls at the same time.

Table.5. Effect of *B. Chinese* and *B. marginatum* on ear edema of mice (n=10)

Tranches	Dosage	Ear swelling degree
Model	-	6.5 +/- 2.01
Bupleurum high dose group	12	3.4 +/- 2.63
Bupleurum middle dose group	6	4.2 +/- 2.57
Bupleurum low dose group	3	4.6 +/- 2.60
Leaf Bupleurum high dose group	12	4.0 +/- 2.75
Leaf Bupleurum middle dose group	6	5.7 +/- 2.11
Leaf Bupleurum low dose group	3	5.3 +/- 1.49
Prednisone acetate group	5 mg·kg ¹	2.0 +/- 1.63

The crude saikosaponins, saikosaponins, and volatile oil of saikos have anti-inflammatory effects. Saikosaponin (ss) has an inhibitory effect on the inflammatory response caused by a variety of inflammatory agents in normal or no-adrenal rats, and it is effective when administered orally or by injection. Its anti-inflammatory effect involves multiple links: reducing capillary permeability; inhibiting the migration of white blood cells; inhibiting the proliferation of granulation tissue. The anti-inflammatory mechanism of *Bupleurum* is more complicated. Saikosaponin can excite the hypothalamic-pituitary-adrenal cortex endocrine axis, promote the secretion of ACTH by the pituitary, and promote the secretion of adrenocorticotrophic hormone (ACTH) and endogenous glucocorticoid (GC). Renal tissue glucocorticoid receptor (GR) level and GC-GR system function,

inhibit PLA2, Gs, Ts and other inflammatory mediators to achieve anti-inflammatory effects. In addition, it may also directly inhibit the release of inflammatory substances.

5. Bupleurum for anti-inflammatory

The crude saikosaponins, saikosaponins, and volatile oil of saikos have anti-inflammatory effects. Saikosaponin (ss) has an inhibitory effect on the inflammatory response caused by a variety of inflammatory agents in normal or no-adrenal rats, and it is effective when administered orally or by injection. Its anti-inflammatory effect involves multiple links: reducing capillary permeability; inhibiting the migration of white blood cells; inhibiting the proliferation of granulation tissue. The anti-inflammatory mechanism of Bupleurum is more complicated. Saikosaponin can excite the hypothalamic-pituitary-adrenal cortex endocrine axis, promote the secretion of ACTH by the pituitary, and promote the secretion of adrenocorticotrophic hormone (ACTH) and endogenous glucocorticoid (GC) to increase the secretion of ACTH. Renal tissue glucocorticoid receptor (GR) level and GC-GR system function, inhibit PLA2, Gs, Ts and other inflammatory mediators to achieve anti-inflammatory effects. In addition, it may also directly inhibit the release of inflammatory substances.

Saikosaponin can activate pancreatic acinar cell membrane receptors to increase cellular Ca²⁺ concentration, promote the secretion of pancreatic digestive enzymes, and is dose-dependent. Its dose-effect relationship has saturation characteristics. After 10 mol/LSI administration, 1 to 1 After 2 minutes, the secretion rate of the enzyme reached 16 times the base value, and 95% of the secretion promotion effect was completed in 10 minutes. It can be used to treat acute pancreatitis. The secretion of S-enzyme can prevent or reduce the self-digestion of cells caused by blocked secretion.

Take appropriate amounts of Bupleurum and Bupleurum, add 10 times of water to soak for 0.5h, decoct for 0.5h, decoc 3 times in water, combine 3 times of decoction, and concentrate at normal pressure to a thick extract (density 1.15~1.20, 60°C). The sample of Bupleurum Bupleurum is brown extract, and each 1 gram of the extract sample is equivalent to 6.061g of the original medicinal material; the sample of Bupleurum bamboo leaves is a brown-yellow extract, and each 1g of the extract is equivalent to 6.618g of the original medicinal material. When administering, it is calculated as native medicinal materials

The experiment is divided into 8 groups, namely model (isovolume distilled water), prednisone acetate (5 mg·kg⁻¹) and Bupleurum spp. high, medium and low dose (12, 6, 3 g·kg⁻¹) groups and bamboo Ye Bupleurum high, medium and low dose (12, 6, 3 g·kg⁻¹) group. ig administration, once a day, for 5 consecutive days. One hour after the last administration, 0.02mL of xylene was evenly applied to the front and back sides of the right auricle of the mouse. After applying xylene, the cervical vertebrae were removed 20 minutes to kill the mouse. Put a 6 mm diameter earpiece on the same part of the ear, weigh it on an electronic balance, and calculate the ear swelling degree: ear swelling degree = right ear piece weight-left ear piece weight.

The results showed that the auricle swelling of the mice in the Bupleurum high-dose group and Bupleurum chinense high-dose group was significantly lower than that of the model group, and the pain threshold of the mice in the Bupleurum high-dose group and Bupleurum chinense high-dose group was higher than that of the control group. Significantly prolonged, indicating that high-dose Bupleurum and Bupleurum bamboo have anti-inflammatory and analgesic effects.

6. Conclusion

Bupleurum has significant effect in treating the liver cancer as the increase in ALT and AST, and remiss depression through regulating the liver. The research on mice indicating that Bupleurum and Bupleurum bamboo have anti-inflammatory and analgesic effects. And they are clinically mainly used to treat fever caused by various inflammations.

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