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# Is There a Role for a Traditional Herbal Formula in the Treatment of Hepatitis C?

## A Review of *Sho-saiko-to* (Xiao-chai-hu-tang)

Jenny Lam

Hepatitis C virus infection is prevalent in the United States, with an estimated 3.9 million people living with the disease.<sup>1</sup> In 85% of cases, acute hepatitis C proceeds to chronic infection, 20-25% progress to cirrhosis, and of these 5% may develop hepatocellular carcinoma (HCC) annually.<sup>2</sup> It is the most frequent indication for liver transplantation, however this does not preclude disease recurrence.<sup>3</sup> The pathogenesis of hepatitis is related to the immune-mediated hepatocyte injury secondary to cytotoxic T-cell activation and cytokine release. Inflammation activates parenchymal stellate cells, initiating a fibrogenic cascade. The chronic cycle of oxidative damage, inflammation, necrosis, fibrosis and regeneration raises the potential for malignant transformation.<sup>4</sup> While cirrhosis is significantly associated with hepatocellular carcinoma, it has been shown that non-cirrhotic livers with histologic evidence of advanced fibrosis have also developed HCC.<sup>5</sup> Levels of fibrosis and inflammation are prognostic factors for end stage liver disease. Thus, if the host immune and fibrogenic response were contained, the progression of hepatitis C infection to HCC could be slowed or halted.

Current treatment options include interferon/ribavirin dual therapy, which has a 55% overall response rate, and the newer triple drug therapy regimen with novel antivirals telaprevir and boceprevir which has produced viral response in 30% of previous nonresponders to interferon /ribavirin dual therapy.<sup>2</sup> These newer drugs have improved outcomes for hepatitis C patients dramatically but there is still a significant number who are either intolerant to the side-effects of interferon which include bone marrow suppression, depression, and rash,<sup>6</sup> or do not respond to triple therapy, especially those with hepatitis C genotype 1.<sup>7</sup> Alternative therapies may have a place in treating these patients whose treatment is contraindicated or ineffective.

Sho-saiko-to (SST), also known as Xiao-chai-hu-tang (TJ-9), is a traditional herbal formula that has been wide-

ly used in China and Japan for many centuries in treating chronic liver disease. SST comprises a mixture of seven herbs in a 7.5 g daily formulation: *Bupleurum falcatum*, *Pinellia ternate*, *Scutellaria baicalensis*, *Zizyphus jujuba*, *Panax ginseng*, *Glycyrrhiza*, and *Zingiber officinale*.<sup>8</sup> Many in-vitro and animal studies published in Japan have shown anti-oxidative, anti-proliferative and anti-inflammatory effects.<sup>9</sup> However, randomized controlled trials in humans are few in number.

In-vitro, SST was shown to induce apoptosis in HCC and cholangiocarcinoma cell lines, inhibit cell proliferation and DNA synthesis, and induce cell cycle arrest in phase G0 and G1.<sup>10</sup> In rat studies, SST decreased lipid peroxidation with subsequent decreases in inflammatory response, hepatic stellate cell activation and procollagen formation.<sup>11,12</sup> This is theoretically supposed to decrease fibrosis and cirrhosis, as well as the cycle of hepatocyte injury and regeneration, leading to a decrease in preneoplastic lesions. Rats with experimental hepatic fibrosis secondary to DMN and PS treated with 1.5% TJ-9 showed a reduction in fibrosis,  $\alpha$ -SMA (marker of stellate cell activation), decreased BrDU incorporation (DNA replication), inhibition of oxidative burst and lipid peroxidation. The flavonoids baicalein and baicalin were isolated and identified as active compounds, shown to suppress superoxide anion production.<sup>13</sup> SST-fed rats experienced reduced reactive oxygen-mediated DNA mutations and decreased rates of hepatocarcinogenesis compared to controls.<sup>14</sup> Several rat models of hepatitis induced by other hepatotoxins such as CCl<sub>4</sub> and D-galactosamine have shown decreased levels of transaminases, fatty degeneration and necrosis.<sup>9</sup>

A multicenter randomized controlled trial in humans by Hirayama et al. in 1989 followed 220 patients with chronic active hepatitis by liver biopsy randomized to either SST for 12 weeks or placebo with cross-over to SST.<sup>15</sup> Hirayama and colleagues found that mean AST and ALT levels were significantly ( $P < 0.05$ ) decreased

in the treatment group compared to placebo group by 12 weeks. After cross-over, the difference was nullified by the end of week 24. No difference in HBeAg decrease or anti-HBe increase was found at any time between the two groups. This study would have benefited from a longer intervention period, since there was fluctuation in values in both groups over the short term. In addition, the specific statistical tests used were not clearly defined.

In a 1995 landmark prospective randomized trial by Oka et al., 260 patients with cirrhosis were given the SST herbal formula in addition to conventional drug therapy and compared to control group with conventional drug therapy alone. A significant ( $P=0.02$ ) difference was found in the incidence of hepatocellular carcinoma and survival over 5 years ( $P=0.04$ ) in patients without HBsAg, most of whom were HCV positive.<sup>16</sup> When HBsAg status was not taken into account, there was no difference in overall incidence between trial and control groups. Conventional therapy was not defined in the study and the control group was not given placebo. Therefore, this may not discount the effect of believing that one is receiving effective treatment.<sup>17,18</sup>

In the United States, a single arm phase II trial of 24 patients with hepatitis C who were not candidates for interferon therapy received 2.5 g SST 3 times daily for 12 months, and 67% experienced decreased AST, 75% experienced decreased ALT, and 38% had improved Knodell histological score.<sup>19</sup> Viral load response was mixed, with 7 patients showing reductions, 10 increases and 7 indeterminate. 5 patients had a two-point improvement in histological score on biopsy, which was deemed to be an adequate response rate to warrant larger phase III trials. This study was limited by small sample size, lack of control group, and high drop out rate (24 subjects completed of 41 enrolled). The high drop out rate may result in confounding if the patients who dropped out and the patients who completed the study differ in key respects.

SST should be treated as a drug with potential interactions and side effects. It has shown to decrease xanthine oxidase and CYP1A2 activity and therefore may result in unknown herb-drug interactions.<sup>20</sup> It is not without adverse effects, as case reports have noted increased rates of interstitial pneumonitis and a risk

of hepatic injury due to the herb formula itself.<sup>21</sup> SST can be used in addition to but should not be a substitute for conventional therapy or delay treatment initiation. It is an option for patients who do not qualify for standard treatments. Thus far, clinical studies of SST have suffered from limitations and weak statistical interpretation. Additional adequately powered, randomized controlled studies are needed to study the effects of sho-saiko-to on chronic liver disease.

Herbals and botanicals historically have brought about numerous major drugs used to treat disease, ie. digoxin (digitalis), statins (red yeast), and atropine (belladonna) to name a few. Old Eastern medicinal remedies which have undergone centuries of herbal practitioners' observations are an underutilized source for clinical study under current scientific standards. It is often difficult to evaluate the effects of herbals since they are composed of several compounds in varying doses.

The sale of over-the-counter herbals and supplements is largely an unregulated market, and consumers today are increasingly taking these products for their purported disease-fighting properties. It is imperative for physicians to be aware of this trend, as herbals can have interactions with prescribed medications and delay appropriate care.

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