SCHIZANDRA

Schisandra chinensis (Turcz.) Baill.

Family

Schisandraceae.

Parts Used

Fruit.

Description

Schizandra is a deciduous vine from the Schisandraceae family. Native to China, this perennial plant has also been found in the adjacent regions of Russia and Korea. Schisandra is often grown as an ornamental plant, it is also sometimes known as Magnolia vine.

The vines are woody and glabrous and the deep green leaves are elliptic or oval shaped with a papery to glossy, leathery quality. In autumn the leaves change colour to an attractive yellow. The small white-cream, unisex flowers are generally solitary and after flowering form grapelike clusters of red berry-like fruits which are high in vitamins.

Traditional Use

Schizandra has been used and revered in traditional Chinese medicine for centuries. Schizandra is also known as Wu Wei Zi – which means the “five-flavoured seed” because it tastes sour, bitter, sweet, acrid and salty and also represents the five elements in TCM.

The ancient Chinese classified the herb in many ways - as a stimulant, tonic, antiseptic, relaxant and astringent. Schizandra has traditionally been used to treat a wide range of different ailments including coughs, fatigue, impotence, memory loss

and nervous complaints. It has perhaps been most acclaimed for promoting longevity and increasing physical and mental stamina.

The fruit is used medicinally while the fibers are used to make rope. The stems, leaves, and fruit are also used to extract a volatile oil.

Constituents

Dibenzocyclooctadiene lignans (25 different sub types – including angeloylgomisin, schizandrins, tigloylgomisin, benzoylgomisin, fargesin, eudesmin and gomisin)[1,2] schisandrols, triterpenic acids & lactones, geranylgeranoic acid, citric acids and volatile oil. It also contains an array of vitamins and trace elements including vitamins C & E, iron, copper, manganese, zinc, magnesium, potassium, and phosphorus.

Actions

Antioxidant, anticancer, anti-inflammatory, adaptogen, immune-modulating, hepatoprotective, antitussive, astringent, nervine, sedative.

Pharmacological Activity

Anticancer Activity

A chemical constituent isolated from Schizandra, geranylgeranoic acid (GGA), has been shown to induce apoptosis in a human hepatoma-derived cell line, HuH-7.[3]

The cytotoxicity of two constituents schisandrolic acid and isoschisandrolic acid from Schisandra were evaluated in several cancer cell lines and primary cultured normal mouse hepatocytes.

The two triterpenoids showed moderate cytotoxic activity on all tested cell lines – with their action believed to be via G(0)/G(1) arrest and subsequent apoptosis.[4]

The upregulation of phase II detoxification genes is believed to play an important role in cancer prevention. Extracts of Schizandra were shown to specifically up-regulate phase II enzymes and showed potential for liver cancer prevention.[5]

A compound (KY88) from Schizandra may affect the elimination of Hepatitis B virus, strengthen the immune system, as well as stimulate liver cell regeneration. KY88 was shown to inhibit hepatocellular carcinoma cell proliferation through a decreased secretion and gene expression of surface antigens to Hepatitis B virus.[6]

Dibenzocyclooctadiene lignans from Schizandra were examined and Wuweizisu C was one lignin that was shown to decrease the membrane potential and modulate [Ca(2+)](i) concentration in C6 glioma cells without effecting on cell viability.[7]

Schisandrin B, a compound from Schizandra chinensis was shown to inhibit P-glycoprotein. P-glycoprotein-mediated drug efflux is one of the major causes of cancer multidrug resistance (MDR). Inhibition of P-glycoprotein could reverse cancer MDR and be a promising agent in cancer treatment. Schisandrin B was able to reverse the drug resistance of four MDR cell lines characterized with overexpression of P-glycoprotein and fully restored the intracellular drug accumulation by interacting with P-glycoprotein.[8]

A polysaccharide from Schizandra (FSP) has been shown to inhibit tumour growth through apoptosis and the activation of immunocytes, but not via killing tumour cells directly. In addition, high concentration FSP combined with cyclophosphamide can enhance antitumour activity in S180-bearing mice.[9]

A herbal extract MINA-05, (containing Schizandra, soybean, Trichosanthes and yucca) was shown to induce cell cycle arrest, inhibit cell growth, reduce prostate cell regrowth *in vitro*, and reduce lymph node invasion. Schizandra was shown to induce apoptosis of prostate cancer cells by inhibiting androgen receptor expression.[10]

The influence of a plant preparation AdMax on immunity in ovarian cancer patients was studied. The preparation contains *Leuzea carthamoides*, *Rhodiola rosea*, *Eleutherococcus senticosus* and *Schizandra chinensis*. Twenty eight patients with stage III-IV epithelial ovarian cancer were treated once with 75mg/m(2) cisplatin and 600mg/m(2) cyclophosphamide. Peripheral blood was collected 4 weeks after the chemotherapy. In patients who took AdMax (270mg a day) for 4 weeks following the chemotherapy, the mean numbers of T cell subclasses were increased in compared to controls. In patients who took AdMax, the mean amounts of IgG and IgM were also increased. The obtained results suggest that the combination of extracts

from adaptogenic plants may boost the suppressed immunity in ovarian cancer patients who are subject to chemotherapy.[11]

Antioxidant Activity

The antioxidant action of a lignan-enriched extract of Schizandra (FS) and an anthraquinone-containing extract of *Polygonum multiflorum* (PME) were compared with their respective active constituents schisandrin B (Sch B) and emodin. Their effect on hepatic mitochondrial glutathione antioxidant status in control and carbon tetrachloride (CCl 4)-intoxicated mice were examined. Schizandra and the active constituent SchB were found to be more potent than polygonum extracts or vitamin E. The hepatoprotection correlated with an enhancement in hepatic mitochondrial glutathione antioxidant status.[12]

Schizandra has been shown to inhibit the secretion of pro-inflammatory cytokines through blockade of IkappaB degradation and NF-kappaB activation suggesting a modulation of mast cell activation in inflammatory conditions.[13] Gomisin a lignan from Schizandra was found to inhibit the biosynthesis of leukotrienes by preventing the release of arachidonic acid. The preventive effect on the arachidonic acid cascade may be partially associated with the inhibitory effect of Schizandra on liver injuries.[14]

The antioxidant activity of nine lignans from Schizandra were studied and seven were shown to inhibit iron/cysteine-induced lipid peroxidation as well as superoxide anion production in the xanthine/xanthine oxidase system suggesting potent antioxidant activities.[15]

Schizandra extract and its active component schizandrin A have been shown to have a remarkable reversal effect on multi-drug resistance in cancer cells by enhancing apoptosis and inhibiting both the function and expression of P-glycoprotein and total protein kinase C.[16]

Schisandrin B (Sch B), a dibenzocyclooctadiene derivative isolated from the fruit of *Schizandra chinensis*, has been shown to enhance mitochondrial antioxidant status in liver, heart and brain tissues in rodents. The effect of long-term schisandrin B treatment on cerebral ischemia/reperfusion (I/R) injury was examined in rats and found to be protective. The cerebroprotection was associated with an enhancement in cerebral mitochondrial antioxidant status as well as improved mitochondrial structural integrity, thereby protecting against I/R injury.[17]

The protective effects of Schizandra on adriamycin-induced cardiotoxicity was examined in rats. Adriamycin (ADR) is an effective chemotherapeutic agent against cancers but its clinical use is limited due to its cardiotoxicity. Compared to controls, administration of schizandra before and concurrent with ADR significantly reduced mortality and the amount of ascites, while SOD activities increased with a concomitant decrease in lipid peroxidation.[18] Another study looked at the protection afforded by Schizandra on gentamicin-induced nephrotoxicity. The nephroprotection by Schizandra was associated with an enhancement in renal mitochondrial antioxidant status and improved mitochondrial functional and structural integrity.[19]

Schizandra and ligustrum, were examined for their role on the laying performance, antioxidant status and immunity of hens during heat stress. The results suggested that diets supplemented with 1% of either herb may enhance egg production, immune function, and antioxidant status of hens during heat stress.[20]

Schizandra was found to have an antibacterial action on salmonellosis. It was combined along with the other herbs prunus and coptis and when given to animals infected with different strains of salmonella, the animals did not show any of the clinical signs and rarely showed histological damage associated with the disease.[21]

Anti-inflammatory Activity

The effect of schisandrin on plasma nitrite concentration in lipopolysaccharide (LPS)-treated mice was evaluated. Schisandrin significantly inhibited carrageenan-induced paw edema and acetic acid-induced vascular permeability in mice. Furthermore, schisandrin had a protective effect on lipopolysaccharide (LPS)-induced sepsis. The anti-inflammatory properties of schisandrin result overall from the inhibition of nitric oxide production, prostaglandin release, cyclooxygenase-2 and inducible nitric oxide synthase expression.[22]

The anti-inflammatory mechanisms of Schizandra compounds were found to vary depending on whether macrophages were treated with schisandrin before or after LPS. The main difference was inhibitor kappaBalpha (IkappaBalpha) degradation was not inhibited when macrophages were pretreated by LPS before schisandrin and was weakly inhibited when macrophages were pretreated by schisandrin before LPS.[23]

Schizandra compounds including schizandrins, schisandrols, gomisins, fargesin, eudesmin and lirioresinol B dimethyl ether, were examined for antiallergic actions. Constituents such as schisandrol A and gomisins showed potent inhibitory activity on 5-LOX-catalysed leukotriene production, but were much less active on cyclooxygenase-2-catalysed prostaglandin E(2) and inducible nitric oxide-catalysed NO production. These compounds have the potential to be developed as novel antiallergic agents.[24]

The effect of Schizandra was examined for its effect on induced pro-inflammatory cytokine secretion in the human mast cell line HMC-1. Schizandra was found to suppress induced TNF-alpha, IL-6, and GM-CSF production in dose-dependent manners suggesting a mechanism of action of this medicine in the modulation of mast cell activation in inflammatory conditions.[25]

Dibenzocyclooctadiene lignans from Schizandra were examined for their anti-inflammatory actions in mice after a tumor-promoting inflammatory agent was applied to the ears. Gomisin A, gomisin J, and wuweizisu C inhibited the inflammatory activity induced by the tumour promoting agent in mice and at higher doses Gomisin A also markedly suppressed the promotion on skin tumor formation in mice following.[26]

Hepatic Activity

A comparative study on the hepatoprotective activity of the Schizandra compound, Eklikit ,and the St Mary's thistle, Legalon, after acute alcohol intoxication was conducted. Eklikit was shown to possess membrane protective and expressed hepatoprotective activity in equal to or in excess of Legalon.[27]

TJN-101, a lignan from Schizandra was examined on liver regeneration after partial hepatectomy. The mitotic index and the level of DNA synthesis and ornithine decarboxylase increased after partial hepatectomy and their increase was significantly enhanced by TJN-101.[28] Another study suggested that TJN-101 may suppress the fibrosis proliferation and accelerate both the liver regeneration and the recovery of liver function after partial hepatectomy in chronic liver injury. [29]

Schizandra has been shown in many studies to enhance hepatic clearance of toxins and protect liver cells from damage. It works via facilitating both antioxidant and phase I detoxification pathways and inhibiting liver fibrosis. These include aflatoxin, cadmium chloride[30] and menadione.[31] Another study examined the liver protection afforded by the active constituent from Schizandra, gomisin A, on D-galactosamine and lipopolysaccharide -induced hepatic apoptosis and liver failure. The beneficial effects of gomisin were shown to be via reduced oxidative stress and its antiapoptotic activity.[32]

Schizandra has also been shown to prevent oxidative tissue damage by the drug tacrine, which is a known hepatotoxin used in anti-Alzheimer's therapy.[33]

Schizandra has also shown to be a potent hepatoprotective via glutathione antioxidant initiation and improving phase I oxidative metabolism for carbon tetrachloride.[34,35,36,37,38,39] One showed its effects may be related to the increase in the resistance of hepatic mitochondria to Ca2+-stimulated permeability transition.[40]

Pharmacological studies on animals have shown that Schizandra increases physical working capacity and affords a stress and oxidative-protective effect against a broad spectrum of harmful factors including heat shock, skin burn, cooling, frostbite, immobilisation, swimming under load in an atmosphere with decreased air pressure, aseptic inflammation, irradiation, and heavy metal intoxication.[41]

Chronic hepatitis C virus (HCV) infection is associated with a defective host antiviral immune response and intrahepatic oxidative stress that leads to inflammation and necrosis of hepatic cells. A range of antioxidants and herbal hepatoprotectives including Schizandra were examined and were found to normalise liver enzymes, decrease viral load and improve histology - enhancing the overall response rate of the patients.[42] Schizandra was also employed in patients infected with the Hepatitis

B virus and found to reduce circulating monocyte numbers which may reduce the self-inflicted host immune injury to hepatocyte which may testify the hepatoprotective ability of the herb.[43]

Gastrointestinal Activity

Russian studies have found Schizandra to be useful in the treatment of acute gastrointestinal diseases, gastric hyper- and hypo-secretion, chronic gastritis, stomach and duodenal ulcers.[44]

Lipid Regulating Activity

The effects of the constituent schisandrin on liver and serum lipid contents were investigated in mice with experimentally-induced hypercholesterolaemia. Schisandrin treatment was able to decrease hepatic total cholesterol and triglycerides and increase liver weight.[45]

A herbal medicine known as Shengmai San (SMS), comprised of *Panax ginseng*, *Schizandra chinensis* and *Ophiopogon japonicus* is a traditional Chinese medicine used for treating coronary heart disease. A study investigated the effects of SMS on the plasma and liver lipids, lipid peroxidation and antioxidant systems in liver and heart of cholesterol-fed rats. Results indicated that the SMS may reduce hepatic lipids and lipid peroxidation in rats.[46]

Another study found that the combined administration of sesamin with schizandra extract could improve blood fluidity after 1 week of oral intake and this effect was sustained up to 2 weeks.[47]

Adaptogenic Activity

In healthy subjects, Schizandra increases endurance and accuracy of movement, mental performance and working capacity, and generates alterations in the basal levels of nitric oxide and cortisol in blood and saliva with subsequent effects on the blood cells, vessels and CNS.[48]

The effects of schizandra on the function of the pituitary-adrenal cortex, gonadal axis and carbohydrate metabolism in rats undergoing experimental chronic psychological stress, navigation and strenuous exercise were examined. Schizandra can reduce the levels of corticosterone and glucose and also protect the structure of the adrenal cortex.[49]

A combination of *Eleutherococcus senticocus*, *Schizandra chinensis* and *Rhodiola rosea* was used in mice to examine adaptogenic effects. The formula strongly augments endurance of mice, increasing the time taken to exhaustion approximately seven fold. It was concluded that adaptogens induce an increase of heat shock proteins which are regarded as a defense response to stress and serve to increase tolerance to stress.[50] The same herbs given as a single administration effectively increase mental performance and physical working capacity in humans.[51]

Memory Enhancing

The effect of schizandrin, a component of Schizandra was studied on memory impairment in rats. Scopolamine, a non-selective muscarinic receptor antagonist, markedly impair spatial memory in an eight-arm radial maze and also impairs the passive avoidance response. Schizandrin significantly reversed the scopolamine-induced impairment of spatial memory and impairment of the passive avoidance response. The effects were through enhancing cholinergic function.[52]

ESP-102, a standardized combined extract of *Angelica gigas*, *Saururus chinensis* and *Schizandra chinensis*, was examined on learning and memory deficit in mice. Acute oral treatment (single administration prior to scopolamine treatment) of mice with ESP-102 significantly reduced scopolamine-induced memory deficits in the passive avoidance performance test. Another noteworthy result included the fact that prolonged oral daily treatments of mice with much lower amounts of ESP-102 (1 and 10mg/kg body weight) for ten days reversed scopolamine-induced memory deficits. The results suggest that ESP-102 may protect against neuronal cell death and cognitive impairments often observed in Alzheimer's disease, stroke, ischemic injury and other neurodegenerative diseases.[53]

The herbal combination of *Biota orientalis*, *Panax ginseng* and *Schizandra chinensis*, was studied regarding learning and memory performance in mice. While it had no effect on memory registration, consolidation and retrieval processes or on motor activity in normal mice, it reduced the ethanol-induced and scopolamine-induced impairment of memory registration. The preparation also improved the electroconvulsive shock-induced impairment of memory consolidation.[54]

Sedative and Anxiolytic Activity

Numerous clinical trials in Russia have demonstrated the efficiency of Schizandra in neurasthenia, neuralgic and psychiatric disorders including neurosis, psychogenic depression, astheno-depressive states, schizophrenia and alcoholism.[55]

The sedative and hypnotic activities of Schizandra fruit were studied in mice and rats and were found to significantly inhibit the motor activity of mice compared to normal. Results also showed SY3 potentiated pentobarbital-induced sleep by not only increasing the number of falling asleep and prolonging sleeping time but also reducing sleep latency.[56]

Indications

- Mental and physical stress
- Oxidative stress, inflammatory disorders
- Liver toxicity, hepatitus and compromised liver function
- Hypercholesterolaemia
- Lowered immunity and cancer
- Memory impairment, Alzheimers
- Insomnia
- Gastrointestinal disorders including ulcers and gastritis

Energetics

Warming.

Use in Pregnancy

Use in pregnancy is best avoided, though it is often used in late pregnancy to facilitate labour.

Drug Interactions

Avoid with sirolimus (selective immune-suppressing drug) and tacrolimus (immunosuppressive drug). Caution with benzodiazepines (e.g. midazolam), phenobarbital and warfarin.

Schizandra and liquorice and their selected constituents were found to activate the xenobiotic nuclear receptor pregnane X receptor (PXR) and induce the expression of drug-metabolizing enzymes and transporters in reporter gene assays and in primary hepatocyte cultures. The affected enzymes and transporters include CYP3A and 2C isozymes and the multidrug resistance-associated protein 2. In rats, the herbs increased the metabolism of the co-administered Warfarin and the herbs should be avoided in PXR-mediated drugs.[57]

Another study was conducted to identify Schizandra fruit components capable of having inhibitory effects on CYP3A4 by surveying the effect on human liver microsomal erythromycin N-demethylation activity. The results indicate that gomisin C is a mechanism-based inhibitor that not only competitively inhibits but irreversibly inactivates CYP3A4.[58]

Contraindications

None known.

Administration and Dosage

Liquid Extract:	1:2
Alcohol:	45%
Weekly Dosage:	25 to 60mL
Dried herb:	500mg to 5g daily.

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