

# Schisandra chinensis

## Introduction

A brief literature review of *Schisandra chinensis* will be presented in this essay. It will clearly define the method of research, give details of botanical and common names, and discuss traditional use and western herbal medicine use. Details of plant chemistry will be outlined; in addition, the relationship between different hepatoprotective effects and different chemical structures of Schisandrin A, B & C will be clarified. Prominent *in vivo* research on Schisandrin B active constituent and human clinical studies with whole plant extracts will be summarized. Finally pharmacokinetics, toxicity and herb-drug interactions will be considered. Due to time restrictions and word limits this review will focus on the Schisandrin active constituents, specifically Schisandrin B and the corresponding reported action of hepatoprotection.

## Method

This literature review used information accessed from current Chinese *Materia Medica* texts written by well-known authors such as Bensky and Zhu. Current Western Herbal Medicine texts written by Bone, Braun & Cohen and the American Herbal Pharmacopoeia on *Schisandra chinensis* were also used. Full text journal articles were found in the University of Western Sydney (UWS) databases including ScienceDirect and PubMed, keywords used: *Schisandra chinensis*, Schisandrin and Gomisin A. Some full text articles, referenced by Bone, Upton, Braun & Cohen, were found by searching back through editions of e-journals held by UWS. Unfortunately the university only holds recent copies of many important journals such as year 2000 onwards editions of *Planta Medica* but fortunately has older editions of the journals *Molecular and Cellular Biochemistry* and *Biochemical Pharmacology*.

## Botanical and common names

According to the Chinese *Materia Medica* (Bensky, Clavey & Stoger, 2004:858) the standard species are *Schisandra chinensis* (Turcz.) Baill. and *Schisandra sphenanthera* Rehd. & Wils. of the Magnoliaceae family, the pharmaceutical name is *Schisandrae Fructus*. *Schisandra* species grow in China, Japan, Eastern Russia, the Himalayas and Korea (Hancke, Burgos & Ahumada, 1999:451). The common names are Schisandra in English, Wu Wei Zi (*S. chinensis*) or Northern Schisandra and Hua Zhong Wu Wei Zi (*S. sphenanthera*) or Southern Schisandra in Mandarin, Gomishi in Japanese and Omija in Korean (Hancke et al, 1999:452). The seeds and fruit are the parts used in herbal medicine, good quality is indicated by large fruit with thick, purplish red, fleshy and oily pulp with an intense aroma. In China *S. sphenantherae* is considered weaker in strength with no tonic action and thus is used for different conditions (Bensky et al, 2004:861). *S. sphenantherae* is the most commonly traded substitute for *S. chinensis* (Upton, 1999:6).

## Traditional use

*Schisandra* first appeared in the Divine Husbandman's Classic of the *Materia Medica*, a Traditional Chinese Medicine (TCM) text dating back to the first century BC (Upton, 1999:1). The Chinese pin yin name 'Wu Wei Zi' translates to five-taste fruit, giving it a special place in TCM due to the importance of the relationship between taste and herbal action. Although *Schisandra* contains five flavours, it is primarily used for its sour taste and quality of warmth. In TCM it is classified in the astringent herb category, herbs that

act to 'draw fluid in' (Zhu, 1998:653). The main actions and indications of Wu Wei Zi are to hold the leakage of Lung qi and stop coughs, to tonify and enrich the Kidneys, to contain the essence and stop diarrhea. It is useful for nocturnal emissions, vaginal discharge, spermatorrhea and urinary frequency due to Kidney deficiency. It quiets the spirit while calming and holding the heart qi, useful for irritability, insomnia, palpitations and dream-disturbance.

bed sleep due to damage of the blood and yin of the Heart and Kidneys. Wu Wei Zi is used to inhibit sweating and generate fluids; good for nightsweats, spontaneous or excessive sweating especially when accompanied by a dry throat or thirst (Bensky, Clavey & Stoger, 2004:859). Consequently, Schisandra is considered to be both a tonic and an astringent, primarily used for deficiency conditions of the Kidney, Lung and Heart due to a lack of qi and body fluids.

#### Western Herbal Medicine Use

The main actions and indications of Schisandra in Western Herbal medicine (WHM) are as a hepatoprotective, useful for acute or chronic liver disease, chemical liver damage, poor liver function and improving the detoxifying ability of the liver. As an antioxidant, adaptogenic, nervine tonic and mild antidepressant useful for improving mental and physical performance, endurance and adaptation to stress. It is used for chronic cough and asthma due to its antitussive effects and can be used to assist childbirth due to its oxytocic effects (Bone, 2003:405; Braun & Cohen, 2005:327). Correlations between WHM use are seen in chronic cough and asthma and TCM use with leakage of Lung qi. There may be correlations between the adaptogenic, nerve tonic and anti-depressant WHM use and the TCM tonic and Heart deficiency use. Interestingly, TCM does not refer to liver conditions, although as will be discussed clinical trials in China used Schisandra to treat hepatitis.

#### Chemistry

The fruit and seeds of Schisandra plants contain large amounts of lignan compounds, which are phenols, a large group of plant constituents that are aromatic alcohols (Pengelly, 2004:15). Lignans are dimeric, made up of two simple identical molecules, with phenylpropane (C<sub>6</sub>C<sub>3</sub>) components connected to their side chains at the carbon 8 positions to make three-dimensional networks (Pengelly, 2004:20). In the species *S. chinensis* the principal pharmacological active compounds are thought to be the dibenzo[a,c]cyclooctadiene lignans, these lignans can be isolated from the unhydrolyzed fraction of the seed oil (Upton, 1999:6). Forty lignans have been identified, the greatest number of lignans are Schisandrol A (up to 5.17%) and Schisandrin B or  $\gamma$ -schisandrin (up to 5.00%). Other primary lignans are Schisandrin A or deoxyschisandrin, Schisandrol B also known as Gomisin A due to different nomenclature used by Japanese researchers, Gomisin N, Schisantherin A and B (Zhu, 1998:654; Upton, 1999:6). Schisandra also contains volatile oil constituents, glycosides and organic acids (Bensky et al, 2004:861).

#### Different chemical structures of Schisandrin A, B & C

Differences in chemical structure result in different actions of the constituents, the presence of the methylenedioxy group, seen Schisandrin B and C, significantly increases the hepatoprotective effect. Whereas the presence of the hydroxy group at C-7 seen in Schisandrin A results in a decreased hepatoprotective effect (Upton, 1999:6). A study randomly pretreated mice with Schisandrin A, B or C intragastrically at a daily dose of 1mmol/kg for three days before administering an oral dose of Carbon Tetrachloride (CCl<sub>4</sub>) at 0.1mL/kg. Hepatic tissue samples were analyzed and levels of

plasma alanine aminotransferase (ALT) and hepatic mitochondrial reduced glutathione (GSH) recorded (Ip, Ma, Che & Ko, 1997:317). Researches found that pretreatment with schisandrin B and C completely prevented CCl<sub>4</sub> hepatotoxicity evident by significant decreases in plasma ALT activity increases in the hepatic mitochondrial GSH levels and glutathione reductase activity. On the contrary pretreatment with Schisandrin A offered no protection evident by no change in ALT or GSH levels. Intoxication by CCl<sub>4</sub> leads to increased oxidative stress and for cell survival mitochondrial glutathione redox is essential. Researchers concluded that hepatoprotection given by Schisandrin B and C was shown by increases in mitochondrial GSH levels stimulated by the methylenedioxy group of the dibenzocyclooctadiene skeleton of Schisandrin (Ip et al, 1997:319).

#### Animal Studies

A large number of animal studies based on similar methods as described above support the hepatoprotective effects of Schisandrin B. Most studies have used mice or rats subjected to chemicals such as carbon tetrachloride (CCl<sub>4</sub>) which is mostly metabolized in the liver by the cytochrome P450 system, the pathogenesis of CCl<sub>4</sub>-induced hepatic damage involves reactive oxidant species arising from this metabolism (Ip et al, 1997:318). A study demonstrated that pretreatment with Schisandrin B can enhance the hepatic glutathione antioxidant system in mice. Oral administration of 1.6g/kg of an lignan-enriched extract was given for two days prior to CCl<sub>4</sub> intoxication; pretreatment with Schisandrin B resulted in 100% increase in glutathione reductase activity, 26% increase in hepatic glucose-6-phosphate activity and a 16% increase in liver glutathione levels. Researchers established a dose-dependant range for Schisandrin B between 0.2-3.2g/kg (Upton, 1999:13). Follow-up studies found that the whole fruit extract and Schisandrin B produced similar hepatoprotective effects with increasing doses over three days of 1-4mmol/kg producing dose-dependant increases in glutathione reductase activity and hepatic glutathione S-transferase activity (Upton, 1995:13).

Another study out of the same laboratory compared Schisandrin B with alpha-tocopherol on lipid peroxidation. Mice were pretreated with 0.3mmol/kg or 3mmol/kg of Schisandrin B or 3mmol/kg of alpha-tocopherol and compared to a control group. Hepatocellular damage was assessed by measuring ALT levels and results were as follows:

MDA – indirect index of in vivo lipid peroxidation  
(pmol/mg tissue)  
Plasma ALT (U/L)

Control

60+- 1  
14.4 +-0.7

CCl<sub>4</sub> Control

87+-6  
12526 +-797

Sch B 0.3mmol/kg

68+-3  
1008 +-447.4

Sch B 3.0mmol/kg  
56+-2  
24.1 +-4.6

Alpha-toc 3.0mmol/kg  
89+-9  
12904 +-873

(Mak, Ip, Li, Poon & Ko, 1996:162).

Researchers concluded that Schisandrin B inhibits lipid peroxidation while producing no pro-oxidant activity and this contributes to its hepatoprotective action (Mak, Ip, Li, Poon & Ko, 1996:164). Hepatoprotection of Schisandra has been attributed to the inhibition of binding of CCl<sub>4</sub> metabolites to liver microsomal lipids and CCl<sub>4</sub>-induced lipid peroxidation (Ip & Ko, 1996:1687). Another study compared Schisandrin B and Butylated Hydroxytoluene (BHT), a synthetic phenolic antioxidant. Following the same methods as described in the previous study the researchers found that only Schisandrin B could sustain increased hepatic mitochondrial GSH levels, sustain high hepatic ascorbic acid levels (VC) and additionally prevent decrease in hepatic alpha-tocopherol levels (VE). This ability represents crucial antioxidant actions resulting in hepatoprotection and possible inhibition of CCl<sub>4</sub> metabolism (Ip & Ko, 1996:1691).

A more recent study evaluated the potential activity of Schisandra on phase one drug metabolism (Zhu, Lin, Yeung & Li, 1999:61). Whole fruit were soaked to remove flesh and isolate the seeds, which were then dried and ground before being refluxed with 70% ethanol for two hours and then concentrated by removing solvent (Zhu et al, 1999:62). The final aqueous extract was given to rats (dose of lignan fraction equal to 160mg/kg) 24hrs before CCl<sub>4</sub> and dosed again 30mins and 6hrs prior to each CCl<sub>4</sub> dose. A single dose of antipyrine at 80mg/kg was given to the rats with damaged livers and levels of liver enzyme serum glutamic-pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT) and cytochrome P450 were measured. Antipyrine is a low extraction and protein bound drug, which is mostly metabolized through phase one cytochrome P450 enzymes, hence is an excellent marker for hepatoprotective activity. Microscopic features were identified and TLC comparisons completed to confirm identification of the Schisandra chinensis species (Zhu et al, 1999:64). Researchers found that CCl<sub>4</sub> substantially increased elimination half-life of antipyrine from 2.59+-1.04/hr to 11.25+-3.91/hr and decreased its clearance from 65.94 to 10.84 ml/h compared to the control. Pretreatment with Schisandra substantially improved antipyrine elimination half time to 3.30+-0.52/hr for 30min group and 3.58+-1.05/hr for 6 hr group and clearance time to 49.06+-21.75 ml/h and 21.10+-10.42 ml/h respectively. Furthermore, normalization of SGPT, SGOT and P450 levels were observed with pretreatment of Schisandra. Researchers concluded that Schisandra lignans show a strong hepatoprotective effect on Phase one oxidative metabolism, especially seen in the 30mins pretreatment group (Zhu et al, 1999:64). This suggests rapid scavenging of the free radicals and the rate of drug metabolism is related to the metabolic enzymes in hepatocytes (Zhu et al, 1999:67).

#### Human Studies

Human studies done in China have reported that more than 5000 cases of different types of hepatitis have been treated with Schisandra preparations resulting in a short-term effect of lowering serum glutamic-pyruvic transaminase (SGPT). The onset of action for Schisandra was about twenty days and SGPT was normalized in 75% of

treated cases. Elevated levels of SGPT were found in eighty-six cases of hepatitis due to drug toxicity and levels of SGPT were normalized in eighty-three cases after 1-4 weeks of treatment with Schisandra (Chang and But, 1996:205). Unfortunately, specific details of Schisandra preparations, dosage and research methods are not given; references used are hospital records from the 1970's.

Many authors (Bone, 2003:407; Zhou, Lui & Chen, 1991:107, Upton, 1999:13) refer to a controlled study which compared the use of a liver extract and vitamin E (control group) to tablets made of an ethanol extract of 1.5g of Schisandra containing 20mg of lignans. The study comprised of one hundred and eighty-nine patients with chronic viral hepatitis B and elevated SGPT levels. Seventy-three patients of the one hundred and seven patients (68%) given Schisandra had normal SGPT levels within four weeks whereas only thirty-six patients of the eighty-two patients (44%) in the control group had normal SGPT levels within eight weeks. Due to time constraints of this literature review details of references used by these authors were unable to be accessed. It is important to note that SGPT levels tend to rise again in 46-69% of patients after discontinuing the use of Schisandra within three months especially in chronic persistent hepatitis, but repeat use of Schisandra normalized SGPT

levels (Chang and But, 1996:205). In view of these clinical studies, an anti-hepatotoxic drug (DDB) derived from Schisandrin C was developed and is used with success in China for chronic viral and drug-induced hepatitis (Upton, 1999:13; Braun & Cohen, 2005:328). These studies represent the limited amount of data available on the hepatoprotective effect of Schisandra in human studies.

#### Pharmacokinetics

Healthy male subjects were given 15mg of Schisandrin orally and using gas chromatography the average maximum plasma concentration was reported to be 96.1 ± 14.1 ng/mL and found up to eight hours after administration (Upton, 1999:12). In rats given 8mg of Schisandrol A orally, rapid gastrointestinal absorption ( $t_{1/2} = 58$  minutes) and wide tissue distribution was observed. In vitro and in vivo studies in rats have led researchers to suggest that Schisandrin is metabolized in liver microsomes by different routes which includes hydroxylation of alkyl substituents and demethylation of methoxy groups on the aromatic ring (Upton, 1999:12).

#### Toxicity and Herb-Drug Interactions

According to Chinese Materia Medica recommended dose is 2-6 gms in a decoction or 1-3 gms in a dried herb powder form (Chen & Chen, 2004:986; Bensky et al, 2004:858). According to western herbal medicine texts recommended dose is 3.5-8.5ml of 1:2 liquid extract or 1.5-15g of dried herb per day (Bone, 2003:405; Braun & Cohen, 2005:328). Over dosage may cause mild gastrointestinal symptoms such as abdominal discomfort, heartburn, stomach pain and reduced appetite. Allergic papular rashes on the lower back, chest, eyelids and backs of the hands and one case of sinus tachycardia after a 10g dose have been reported (Bensky et al, 2004:861; Bone, 2003:405; Upton, 1999:19). It is contraindicated in pregnancy except to assist in childbirth (Upton, 1999:19; Bone, 2003: 405). Schisandra appears to be free from toxicity when given orally, doses up to 1.6g/kg of crude berries given to mice for ten days resulted in very mild toxic effects. The LD50 in mice of a petroleum-ether extract containing 10% Schisandrin was  $po = 10.5g/kg$  and  $ip = 4.4g/kg$  (Upton, 1999:20). Herb-Drug interactions are quite possible on the basis of in vivo demonstration of the CYP450 induction but as yet research has not been undertaken in this area (Braun & Cohen, 2005:328).

## Conclusion

This review has discussed a variety of aspects of the herb *Schisandra chinensis* including traditional use, western herbal use, plant chemistry, research on the hepatoprotective effect of Schisandrin B compiled from animal and human studies. In animal studies, doses are very high compared to clinical herbal use therefore the very foundation of the research is flawed resulting in a very limited application. In addition, most of the studies are conducted with purified lignans or lignan-fortified *Schisandra* extracts making it difficult to correlate the findings with human use of crude *Schisandra* preparations (Upton, 1999:12). Human studies compiled on whole plant extracts of *Schisandra* are virtually non-existent. A great deal more research needs to be done to evaluate the actual hepatoprotective effect of *Schisandra chinensis* for application in clinical western herbal medicine practice.

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