

Integrated Therapy for Chronic Hepatitis in Taiwan

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In Taiwan, conventional treatment for chronic hepatitis B (HBV) and chronic hepatitis C (HCV) infections has been well-defined for more than 30 years [1,2] and the risk of comorbidity with hepatic cirrhosis [3,4] and hepatic carcinoma [5-8] has been controlled for via interferon-based therapy with ribavirin. However, some patients who have received the interferon-based therapy have experienced side effects such as flu-like symptoms (headache, tiredness, and weakness), gastrointestinal discomfort (nausea, vomiting, diarrhea, and loss of appetite), fever, trouble sleeping, and low levels of white blood cells [9-13]. Hence, many patients who have refused the interferon-based therapy or been deemed unable to receive it have sought to relieve the discomforts of chronic hepatitis by integrating conventional medicine with Chinese herbal medicine (CHM) [14].

In a randomized, controlled six-week trial of a modified Chinese herbal formula, Kuan-Sin-Yin decoction (KSY) [15] with 57 HBV patients, the AST and ALT serum levels of those receiving full-dose KSY were observed to decrease significantly more than those of the control group, who received a 16-times dilution of KSY. Specifically, the treatment group's AST and ALT fell by 25.2% and 17.8%, respectively, more than the control group's did. KSY was also used to treat 70 HCV patients, in a double-blind, randomized and placebo-controlled six-week trial [16]; the results revealed that KSY reduced AST and ALT serum levels by 20 IU/L ($p = 0.027$ and 0.047), and significantly decreased the HCV viral load, by 0.3 log units ($p = 0.047$).

The Rong-Yang team from Taipei Veterans General Hospital utilized Taiwan's national health insurance research database (NHIRD) [14] to identify the Chinese herbal formulae and single herbs that have been most popularly used for treating patients with chronic hepatitis. The top five formulae were Long-Dan-Xie-Gan-Tang, Jia-Wei-Xia-Yao-San, Xiao-Chai-Hu-Tang, Yin-Chen-Wu-Ling-San, and Chai-Hu-Qing-Gan-Tang, and the top five single herbs were Dan-Shen (*Salvia miltiorrhiza*), Yin-Chen-Hao (*Artemisia capillaris*), Hu-Gon (*Polygonum cuspidatum*), Huang-Shui-Cha (*Solanum incanum*), and Yu-Jin (*Curcuma aromatica*). Additional research using the NHIRD revealed a high prevalence of CHM use among HCV patients in Taiwan, as well as its specific patterns [17]: including that Jia-Wei-Xiao-Yao-San and Dan-Shen were the most commonly used Chinese herbal formula and Chinese single herb. Based on these preliminary findings, the Rong-Yang team conducted a 12-week randomized, double-blind, placebo-controlled crossover trial of Rong-Yang-Jyh-Gan-Tang (RYJGT) among 36 HCV patients [18]. RYJGT is composed of Long-Dan-Xie-Gan-Tang, Jia-Wei-Xia-Yao-San, Dan-Shen, and Hou-Po (*Magnolia officinalis*) in a ratio of 3 gm : 10 gm : 1.5 gm : 0.5 gm. The trial results showed that 51.7% of the HCV patients had decreased HCV RNA serum levels after RYJGT treatment, as compared to just 25.8% in the placebo group ($p = 0.036$). Moreover, subgroup analysis from traditional Chinese medicine pattern showed that those members of the "Damp-Heat" and "Liver Qi Depression" patient subgroups who underwent RYJGT treatment experienced significant decreases in their serum HCV RNA titer, while their placebo-treated counterparts did not.

Another team investigated whether a combination of lamivudine with various CHMs could lower the risk of mortality in HBV patients, and found that CHMs do have the potential effect for reducing death rate (adjust HR: 0.45, 95% CI: 0.27 - 0.76, $p < 0.01$) [19]. The same study also suggested that among all the integrated treatments tested, the one that included Jia-Wei-Xia-Yao-San carried by far the lowest risk (adjust HR: 0.26, 95% CI: 0.08 - 0.83, $P = 0.02$).

Based on the above NHIRD studies and clinical trials, it would appear that therapies integrating CHM and conventional medicine may be efficacious for HBV and HCV patients, and that such therapies could reduce their risks of mortality. However, some chronic hepatitis patients who received CHMs containing Chai-Hu (*Radix bupleuri*) experienced a high risk of liver injury, with the odds ratios for Xiao-Chai-Hu-Tang, Long-Dan-Xie-Gan-Tang, and Jia-Wei-Xia-Yao-San being 1.90 (95% CI: 1.30 - 2.77), 3.52 (95% CI: 1.56 - 7.98), and 2.07 (95% CI: 0.72 - 5.92), respectively [20]. Moreover, such risk was observed to increase by 2.19 (95% CI: 1.66 - 2.89) with the addition of each 19 gm dose of Chai-Hu. Hence, larger-scale surveys and well-defined clinical trials of the efficacy and safety of the above CHMs should be conducted.

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