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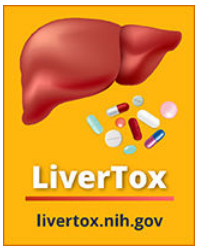

Sho Saiko To and Dai Saiko To

Updated: August 15, 2020.

OVERVIEW

Introduction

Sho-saiko-to is an herbal mixture used in Kampo medicine in Japan to treat liver disease and known elsewhere in different formulations as Dai-saiko-to and Xiao Chai Hu Tang, and also spelled as Syo-saiko-to. Both Sho-saiko-to and Dai-saiko-to have been implicated in rare instances of clinically apparent acute liver injury.

Background

Sho-saiko-to is the Japanese name for a widely used mixture of at least 7 herbs that are used together in Kampo medicine to treat patients with liver disease, being purported to decrease the progression of hepatic fibrosis and lessen the likelihood of hepatocellular carcinoma. In traditional Chinese medicine, it has been used for centuries (dating to the Han Dynasty) to treat fever, stomatitis and gastrointestinal disorders. Sho-saiko-to is widely used in Japan to treat patients with chronic hepatitis. Other names for this mixture include TJ-9 and, in China, Dai-saiko-to and Xiao Chai Hu Tang. These products may have somewhat different combinations of herbs. Typically, they contain Bupleurium root (Chai hu), Pinelliae tuber (Ban xia), Scutellaria baicalensis root (Chinese skullcap), ginseng root, ginger rhizome, glycyrrhiza root (licorice), and jujube fruit. Sho-saiko-to has been shown to have antioxidant and cytoprotective properties in vitro and to protect against experimental hepatic injury in several animal models. The components responsible for the hepatoprotective activity of Sho-saiko-to are thought to be saponins (saikosaponin A, B, C and D) and the antioxidants, baicalin and baicalein, which resemble silybinin chemically and appear to have similar properties in vitro and in vivo. The clinical efficacy of Sho-saiko-to in humans has not been well demonstrated, resting largely upon small studies with uncertain clinical endpoints. Sho-saiko-to is usually described as having no significant side effects. Uncommon adverse events include interstitial pneumonitis and hepatitis. This herbal mixture is rarely used in the United States, but Scutellaria root is a component in several multiingredient herbal supplements.

Hepatotoxicity

Several case reports have suggested that Sho-saiko-to and Dai-saiko-to are capable of causing rare instances of clinically apparent acute liver injury. The time to onset of liver injury ranged from 3 to 8 weeks and the pattern of serum enzyme elevations was usually hepatocellular. The onset was marked by nausea, abdominal discomfort and fatigue, followed shortly by jaundice. The injury resolved rapidly on stopping the herbal (within 4 to 8 weeks). Most instances of acute liver injury attributed to Sho-saiko-to have occurred in patients with chronic liver disease, most frequently chronic hepatitis C. However, the appearance of jaundice with sudden rise in serum aminotransferase levels is distinctly unusual during the course of chronic hepatitis C and the description

of several instances of recurrence on reexposure makes the reports convincing. The component responsible for the injury is not known but is suspected to be Scutellaria baicalensis, also known as Chinese skullcap.

Likelihood score: B (rare but likely cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism of hepatotoxicity of Sho-saiko-to is unknown and, because it is an herbal mixture, the specific ingredient responsible for injury is unclear. Among the constituents, perhaps Scutellaria (skullcap) is the most likely hepatotoxic fraction. The possibility always exists that the rare instances of acute liver injury due to this Sho-saiko-to were due to contamination or misidentification of the herbals.

Outcome and Management

Hepatotoxicity attributed to Sho-saiko-to is usually mild to moderate in severity and rapidly reversible with stopping the medication. No case of acute liver failure, chronic hepatitis or vanishing bile duct syndrome due to Sho-saiko-to or similar herbal mixtures have been described in the literature. Recurrence upon reexposure is frequent and should be avoided.

Drug Class: Herbal and Dietary Supplements, Chinese and Other Asian Herbal Medicines

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Sho-Saiko-To – Generic

DRUG CLASS

Herbal and Dietary Supplements

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Sho-Saiko-To, Dai-Saiko-To	63364-01-2	Herbal mixture	Not applicable

ANNOTATED BIBLIOGRAPHY

References updated: 15 August 2020

Zimmerman HJ. Unconventional drugs. Miscellaneous drugs and diagnostic chemicals. In, Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott,1999: pp. 731-4.

(Expert review of hepatotoxicity published in 1999; hepatotoxicity of Asian herbal products and teas are discussed generally without focus on any specific product or herb).

Seeff L, Stickel F, Navarro VJ. Hepatotoxicity of herbals and dietary supplements. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 631-58.

(Review of hepatotoxicity of herbal and dietary supplements [HDS] discusses Chinese and other Asian herbal medicines including Sho-saiko-to).

PDR for Herbal Medicines. 4th ed. Montvale, New Jersey: Thomson Healthcare Inc. 2007.

(Compilation of short monographs on herbal medications and dietary supplements, including sections on ma huang, but not specifically on Sho-saiko-to).

Mizoguchi Y, Miyajima K, Sakagami Y, Yamamoto S. Nippon Naika Gakkai Zasshi. 1986;75:1453–6. [A severe case of drug-induced allergic hepatitis in herbal medicine]. Japanese. PubMed PMID: 3805846.

(A 27 year old developed jaundice 6 weeks after taking Kinshigan, a Kampo herb with rapid recovery, but recurring with a more severe course 2 weeks after restarting [bilirubin 28.5 mg/dL, ALT 166 U/L, Alk P 1.5 times ULN, 1% eosinophils]; among 18 ingredients, Scutellariae radix).

Satake I, Maeda M, Koyama W, Sakamoto S, Koizumi S, Kanayama M. A case of hepatic injury caused by an herb drug. Acta Hepatol Jpn. 1986;27:238–41.

Carlsson C. Herbs and hepatitis. Lancet. 1990;336:1068. PubMed PMID: 1977040.

(Analysis of laboratory results from 395 patients found higher ALT levels among 53 patients taking herbals [55 U/L] than among those who did not [12 U/L]).

Marutani K, Matsuo S, Nishijima T, Watanobe T, Ishida Y, Sasaki K, Kameda C, Itoh S. Light and electron microscopic findings in the liver of five patients with syo-saiko-to-induced hepatitis. Jpn J Gastroenterol. 1990;87:640.

Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. Unconventional medicine in the United States. Prevalence, costs, and patterns of use. N Engl J Med. 1993;328:246–52. PubMed PMID: 8418405.

(Among 1539 adults interviewed by telephone, 34% used an unconventional therapy during the previous 12 months, including 3% using herbal medicines).

Itoh S, Marutani K, Nishijima T, Matsuo S, Itabashi M. Liver injuries induced by herbal medicine sho-saiko-to (xiao-chai-hu-tang). Dig Dis Sci. 1995;40:1845–8. PubMed PMID: 7648990.

(4 cases, 42-58 year old women, taking Sho-saiko-to for 3-7 weeks, developed liver test elevations, 2 with jaundice, 2 with recurrence on restarting [peak ALT 135 to 1335 U/L], with resolution within 2 to 3 months upon stopping).

Kamiyama T, Nouchi T, Kojima S, Murata N, Ikeda T, Sato C. Autoimmune hepatitis triggered by administration of an herbal medicine. Am J Gastroenterol. 1997;92:703–4. PubMed PMID: 9128330.

(55 year old woman with chronic hepatitis developed jaundice one month after starting Dai-saiko-to [bilirubin 11.2 mg/dL, ALT 390 U/L, ANA 1:2560], responding rapidly to prednisone therapy).

Matsuda R, Takahashi D, Chiba E, Kawana I, Tomiyama M, Ebira H, Ikegami T, et al. Nihon Shokakibyo Gakkai Zasshi. 1997;94:787–91. [A case of drug induced hepatitis and interstitial pneumonia caused by a herbal drug, Dai-saiko-to]. Japanese. PubMed PMID: 9396337.

(65 year old man developed dyspnea and interstitial pneumonitis with abnormal liver tests 4 weeks after starting Dai-saiko-to for autoimmune dermatitis, stopping at 6 weeks [bilirubin 1.2 mg/dL, ALT 675 U/L, Alk P 1070 U/L], resolving within a month of stopping).

Shimizu I. Sho-saiko-to: Japanese herbal medicine for protection against hepatic fibrosis and carcinoma. J Gastroenterol Hepatol. 2000;15 Suppl:D84–90. PubMed PMID: 10759225.

(Review of composition, clinical efficacy and mechanism of action of Sho-saiko-to; contains 7 herbs, including Bupleurum root, Pinellia tuber, and Scutellaria root, and Glycyrrhiza root; active components likely to be saikosaponins and the antioxidants, baicalin and baicalein, which resemble silybinin).

Stedman C. Herbal hepatotoxicity. Semin Liver Dis. 2002;22:195–206. PubMed PMID: 12016550.

(Review and description of patterns of liver injury associated with hepatotoxicity from herbal products, including discussion of risk factors and herb-drug interactions).

Ernst E. Adulteration of Chinese herbal medicines with synthetic drugs: a systematic review. J Intern Med. 2002;252:107–13. PubMed PMID: 12190885.

(Systematic review of literature on adulteration of herbals with conventional medications, in 15 case reports and 2 cases series of 21 patients; contaminants identified in up to 24% of products were NSAIDs, corticosteroids, benzodiazepines, diuretics and diabetes medications).

Schiano TD. Hepatotoxicity and complementary and alternative medicines. Clin Liver Dis. 2003;7:453–73. PubMed PMID: 12879994.

(Comprehensive review of herbal associated hepatotoxicity, including common patterns of presentation with discussion of Chinese herbal medicines, including Jin Bu Huan, Ma Huang, Shou Wu Pian, and Sho-saiko-to).

Hsu LM, Huang YS, Tsay SH, Chang FY, Lee SD. Acute hepatitis induced by Chinese hepatoprotective herb, xiao-chai-hu-tang. J Chin Med Assoc. 2006;69:86–8. PubMed PMID: 16570576.

(52 year old woman developed jaundice 1.5 months after starting Xiao Chai Hu Tang, known in Japan as Syo-saiko-to [bilirubin 1.9 mg/dL, ALT 2028 U/L, Alk P 213 U/L], resolving within 2 months of stopping).

Yuen MF, Tam S, Fung J, Wong DK, Wong BC, Lai CL. Traditional Chinese medicine causing hepatotoxicity in patients with chronic hepatitis B infection: a 1-year prospective study. Aliment Pharmacol Ther. 2006;24:1179–86. PubMed PMID: 17014576.

(Among 45 patients with chronic hepatitis B hospitalized because of liver dysfunction at Queen Mary Hospital, Hong Kong during 2004, 7 appeared to have liver injury caused by traditional Chinese herbal medications, marked by worsening of liver tests, lack of IgM anti-HBc and low or no detectable HBV DNA; 2 died and two underwent liver transplantation).

Wai CT, Tan BH, Chan CL, Sutedja DS, Lee YM, Khor C, Lim SG. Drug-induced liver injury at an Asian center: a prospective study. Liver Int. 2007;27:465–74. PubMed PMID: 17403186.

(Prospective survey of drug induced liver injury presenting over 26 months at a single hospital in Singapore identified 31 cases, ages 18-9 years, 55% male, Chinese traditional medicines being implicated in 17 [55%] and Malay agents in 5 cases [16%], adulterants were found in 9 of 31 tested traditional agents [codeine, corticosteroids, metformin, mercury, nonsteroidal antiinflammatory agents]).

Seeff LB. Herbal hepatotoxicity. Clin Liver Dis. 2007;11:577–96. PubMed PMID: 17723921.

(Review of herbal induced hepatotoxicity, including Chinese herbal medicines such as Sho-saiko-to, Chaso, Onshido, Jin Bu Huan, Ma Huang and Shou Wu Pian).

García-Cortés M, Borraz Y, Lucena MI, Peláez G, Salmerón J, Diago M, Martínez-Sierra MC, et al. Liver injury induced by "natural remedies": an analysis of cases submitted to the Spanish Liver Toxicity Registry. Rev Esp Enferm Dig. 2008;100:688–95. PubMed PMID: 19159172.

(Among 521 cases of drug induced liver injury submitted to Spanish registry, 13 [2%] were due to herbals, including Camellia sinensis [green tea], Cassia angustifolia [senna], kava, valerian, Rhamnus purshianus [cascara], fitosoja [soy plant], biosoja [soy extract], Aesculus hippocatanum [horse chestnut], chitosan [deacetylated chitin], and Couterea latifloral [Copalchi]).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology. 2008;135:1924–34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, 9% of cases were attributed to herbal medications and dietary supplements [HDS] but none specifically to Sho-saiko-to).

Navarro VJ. Herbal and dietary supplement hepatotoxicity. Semin Liver Dis. 2009;29:373–82. PubMed PMID: 19826971.

(Overview of the regulatory environment, clinical patterns, and future directions in research with HDS including traditional Chinese herbal medicines and Sho-saiko-to).

Wang YP, Shi B, Chen YX, Su J, Jiang CF, Xie WF. Drug-induced liver disease: an 8-year study of patients from one gastroenterological department. J Dig Dis. 2009;10:195–200. PubMed PMID: 19659787.

(Among 30 patients with drug induced liver disease seen at a single medical university in Shanghai between 2000 and 2008, 12 were due to Chinese herbs, but specific agents were not discussed; 9 patients were jaundiced and 6 had hepatocellular, 3 cholestatic and 2 mixed patterns of injury).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology. 2010;52:2065–76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 [11%] were attributed to drug induced liver injury of which 12 [9%] were due to herbals, but none were attributed specifically to Sho-saiko-to).

Lee JK, Kim JH, Shin HK. Therapeutic effects of the oriental herbal medicine Sho-saiko-to on liver cirrhosis and carcinoma. Hepatol Res. 2011;41:825–37. PubMed PMID: 21682829.

(Review of the efficacy and safety of Sho-saiko-to as therapy of liver disease, mentions side effects of interstitial pneumonitis and 3 case reports of hepatic injury).

Stickel F, Kessebohm K, Weimann R, Seitz HK. Review of liver injury associated with dietary supplements. Liver Int. 2011;31:595–605. PubMed PMID: 21457433.

(Review of current understanding of liver injury from herbals and dietary supplements focusing upon Herbalife and Hydroxycut products, green tea, usnic acid, Noni juice, Chinese herbs, vitamin A and anabolic steroids; Sho-saiko-to is not discussed).

Deng G, Kurtz RC, Vickers A, Lau N, Yeung KS, Shia J, Cassileth B. A single arm phase II study of a Far-Eastern traditional herbal formulation (sho-sai-ko-to or xiao-chai-hu-tang) in chronic hepatitis C patients. J Ethnopharmacol. 2011;136:83–7. PubMed PMID: 21527335.

(Among 42 patients with chronic hepatitis C who were treated with Sho-saiko-to [2.5 g three times daily] for 12 months, ALT levels decreased in 67% and increased in 29%, while liver histology did not change overall; side effects were not mentioned).

Teschke R, Wolff A, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: a tabular compilation of reported cases. Liver Int. 2012;32:1543–56. PubMed PMID: 22928722.

(A systematic compilation of all publications on the hepatotoxicity of specific herbals identified 185 publications on 60 different herbs, including 2 reports of Xiao Chai Hu Tang: [Itoh 1995] and Hsu [2005]).

Navarro VJ, Barnhart H, Bonkovsky HL, Davern T, Fontana RJ, Grant L, Reddy KR, et al. Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network. Hepatology. 2014;60:1399–408. PubMed PMID: 25043597.

(Among 85 cases of HDS associated liver injury [not due to anabolic steroids] enrolled in a US prospective study between 2004 and 2013, none were attributed to Sho-saiko-to but two cases were due to Move Free, a product that contains Scutellaria baicalensis).

Douros A, Bronder E, Andersohn F, Klimpel A, Kreutz R, Garbe E, Bolbrinker J. Herb-Induced Liver Injury in the Berlin Case-Control Surveillance Study. Int J Mol Sci. 2016;17:E114. pii. PubMed PMID: 26784183.

(Among 198 patients with suspected drug induced liver injury seen at Berlin Hospitals and enrolled in a prospective database, 10 were attributed to herbal supplements but none were attributed to Sho-saiko-to or Scutellaria radix).

Brown AC. Liver toxicity related to herbs and dietary supplements: Online table of case reports. Part 2 of 5 series. Food Chem Toxicol 2017; 107(Pt A): 472-501.

(Description of an online compendium of cases of liver toxicity attributed to HDS products, does not list Sho-saiko-to but lists two cases of liver injury attributed to skullcap [Estes 2003, Hullar 1999]).

Hsueh TP, Lin WL, Tsai TH. Pharmacokinetic interactions of herbal medicines for the treatment of chronic hepatitis. J Food Drug Anal. 2017;25:209–18. PubMed PMID: 28911662.

(Discussion of herbal medications used to treat chronic liver disease including Sho-saiko-to and their interactions with other medications; does not discuss hepatotoxicity).

Enomoto Y, Nakamura Y, Enomoto N, Fujisawa T, Inui N, Suda T. Japanese herbal medicine-induced pneumonitis: A review of 73 patients. Respir Investig. 2017;55:138–44. PubMed PMID: 28274529.

(Review of the literature on pneumonitis caused by Japanese herbal medications identified 73 cases in 59 articles, including 19 cases attributed to Sho-saiko-to; no mention of liver injury).

Shimada Y, Fujimoto M, Nogami T, Watari H, Kitahara H, Misawa H, Kimbara Y, et al. Recurrent drug-induced liver Injury caused by the incidental readministration of a Kampo formula containing Scutellariae radix. Intern Med. 2018;57(12):1733–40. PubMed PMID: 29434136.

(67 year old woman with depression developed liver test abnormalities within 4 days of starting 4 medications including Sho-saiko-to [bilirubin 1.1 mg/dL, ALT 139 U/L, Alk P 362 U/L], which resolved within 2-3 months of stopping all medications and arose again 1 year later when she restarted Sho-saiko-to [bilirubin 1.3 mg/dL, ALT 800 U/L, GGT 373 U/L], resolving within a month of stopping; attributed to Scutellariae radix based upon lymphocyte stimulation tests).

Zhao T, Tang H, Xie L, Zheng Y, Ma Z, Sun Q, Li X. Scutellaria baicalensis Georgi. (Lamiaceae): a review of its traditional uses, botany, phytochemistry, pharmacology and toxicology. J Pharm Pharmacol. 2019;71:1353–69. PubMed PMID: 31236960.

(Review of the chemistry, clinical uses and toxicity of Scutellaria baicalensis, a major ingredient in many traditional Chinese medicines, which contains more than 40 compounds including flavonoids [baicalin, mogonin], terpenoids, volatile acids and polysaccharides; the herb is used for liver protection, and treatment of diarrhea, vomiting, and high blood pressure, known as Huang Qin [yellow reed]; "there is no obvious adverse reaction in the oral preparation of Scutellaria baicalensis", but it may cause stomach discomfort, diarrhea and other minor symptoms in some patients).