**A Classic Herbal Formulation’s Clinical Research for Modern-Day Liver Disease**

by Jipu (Dan) Wen, MS, MD and Stephanie Pina, ND

**Introduction**

The growing use of herbal medicines in treating conventional pathology has increased tremendously in the last few decades, sparking interest from the Western scientific community. In an attempt to understand individual herbs and formulas, research has been focused on identifying active single chemical constituents and possible herb/drug interactions for specific modern indications. Sho-saiko-to (SST), a classical Chinese herbal formula, also known as Xiao Chai Hu Tang and Minor Bupleurum, has been extensively researched by the Chinese and Japanese scientific pharmaceutical communities. This traditional formula has emerged from the pages of ancient texts as a formula with therapeutic benefits for chronic liver disease. Over 100 English research publications have documented SST’s anti-inflammatory, antifibrotic, and chemopreventative effects on chronic liver disease illnesses, including Hepatitis B and C. SST is currently being investigated in two, ongoing phase II Investigative New Drug (IND) clinical studies in the United States. The first, at Memorial Sloan-Kettering Cancer Center in New York, has reported preliminary data for nonresponding patients or those with contraindications to interferon-based therapy for hepatitis C. A second trial at the University of California at San Diego involves patients with liver cirrhosis caused by hepatitis C.

**Traditional Source of a Potent Formula**

Prior to its use in liver disease, SST was first described and referenced over 30 times in the ancient class Chinese textbook, *Shang Han Lun*, written by Zhang Zhong Jing around 200 AD during the Han Dynasty. This text is a source for classical Chinese herbal formula strategies based on the principle that disease comes from pathogens entering six layers of the body. Correct herbal prescription was determined by the stage of illness, location and nature of pathological changes, strengthen of the pathogen, and disease development. Recorded under the Chinese pinyin name, *Xiao Chai Hu tang*, this seven-herb formula was used to treat diseases found in the Shaoyang stage with symptoms such as alternating chills and fever, nausea and vomiting, pain and fullness in the chest and hypochondratic area, poor appetite with bitter taste in the mouth, and irritability.

A possible link to the formula’s traditional indications and the treatment of chronic liver disease may lie with the connection between the formula’s classical indications and those symptoms commonly associated with Hepatitis B and C, as well as known adverse reactions to interferon used in its treatment. Xiao Chai Hu Tang, used by Japanese Kampo herbalists, has become a common treatment for a variety of disorders, including Liver/Gallbladder conditions in modern-day traditional Chinese medicine practice. Sho-saiko-to was one of the first herbal formulas allowed under prescription by physicians and pharmacists by the Japanese Ministry of Health, Labor, and Welfare in 1970s. With Japanese national health insurance coverage of “approved” herbal formulas, research into SST’s active constituents and their effects on liver disease increased, and by the end of the last century, 1.5...
Researchers have demonstrated that SST contains active components that can address chronic liver disease. For example, glycyrrhizin, a triterpenoid saponin extract from licorice root, reduced serum aminotransferases both in vitro and in vivo, including aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and it has been shown to improve hepatic fibrosis.5,6 Baicalin, a major flavonoid in baical skullcap, has antiproliferative and antifibrotic effects when tested in rats with cirrhosis.7 Another flavonoid in baical skullcap, baicalein, has antiproliferative and antifibrotic effects when tested in rats on an aminotransferase (ALT), and it has been shown to suppress acute hepatic injury and bring about an early recovery in liver function.8

Advanced-stage liver disease leads to fibrosis, due to an overaccumulation of extra-cellular matrix, in which hepatic stellate cells play a central role in the pathogenesis. Many growth factors and cytokines are involved in the activation of hepatic stellate cells, including transforming growth factor (TGF-alpha, TGF-beta1), platelet-derived growth factor, interleukin (alpha, IL-1 and beta, IL-6), and tumor necrosis factor (TNF-alpha). The antifibrotic effect of SST is associated with the downregulation of the mRNA expression of procollagen alpha1 types (I) and (III) and with tissue inhibitors of metalloproteinase TIMP-1 in liver tissue.9 SST also increased the matrix metalloproteinases MMP-2 and MMP-13 activities with reduced TIMP-1,2 activities on hepatic stellate cells, possibly via the P38 pathway.10 SST also stimulated the production of TNF-alpha to inhibit Ito cell proliferation and collagen formation.11

SST has demonstrated significant immunomodulatory activity. In vitro studies demonstrate that SST can induce production of interleukin-1beta, interleukin-6, interferon-γ, tumor necrosis factor-α, and granulocyte-macrophage colony-stimulating factor.12,13 In cultured splenocytes and hepatic mononuclear cells, SST increased CD4/CD8 ratio via a decrease of CD8+ T-cell counts with no effect on CD4+ T-cell counts.14 The chemopreventative effect of SST has been demonstrated in animal studies. The increased level of mRNA expression of cytochrome P-450 enzymes in the liver was observed in association with SST administration.15 In animal models, SST was shown to prevent liver injury and promote liver regeneration. Sakaïda et al. induced fibrosis in rats by a choline-deficient, L-amino acid-defined diet. Using this model, the fibrotic rats treated with SST showed less fibrosis as indicated by reduced liver hydroxyproline and a smaller increase in serum hyaluronic acid compared with control animals and thereby developed fewer preneoplastic lesions.16 The high and low molecular mass fractions of SST extract have been studied in a murine, immunologically induced liver injury model. It was shown that both fractions reduced aminotransferase (AST and ALT) levels and the nitric oxide level in serum caused by the liver injury.17 A DNA adduct by reactive oxygen species, 8-Hydroxy-2'-deoxyguanosine (8-OHdG), is known as a parameter of genetic risk for hepatocarcinogenesis (liver cancer). In a diethylaminoethylcellulose, hepatocarcinogenesis model of rats,

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Table 1. Herbs in Sho-saiko-to

<table>
<thead>
<tr>
<th>English Name</th>
<th>Latin Name</th>
<th>Family</th>
<th>Chinese (Pinyin)</th>
<th>Japanese</th>
<th>Active Compound(s)*</th>
<th>Plant Part</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupleurum</td>
<td>Bupleurum falcatum L.</td>
<td>Apiaceae</td>
<td>chai hu</td>
<td>saiko</td>
<td>saikosaponin a, b, c, d</td>
<td>root</td>
</tr>
<tr>
<td>Pinellia</td>
<td>Pinellia ternate Breitenbach</td>
<td>Araceae</td>
<td>ban xia</td>
<td>hange</td>
<td>homogenisic acid, choline</td>
<td>tuber w/ cork layer removed</td>
</tr>
<tr>
<td>Baical skullcap</td>
<td>Scutellaria baicalensis Georgi</td>
<td>Lamiaceae</td>
<td>huang qin</td>
<td>ougan</td>
<td>baicalin, baicalin</td>
<td>root w/ periderm removed</td>
</tr>
<tr>
<td>Asian ginseng</td>
<td>Panax ginseng C.A. Meyer</td>
<td>Araliaceae</td>
<td>ren shen</td>
<td>ninjin</td>
<td>ginsenoside, panaxic acid</td>
<td>root w/ rootlets removed</td>
</tr>
<tr>
<td>Licorice</td>
<td>Glycyrrhiza uralensis Fisch.</td>
<td>Fabaceae</td>
<td>gan cao</td>
<td>kanzou</td>
<td>glycyrrhizin</td>
<td>root/stolon</td>
</tr>
<tr>
<td>Ginger</td>
<td>Zingiber officinale Rosc.</td>
<td>Zingiberaceae</td>
<td>sheng jiang</td>
<td>shokyo</td>
<td>gingerol, shogoal</td>
<td>root/rhizome</td>
</tr>
<tr>
<td>Jujube</td>
<td>Zizyphus jujube var. inermis Rehder</td>
<td>Rhamnaceae</td>
<td>da zao</td>
<td>daiso</td>
<td>cyclic AMP</td>
<td>fruit</td>
</tr>
</tbody>
</table>

*Active compounds are presumed as primary; in many cases, multiple compounds and/or groups of compounds are believed to exert pharmacological activity in plants and/or plant extracts. Wen, J. Sho-saiko-to: A clinically documented herbal preparation for treating chronic liver disease. HerbalGram, 2007;73:36.
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SST prevents hepatocarcinogenesis in association with inhibition of 8-OHdG formation.22

SST also plays a role in the process of liver regeneration. In a rat model of 70% partial hepatectomized and dimethylnitrosamine-induced liver-injury, SST was shown to induce liver regeneration by increasing the production of hepatocyte growth factor (HGF) and suppressing the production of transforming growth factor-beta (TGF-beta) in the liver and spleen of partial hepatectomized rats.23

Treating Chronic Liver Disease with Sho-saiko-to

SST has been used primarily for treating chronic Hepatitis B patients in Japan. In a randomized trial conducted in Japan in the 1980s, 222 patients with chronic active Hepatitis B diagnosed by biopsy received either SST or placebo for 12 weeks. All patients were off other therapies for at least three months before starting treatment. There were statistically significant differences between groups in AST and ALT, though not gamma-glutamyl transpeptidase (γ-GTP) or cholesterol. There was an increase in Anti-HBeAg antibody (HBeAb) during treatment in the SST but not in the placebo group, although this difference did not reach statistical significance.24 A follow-up study of five years of treatment with SST on 98 Hepatitis patients (59 with hepatitis B and the rest, non-A non-B) revealed similar results.25 Serum levels of AST, ALT, and γ-GTP were significantly reduced. An improvement of liver function was observed in 78% of the Hepatitis B patients and 67% of the non-A, non-B Hepatitis. An uncontrolled trial of SST for Hepatitis B in children reported that seven of 14 became Hepatitis 'e' antigen (HBeAg)-negative at the end of one year. This was reported to compare favorably with the expected clearance rate of 22%.26 The presence of HBeAg in chronic infection is generally considered indicative that hepatitis B virus is actively reproducing, and there is a higher probability of liver damage.

The therapeutic effect of SST in combination with Hepatitis B vaccination in a Hepatitis B carrier has been evaluated in HBV-transgenic mice that expressed similar levels of HBV-related antigens and HBV DNA. The animals received either a SST-enriched diet or a monthly injection of vaccine containing Hepatitis B surface antigen (HBsAg), or both, for 12 consecutive months. The combination therapy induced the completely negative testing for HBsAg on all tested animals after 12 months of treatment with increased levels of IgM, IgG, and antibodies in the spleen lymphocytes. These data confirmed the therapeutic role of SST during HBV infection and inspired optimism of a widespread use of SST during immune therapies.27

Immunomodulation of SST seems to have played a key role in its therapeutic effect on Hepatitis B. The peripheral blood mononuclear cells from eight patients with chronic active Hepatitis B were used with

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**Figure 1. Liver Function Tests at Baseline and After 12 Months of SST Treatment**

**Trend of AST**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 months</th>
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<tbody>
<tr>
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<tr>
<td>0</td>
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</table>

Note: AST improved in 10 patients and worsened in 5 patients.

**Trend of ALT**

<table>
<thead>
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<th></th>
<th>Baseline</th>
<th>12 months</th>
</tr>
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<tbody>
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Note: ALT improved in 11 patients and worsened in 4 patients.

Source: Published as poster presentation at the Annual Society of Integrative Oncology Conference.21
recombinant HBcAg and purified HBsAg. In vitro administration of SST (50, 100, and 300 micrograms/ml) was found to enhance both IFN-gamma and antibody production dose-dependently. SST was able to modulate both cellular and humoral immune responses specific for HBV-associated antigens.

The initial result of the Hepatitis C trial was reported by Memorial Sloan-Kettering Cancer Center in November 2005, using an SST preparation by Honso Pharmaceutical Co., Ltd., Nagoya, Japan, H09. According to the design of the trial, 31 Hepatitis C patients who were non-responders to interferon therapy received SST granules at 2.5 grams three times daily for 52 weeks. Among the 15 patients who completed the study, reductions in ALT were observed in 11 patients and AST in ten patients (Figure 1). This is consistent with the findings by Japanese researchers for SST's anti-inflammatory effect. The reduction of viral load was observed in five of ten detectable patients. The reduction of viral load clinically suggested that SST may also possess direct anti-viral effects. Further studies are needed to confirm these suggested findings. Nine of the detectable ten patients had genotype 1 infection, which does not respond well to interferon therapies. No serious adverse events have been attributed to SST among all 21 patients who enrolled in the trial.

In a controlled study, 80 patients with interferon-resistant Hepatitis C were treated with SST plus unspecified “conventional medicine” or conventional medicine alone. The patients were followed for seven years. During this time, five patients on SST experienced normalization of liver enzymes in full. Enzymes normalized in only one control patient, and none of the controls seroconverted. Conversely, five controls vs. one on SST therapy, progressed to hepatocellular carcinoma.

In an in vitro study on human cells, the effect of SST on production of Interleukin-12 (IL-12), an important regulatory cytokine that initiates and regulates cellular immune responses, on circulating mononuclear cells from 11 HCV-positive liver cirrhosis patients and 12 healthy subjects were studied. The levels of IL-12 produced by the patients’ fractions were significantly lower than those produced by healthy subjects. However, when SST was added to the cultures, the IL-12 production levels in both cell fractions increased approximately threefold, and the levels from the monocyte/macrophage fraction were almost the same as those from healthy subjects. Furthermore, this effect of SST was attributed to baical skullcap root and licorice root, two of SST’s seven herb constituents. Similar findings were reported on adjusting the decreased IL-10 production and the increased IL-4 and IL-5 production of mononuclear cells from Hepatitis C patients by SST. This research suggests that regulation of the cytokine production in patients with Hepatitis C with SST may be useful in the prevention of disease progression.

There is evidence that SST might benefit Hepatitis patients by preventing progression to HCC, a therapeutic action often referred to as chemoprevention. A large prospective study was conducted in Japan in the late 1980s and published in Cancer in 1995 in “the first completed randomized controlled trial of chemoprevention of HCC.” In that trial, 260 patients with cirrhosis were randomized by age, sex, Hepatitis B antigen status, and liver function to treatment with SST or control. HCC was the primary endpoint and was confirmed by angiography, computed tomography, and biopsy. Patients were followed for five years with bimonthly alpha-fetoprotein measurements and quarterly ultrasonography. SST led to a one-third reduction in the incidence of HCC (23% vs. 34%, \( P = 0.071 \)) and a 40% reduction in deaths (24% vs. 40%, \( P = 0.053 \)). The five-year cumulative incidence of HCC was significantly lowered (22% vs. 39%, \( P = 0.024 \), SST group, \( n = 111 \), control group, \( n = 106 \)) by SST among patients without HBsAg, most of whom had anti-C-100-3 antibodies; therefore, it was suggested that SST was particularly effective for patients with Hepatitis C infection.

Reported Side Effects of Sho-saiko-to
SST has been used in China and Japan for hundreds of years without reported major side effects. The only serious adverse event reported in the literature in the past two decades has been pneumonitis (inflammation of the lungs), which was reported only in Japan. The percentage of reported pneumonitis has been relatively small, but worthy of note, as described below.

The first case of the side effect of pneumonitis was reported in Japan in 1989. A 71-year-old woman was admitted to a hospital with pneumonia. The patient complained of dry cough, fever, and severe dyspnea (difficult breathing). Fine
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crepitation (crackling sound) was heard on physical examination of the chest, and a chest X-ray film revealed diffuse reticulonodular shadows in both lung fields. After ceasing all medications, including SST, patient complaints, laboratory data, and chest X-ray were markedly improved. Microscopic examination of transbronchial lung biopsy specimens showed interstitial pneumonitis. The results of a lymphocyte stimulation test were positive for SST. The patient received the challenge test with 2.5g SST twice and developed high fever and dyspnea with hypoxia (low oxygen levels), while the chest X-ray film also revealed diffuse infiltrative shadows similar to that on admission. It was confirmed that this was the first reported pneumonitis due to SST.  

In an analysis of a major manufacturers’ drug monitoring system, SST-related pneumonitis in Hepatitis patients was reported in 74 patients, which is approximately one in 20,000, leading to eight deaths. Among the patients who died, most had an underlying lung disease, had been elderly, had been taking SST longer after the onset of pneumonitis, and had more severe hypoxemia (a condition with low oxygen levels in the blood). As a result of the reported side effect, in 1992, the Japanese Ministry of Health, Labor, and Welfare mandated all SST manufacturers to take a precautionary sentence on the product insert to reflect the potential pneumonitis side effect. It was revised in 1994 to include the contraindication of SST with interferon.  

Interstitial pneumonia has been a side effect of treatment with interferon, and SST may enhance this side effect. Interferon causes neutrophils, important cellular mediators of pulmonary fibrosis, to accumulate in the lung. SST alone may not injure lung tissue, but it increases the effect of interferon. Interestingly, in an early study, intraperitoneal administration of SST in mice induced endogenous secretion of interferon alpha/beta.  

When stimulated by some antigen, SST may overstimulate the neutrophils. Granulocyte elastase and oxygen radicals released from activated neutrophils may damage lung tissue. In another report of five cases, pneumonitis has occurred more frequently with a combination therapy of SST with interferon than when each treatment was given alone.  

Conclusion

The classical herbal formula Sho-saiko-to is one of the most researched herbal formulas within the Japanese and Chinese scientific communities. The clinical studies have shown benefits of the herbal formula for chronic liver diseases such as Hepatitis B, C, and liver cirrhosis. These results may offer another treatment option for the prevention of progression of hepatitis to HCC where other conventional therapies are limited. Practitioners should monitor patients taking the recommended prescription of SST (7.5 grams of granules per day in divided doses) for its possible effect on lung function. Patients who are undergoing interferon therapy or have underlying lung disorders should be particularly cautious when taking SST, as interferon itself can cause severe side effects such as pneumonitis. However, the increasingly well-documented treatment benefits can outweigh the potential adverse effects, since both the potential efficacy and the routes to reducing the risks of the formula are much better understood now than they were ten years ago. SST serves as a key example of how a classical herbal formula is proving itself for modern-day use through scientific research trials.

Jipu (Dan) Wen, MS, MD has nearly 20 years of experience in clinical and laboratory research in China and America in the integration of Chinese and Western medicines, including four years as a faculty member at Guangzhou University of Traditional Chinese Medicine and a three-year, postdoctoral fellowship in gastroenterology at Mayo Clinic. His research at Washington University School of Medicine on absorption of vitamin B12 has been supported by a research grant from National Institutes of Health. Since 2000, Dr. Wen has developed his career within the dietary supplement industry. He is the former Vice-President of World Nutrition Corp. of Phoenix, Arizona, and the current President of Honso USA, Inc., headquartered in Phoenix, Arizona. Honso is the first company established in the United States to distribute Kampo herbal formulas. Dr. Wen has been actively involved with the business development of Chinese herbal medicine in North America in areas such as clinical trials, FDA regulatory issues, marketing, lecturing, and education. He can be reached through e-mail at wen@honso.com.  

Stephanie Pina is a licensed naturopathic physician practicing in Tempe, Arizona who incorporates Chinese medicine into her practice.

Notes


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