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Editorial

Mechanisms of the beneficial effects of Ger-Gen-Chyn-Lian-Tang on acute and chronic liver injury

Ger-Gen-Chyn-Lian-Tang (GGCLT), an officially standardized mixture of Chinese herbal medicines, consists of Puerariae Radix, Scutellariae Radix, Coptidis Rhizoma, and Glycyrrhizae Radix in a ratio of 8:3:3:2.[1] In this issue of the *Journal of the Chinese Medical Association*, Chang and his colleagues[1] evaluated the possible effects and mechanism of GGCLT on thioacetamide (TAA)-induced hepatic injury and fibrosis in mice. Incremental doses (30 mg/kg/day, 100 mg/kg/day, and 300 mg/kg/day) of GGCLT were orally administered to mice for as long as 6 weeks, similar to the intraperitoneal TAA injection period as noted in Chang et al's[1] study. Conclusively, their study reported that chronic GGCLT treatment effectively ameliorated hepatic fibrosis by decreasing hepatic oxidative stress and modulating transforming growth factor (TGF)-β/TGF-β receptor/smooth muscle α-actin signaling in TAA mice.

Cumulative studies had reported the preventive effects of Chinese medicine in experimental models and patients with chronic hepatitis.[2–9] The first active component of GGCLT, pueratin (diadzein 8-C-glucoside) is the major isoflavonoid derived from the Chinese medical herb *Radix puerariae* (kudzu root). In China, *R. puerariae* is known as GeGen, and has been used as a traditional medicine for treating various diseases.[2–6] The protective mechanisms of puerarin, at least in part, are related to its ability to increase superoxide dismutase activity, decrease lipid peroxidation, and enhance fibronolysis.[3] In mice, pretreatment with puerarin prior to administration of carbon tetrachloride (CCl_4) substantially prevented the elevation of liver function and hepatic malondialdehyde (oxidants) formation in a dose-dependent manner. In addition, pretreatment with puerarin significantly prevented both the depletion of reduced glutathione (antioxidants) content and the decrease in glutathione S-transferase activity, and histological liver damage severity in the liver of CCl_4-intoxicated mice.[4] In rats with chronic alcohol-induced liver injury, the liver function test and proinflammatory cytokines were significantly reduced following puerarin treatment. In addition, the endogenous levels of tumor necrosis factor-α (TNF-α) and nuclear factor-κB (NF-κB) proteins in the liver tissue were effectively decreased following the puerarin treatment. Together, these findings demonstrate that puerarin mediates hepatoprotection against alcohol-induced liver injury by the inhibition of inflammatory response and downregulation of the TNFα/NFκB pathway, thereby maintaining metabolic homeostasis in the liver.[5] Additionally, chronic puerarin treatment inhibits endotoxin gut leakage, Kupffer cell activation, endotoxin receptors expression, and alleviate chronic alcoholic liver injury in rats.[6]

The second active component of GGCLT, baicalin is a major bioactive flavonoid isolated from the radix of *Scutellaria baicalensis* GeorGi, which is widely used in traditional Chinese medicine to treat inflammation.[7] In mice, acute baicalin pretreatment protected against lipopolysaccharide/D-galactosamine-induced liver injury, including dose-dependent alleviation of mortality and hepatic pathological damage, decrease of aspartate aminotransferase/alanine aminotransferase release, inhibition of NFκB activity to reduce TNF-α production and increase antioxidants.[8] Moreover, baicalin dose-dependently increased heme oxygenase (HO-1) protein expression and activity. Further, inhibition of HO-1 activity significantly reversed the protective effect of baicalin against lipopolysaccharide/D-galactosamine-induced liver injury.[8] Furthermore, acute baicalin treatment inhibited the typical CCl_4-induced liver damage portal inflammation, centrizonal necrosis, and Kupffer cell hyperplasia, The beneficial effects of baicalin protect hepatocytes by inhibition of the proinflammatory mediators, downregulation of TNF-α/inducible nitric oxide synthase (iNOS) and upregulated HO-1 in mice.[9] The antifibrotic effects of baicalin had also been reported to act through the depression of peroxisomal proliferator-activated receptor γ in hepatic stellate cells.[10]

The third active component of GGCLT, berberine is an active compound in Coptidis Rhizoma (Huanglian) with anti-inflammatory and antioxidative stress effects.[11] It had been reported that acute berberine treatment possesses hepatoprotective effects against CCl_4-induced hepatotoxicity by increasing the hepatic superoxide dismutase activity.[11] *In vitro* study suggested that berberine effectively prevented CCl_4-induced liver fibrosis in mice by inducing cell cycle arrest in G1 phase and a decrease in the number of activated hepatic stellate cells.[12]

Licorice root is an herbal preparation that has been used to reduce liver injury in a number of clinical disorders.[13] The forth active component of GGCLT, glycyrrhizin is the

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principal triterpene component of licorice root that shows beneficial effects for patients with chronic hepatitis C.[13] It had been reported that acute administration of glycyrrhizin alleviates CCl_4-induced acute liver injury, and this protection is likely to be due to the induction of HO-1 and downregulation of proinflammatory mediators.[14] Potenlini is an injectable compound whose active component is glycyrrhizin, which is extracted from licorice. The results suggest that potenlini can inhibit the NFκB binding activity in CCl_4 and ethanol-induced chronic liver injury and cirrhosis.[15]

Taking together, the protective effects of four components, including puerariae, baicalin, berberine, and glycyrrhizin, of GGCLT in acute and chronic liver injury are mainly mediated by the inhibition of hepatic oxidative stress, TNFα/NFκB/iNOS signal pathway, inflammatory mediator release, activated HSCs and upregulation of HO-1. In the Chang et al[1] study, chronic GGCLT treatment prevented liver fibrosis by the inhibition of various profibrogenic markers including oxidative stress, NFκB, TGFβ (receptor), and smooth muscle α-actin (maker of the activated HSCs) in a TAA mice model. Notably, the chronic effects of GGCLT in the TNFα/iNOS and HO-1 signal pathway as well as inflammatory mediators release should be further explored in future studies in a TAA mice model. Nonetheless, the additional traditional herbal medicines reported by Chang et al[1] are noteworthy as potential agents to treat hepatic fibrosis.

Conflicts of interest

The author declares that there are no conflicts of interest related to the subject matter or materials discussed in this article.

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