Bupleurum falcatum, B. chinense

Indications

Liver disorders, such as hepatitis, fatty liver disease, liver cancer, and cirrhosis; liver toxicity as a result of drugs and alcohol; mushroom poisoning.

Mechanism of Action

Flavonoids in *Bupleurum* are credited with hepatoprotective actions and include rutin and narcissin. Narcissin is the dominant flavonoid in *Bupleurum flavum*, whereas other species may be higher in rutin. Narcissin displays an antioxidant action in liver cells that is similar or stronger than that of silymarin, and it is capable of reducing elevated lactate dehydrogenase and malondialdehyde.[1]

Bupleurum also contains saikosaponins, a group of terpenoid compounds credited with immune-modulating effects. *Bupleurum* saikosaponins A, B, C, and D may inhibit hepatitis viruses in the early phases of the viral life cycle by inhibiting entry into cells without significant cytotoxicity to hepatocytes.[2] Saikosaponin B has particularly been shown to inhibit viral particles and prevent viral attachment and cellular entry in cultured human hepatocytes.[2]

Bupleurum saikosaponins may have cytoprotective effects by alleviating stress on the endoplasmic reticulum, stabilizing and restoring mitochondrial function, inducing cell recovery pathways, and inhibiting apoptosis.[3] Saikosaponins have been shown to prevent excessive proliferation of hepatic stellate cells, promote wound healing, and induce apoptosis. These positive effects are associated with decreases in the expressions of extracellular matrix, platelet-derived growth factor, hepatic collagen deposition, and connective tissue growth factor.[4,5,6] These mechanisms are believed to contribute to antifibrotic effects in acute and chronic liver inflammation.

Additional mechanisms of hepatoprotection include cyclooxygenase (COX) inhibition. COX expression has been found to be increased in animal models of induced liver cancer. Saikosaponin D is a COX inhibitor that contributes to inhibiting liver fibrosis in active disease, and it may also provide chemoprevention in chronic inflammatory diseases of the liver.[7] The proinflammatory cytokine tumor necrosis factor-α was also significantly reduced by *Bupleurum chinense.*[8]

Evidence-Based Research

Animal research suggests that *Bupleurum* can protect the liver from carbon tetrachloride,[6] *tert*-butyl hydroperoxide,[1] and acetaminophen[9] and increase the efficacy of 5 fluorouracil against liver cancer.[10] *Bupleurum* may reduce fibrotic changes in the liver,[5,6] improve obstructive jaundice,[11] and decrease hepatocarcinogenesis in chronic liver inflammation.[7] *Bupleurum* exerts a hepatoprotective effect in

galactosamine-induced liver inflammation in mice, significantly reducing aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, and lactate dehydrogenase activities and increasing glutathione and superoxide dismutase at a dose of 400 mg/kg/day.

Safety in Pregnancy and Breastfeeding

Because of hepatoxicity concerns (when taking *Bupleurum* at high doses), *Bupleurum* is contraindicated in pregnancy and lactation.

General Safety

Despite its hepatoprotective effects, *Bupleurum* can also exert hepatotoxic effects at a *very high* dose and duration, and even induce fatal hepatotoxicity at doses from 50 to 125 g/kg in 1–2 weeks' time in rats.[12] The toxic effects included fatty degeneration at moderate doses, progressing to necrotic lesions at the highest dosages. Alcohol extractions of *Bupleurum* have shown greater hepatotoxicity than water extracts.[13]

Possible liver injury in humans has been reported[14] from *B. chinense* with anecdotal reports of inducing fibrosis, even though research has shown the plant to prevent liver fibrosis. There were reports of renal and liver injury associated with the use of an injectable *Bupluerum* preparation in Japan in the 1980s that combined the herb with interferon and other compounds. The adverse effects were proposed to be the result of hypersensitivity reactions and included two cases of hypokalemia and renal failure associated with the use of an intravenous preparation, one of which was fatal via hypersensitivity shock.[15]

One epidemiological study surveyed >600,000 patients hospitalized for hepatitis B infection and investigated any association between the use of *Bupleurum* and the risk of being hospitalized for liver injury. The researchers reported that the use of *Bupleurum* containing traditional Chinese prescriptions of more than 19 g[16] was associated with an increased risk of being hospitalized for liver disease.

A rat toxicity study investigated three dosages of *B. chinense,* 50, 150, and 300 mg/kg, on hepatic function, renal function, and the metabolism of lipids and carbohydrates. They found a dose-dependent hepatic tissue damage associated with increased liver enzymes and visible hepatic tissue damage.[17] *Bupleurum* at a dose of 1 mg/kg for 4 or 8 weeks was also shown to increase liver enzymes (AST and ALT), immunoglobulins, and antinuclear antibody in the blood and to elevate interferon-γ, interleukin-10, and transforming growth factor-β1 levels in liver tissues, along with necroinflammatory changes seen with histological sampling.[18] In summary, the above-mentioned data suggest caution and close monitoring in patients with hepatitis B who concomitantly use interferon and *Bupleurum.*

Saikosaponins may be altered when *B. chinense* root is baked in vinegar, and their absorption may also be altered. It is possible that this extraction method may increase the liver toxicity risk of *Bupleurum* species.

Dosage

Typical dosages are 100–500 mg QD to BID, but *Bupleurum* species are often combined at 50–200 mg in multiherb formula taken QD to BID.

Traditional Uses

The root of various *Bupleurum* species (*B. chinense*, *B. falcatum*) are well-known as medicinal plants in China and are listed in the oldest Chinese materia medica documents, the Shennong's Herbal. *Bupleurum* was described as having the action of "soothing liver and relieving constraint," useful for improving both frank liver symptoms and improving emotional instability such as depression, anxiety, and phobia. *Bupleurum* is used in folk medicine as an anti-inflammatory and pain remedy.

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