Review

**Schisandra chinensis** (Turcz.) Baill

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**Abstract**

Different aspects of the pharmacology of *Schisandra chinensis* fruit and dibenzocyclooctene lignans from this plant are reviewed focusing in particular on the antihapatotoxic, antioxidant and antitumoural activities, and on the effects on physical performance and on the central nervous system. © 1999 Elsevier Science B.V. All rights reserved.

**Keywords:** Schisandra chinensis; Lignans; Antioxidant activity; Antihepatotoxic activity; Antitumoral activity; Physical performance; CNS

**1. Botany**

*Schisandra chinensis* (Turcz.) Baill (Schisandraceae) grows wild in the most Eastern parts of Russia (Primorsk and Chabarowsk regions), the Kuril islands, southern Sachalin and also north-eastern China, Korea and Japan [1]. *Schisandra* species grow mainly in China, Japan, the Himalayas and Jawa. The seeds and the fruit are the parts used in medicine [2–4]. *S. chinensis* is a monoecious liana with attractive leaves and a woody stem. The winding stem, reaching 10–15 m in length and 1.2–1.5 cm in diameter, is twisting around the trunks of trees, climbing to their top. The leaves are alternate, elliptic, cuspidate, with a wedge-shaped base. The flowers are white or slightly cream-coloured, wax-like, unisexual with a pleasant

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smell. The flowers are in clusters of 2–5. When the fruit is ripening, the receptacle is substantially lengthened and turned into a pedicle with the appearance of a grape cluster, 6–8 cm long with several bright red fruits. The fruits, ripen in September–October, have an almost spherical shape and contain 1–2 yellow seeds. The skin and pulp taste sour and sweet. The kernel is pungent, bitter and overall salty. It is called in mandarin ‘wu-wei-zi’, (literal English translation: five-taste fruit), in Japanese ‘Gomishi’, in Korean ‘Omicha’ (Chinese Materia Medica). Experiences of its cultivation were reported [1].

In western botany the Chinese wu-wei-zi was first named Kadsura chinensis in an 1832 publication of the Russian botanist Nikolai S. Turczaninov. In 1856, to honour his most famous colleague K.J. Maximowicz (1827–1891), the Russian botanist Franz J. Ruprecht (1814–1870) created a new genus called Maximowiczia and called the plant Maximowiczia chinensis. In 1866, the French botanist H.E. Baillon (1827–1895) transferred the plant to the genus Schisandra and since that time the plant has been known as S. chinensis (Turcz.) Baill. [3]. The generic name Schisandra is derived from the Greek schizein, meaning ‘to cleave’ and andros, ‘man’, referring to the cleft or separate anther cells on the stamens of S. coccinea. Fructus schisandraceae, of the Chinese Pharmacopoeia, consists of two members: (1) S. chinensis (Turcz.) Baill. (Northern Schisandra) and (2) S. sphenanthera Rehd. et Wils. (Southern Schisandra) [2].

2. Chemistry

Many dibenz[a,c]cyclooctene derivatives, present in different quantities (fruit and seeds: 7.2–19.2%; stems: 1.3–10%) have been isolated from S. chinensis [5–20]. Some of the main structures are shown in Table 1. Biosynthetic precursors to the dibenzocyclooctene derivatives, such as pregomisin and epigalbacin, have been also isolated [20]. The fruits also contain about 1.5% sugars, tannins, colour substances and about 3% of essential oils (citral, β-chamigrene, β-camigrenol, β,β-bisabolene, sesquicarene), organic acids (citric, malic, fumaric and tartaric acid), vitamin C and E, and metals such as copper, manganese, nickel and zinc [21].

3. Pharmacology

S. chinensis is officially listed in the Chinese Pharmacopoeia [22] and indexed as a tonic and sedative. It is also listed in the ‘Shen Nong Ben Tsao Ching’ book, year 1596 (2697 BC) as a superior drug that helps in coughs and prevents asthma. It was first reported in Divine Husbandman’s Classic of the Materia Medica [3]. According to Chinese philosophy the drug has sour and warm properties. It: (a) enters the lung and kidney channels and the stomach meridians; (b) contains the leakage of lung ‘Qi’ and stops coughing (used for deficient lung and kidney patterns with cough and wheezing); (c) restrains the ‘Essence’ and stops diarrhoea (used for nocturnal emission, spermatorrhea, deficiency of the spleen and kidneys); (d) stops
Table 1
Dibenzo(a,c)cycoloctene derivatives from *Schisandra chinensis*

![Chemical structure diagram]

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Note: deoxychisandrin = schisandrin A and wuweizisu A; schisandrin = schisandrol A; schisandrin B = γ-schisandrin and wuweizisu B; gomisin A = schisandrol B; gomisin K₁ = schisanhenol; schisandrin C = wuweizisu C; gomisin C = schisanterin A; gomisin B = schisanterin B; ang, angeloyl; Bz, benzoyl.
excessive sweating (used for deficient ‘Yang’ spontaneous sweating or deficient ‘Yin’ night sweat); (c) calms the spirit (used for forgetfulness and insomnia) [4,10].

S. chinensis fruit has been used for a long time in the Far East as a stimulating and fortifying agent in cases of physical exhaustion, and to inhibit fatigue. The Nanajs tribes used S. chinensis dried berries to combat fatigue in their hunting trips [1].

A monograph on S. chinensis preparations was introduced officially to the Russian Pharmacopoeia in 1961 [23].

3.1. Ant hepatotoxic effect

Several reports indicate that S. chinensis (dried fructus and seed) is an effective liver protective drug [24–26]. In experimental models, Glutamic Piruvic Transaminase (GPT) activities induced by carbon tetrachloride (CCl4) or paracetamol in mice, thiacetamide in rats, and ethinylestradiol 3-cyclopentylether in rabbits were reduced by oral administration of the ethanol extract of the seed of S. chinensis (1–10 g/kg) prior to and after the administration of the hepatotoxic agents [24,25]. The alcoholic extract of S. chinensis kernels reduced elevated GPT levels in mice treated with CCl4 or thioacetamide, while a water extract of the kernels and an ethanol extract of the shells of the seed were ineffective [21]. Primary cultured rat hepatocytes treated with 0.1–1 mg/ml of either an ether, ethyl acetate, methanol or water extract of S. chinensis fruit were effective in reducing the galactosamine and CCl4-induced cytotoxicity [20]. Different lignans isolated from S. chinensis have been associated to this ant hepatotoxic effect [27,28]. Seven lignans isolated from S. chinensis kernels and tested for ant hepatotoxic activity have been shown effective liver protecting drugs [23]. Most of them prevented the elevation of serum GPT levels and the morphological changes of the liver, such as inflammatory infiltration and liver cell necrosis induced by CCl4. Gomisin B (50 mg/kg, p.o.), gomisin A, (50 mg/kg, p.o.), schisandrin C (50–100 mg/kg, p.o.), schisandrin B (50–100 mg/kg, p.o.) deoxyschisandrin (200 mg/kg, i.p.), γ-schisandrin (50–100 mg/kg, p.o.) and gomisin C (200 mg/kg, i.p.) decreased the GPT levels after CCl4 [27]. Gomisin B, gomisin A and schisandrin (at doses of 100 mg/kg, p.o.) were also effective against thiacethamide-induced liver damage in mice [21,27].

In fasting mice, the lignans stimulated the glycogen synthesis, the order of the activity being gomisin A > deoxyschisandrin = γ-schisandrin. The activity of gomisin A was comparable to that of cortisone (100 mg/kg, p.o.). Since similar results were obtained in adrenalectomized mice, the effect of these lignans on glycogenesis seems not mediated by the adrenals [21,27].

Pretreatment of male rats with gomisin A (50 mg/kg, i.p.) prevented the rise in GPT and Glutamic Oxaloacetic Transaminase (GOT) and hepatic necrosis of cells induced by acetaminophen [29]. The repeated administration of gomisin A (30 or 100 mg/kg, p.o., daily for 4 days) induced an apparent increase of liver weight in liver-injured and normal rats [30]. Gomisin A suppressed the increase in serum transaminase activity and the appearance of histological changes such as hepatocyte degeneration and necrosis, inflammatory cell infiltration and fatty deposition
induced in liver by CCl₄, D-galactosamine or D-,L-ethionine [30]. Gomisin A decreased serum triglycerides and lipid contents of the liver. It also increased microsomal cytochrome b₅₆, P-450, NADPH cytochrome C reductase, aminopyrine N-demethylase and 7-ethoxycoumarin O-deethylase and decreased 3,4-benzo[a]pyrene hydroxylase [30].

A hepatoprotective effect of deoxyschisandrin, γ-schisandrin, schisandrin C, gomisin A, and schisandrin has been associated to their inhibitory effect on CCl₄-induced lipid peroxidation and the binding of CCl₄ metabolites to lipids of the liver microsomes [31–33].

Schisandrin B [34] and schisanhenol [35] under oxidative stress, and gomisin A in immunologic liver injury [36] increased the membrane stability of hepatocyte membrane. This effect can be related to a stimulating effect on the hepatic-glutatione antioxidant system [37] and may involve the enhancement of mitochondrial glutathione redox status in rats [38].

It is also suggested that gomisin A (50 mg/kg, i.p.) possesses a liver function enhancing property in normal and injured liver, and that its preventive action on CCl₄-induced cholestasis is sustained by the secretory function of the bile acids independent fraction [39].

Gomisin A and schisandrin B induced hypertrophy and mild hyperplasia, augmenting the liver weight. [¹⁴C]Phenylalanine incorporation, protein content, and hepatic microsomal cytochrome P-450 content were enhanced [40,41]. Gomisin A (10–100 mg/kg, p.o. for 4 days) also increased the liver regeneration in rats after partial hepatectomy, increased the regeneration rate of the liver cells, and improved the serum retention rate of the foreign dye sulfobromophthalain (BSP), which was dose-dependent [42]. In addition, gomisin A also enhanced the incorporation of [¹³C]phenylalanine into liver protein and shortened the hexobarbital-induced sleeping time. These changes caused by gomisin A are similar to those of phenobarbital [42]. However, gomisin A is distinctly different from phenobarbital in the finding that phenobarbital diminished the survival of CCl₄-intoxicated mice, but gomisin A did not [42].

Ultrastructural studies of liver tissue using the transmission electron microscope revealed an increase in rough and smooth endoplasmic reticulum in the groups receiving gomisin A (100 and 300 mg/kg per day). Gomisin A accelerated both the proliferation of hepatocytes and the recovery of liver function after partial hepatectomy and increased hepatic blood flow. It is thought that the liver enlargement caused by repeated administration of gomisin A is associated with the proliferation of endoplasmic reticulum [42].

Gomisin A (10 or 30 mg/kg, p.o. for 3 or 6 weeks) suppressed the fibrosis proliferation and accelerated both the liver regeneration and the recovery of liver function after partial hepatectomy in CCl₄-induced chronic liver injury in rats [43]. Also, gomisin A regenerated the liver tissue after partial hepatectomy by enhancing ornithine decarboxylase activity, which is an important biochemical event in the early stages of liver regeneration in rats [44]. Gomisin A (100 mg/kg, p.o. daily for 14 days) promoted hepatocyte growth after mitosis during regeneration of partially resected rat liver, inducing directly or indirectly an enhanced activation of the
proliferative processes of non-parenchimal cells that involved an increase in \( c-myc \) product, a gene that precedes DNA replication in proliferating cells [45].

The effects of gomisin A on immunologically induced liver injuries have been investigated in vivo and in vitro. Following injection of a small dose of lipopolysaccharide in mice previously treated with heat-killed Propionibacterium acnes, most of the animals died with acute hepatic failure. Gomisin A (5–50 mg/kg, p.o.) reduced dose-dependently the mortality of mice with acute hepatic failure. Histologically, necrosis was suppressed by gomisin A, but infiltration of non-specific inflammatory cells was not affected. In in vitro experiments, the liver cells were injured by antibody-dependent cell-mediated cytotoxicity (ADCC) reaction or activation of macrophage in vitro. Inhibition of the isolated liver cell injuries induced by ADCC reaction or activation of macrophages in vitro, suggested that gomisin A can be markedly protective against immunological liver injuries [46]. In guinea pigs sensitised with trinitrophenylated liver macromolecular protein fraction, gomisin A (50 mg/kg, p.o.) was effective in reducing the acute hepatic failure [47]. Also the acute hepatic failure induced by heat-killed Propionibacterium acnes followed by a small amount of Gram-negative lipopolysaccharide was prevented after 4 weeks of gomisin A (60 mg/kg per day for 4–10 weeks) administration [48]. The survival rate was 80% as compared to 5% of the control group. In Long Evans Cinnamon rats, spontaneously developing hepatitis, treatment with gomisin A did not modify the death rate, but the time of survival was increased by 7–10 weeks as compared with the control group [49].

Leukotrienes are potent inflammatory agents that are thought to play a role in inflammatory liver diseases [50]. In immunological hepatic failure, mononuclear cells are the predominant cells producing leukotrienes. Gomisin A (0.1 mg/ml, added to 10⁷ macrophage cells/ml suspension) produced on the biosynthesis of leukotrienes stimulated in rat peritoneal macrophages by Ca²⁺ ionophore A2318 an inhibitory effect which may be partially associated with its antihapatotoxic effect [51].

3.2. Antioxidant and detoxificant effect

The antioxidant effect of S. chinensis is attributed to the dibenzo[a,c]cyclooctene lignan constituents [52,53]. In in vitro studies, induction of antioxidative enzymes has been observed with S. chinensis lignans which inhibited the lipid peroxidation measured by means of malondialdehyde (MDA) formation induced by iron/cysteine in rat liver microsomes: at 1 mM concentration, schisanhenol, \( S(-)\)-schisandrin C and \( S(-)\)-schisandrin B were shown to be more potent than vitamin E [35]. Schisanhenol (1 mM) and schisandrin B (1 mM) also inhibited gossypol-induced superoxide anion generation in rat liver microsomes. The preventive oral administration (200 mg/kg, once daily for 3 days) of either schisanhenol or schisandrin B reduced liver MDA formation induced by 50% ethanol (15 ml/kg) [54]. In vitro, schisanhenol demonstrated an oxygen scavenging activity in iron/cysteine and NADPH/ascorbic acid method, [55] and CCl₄ (-OH and -CCl₃)-induced lipid peroxidation in hepatocytes [34,56]. The release of GPT and lactate dehydro-
genase (LDH) was also reduced. As a consequence, the hepatocyte viability was increased as well as the integrity of the hepatocyte membrane [35]. Moreover, the hepatoprotective effects of *Schisandra* lignans may be attributed to the enhancement of the hepatic antioxidant system. In fact, schisandrin B and schisanhenol were also able to increase superoxide dismutase, catalase activities in rat liver cytosol, [54] and the function of the hepatic reduced glutathione (GSH) anti-oxidant system [37]. Intragastric pre-treatment of female Balb/c mice with schisandrin B (4–16 mg/kg per day for 3 days) caused dose-dependent increases in hepatic glutathione S-transferase (GST) and glutathione reductase (GRD) activities. In other experiments, 24 h after the last dose of schisandrin B, all rats were treated with CCl₄ (0.1 ml/kg). The activities of glucose-6-phosphate dehydrogenase (G6PDH), Se-glutathione peroxidase (GPX), and gamma-glutamylcysteine synthetase (GCS) are down-regulated to varying degrees in a dose-dependent manner by schisandrin B [37]. The beneficial effect of schisandrin B on the hepatic GSH antioxidant system is more evident after CCl₄ challenge. The hepatoprotection was associated with significant enhancement in hepatic GSH, as indicated by the substantial increase in tissue GSH levels and the corresponding decrease in the susceptibility of tissue homogenates to GSH depletion [37]. The hepatoprotective effect of schisandrin B (8 mg/kg, i.p.) was not affected by 1,3-bis(2-chloroethyl)-1-nitrosourea, an inhibitor of GRD, at a dose of 2 mmol/kg (i.p.) in female Balb/c mice. The mechanism of hepatoprotection by schisandrin B may involve the enhancement of mitochondrial glutathione redox status greatly impaired by CCl₄ intoxication [38].

Interestingly, while well known antioxidant agents such as α-tocopherol acetate did not protect against hepatic damage induced by other hepatotoxins such as aflatoxin B₁ or Cd, *S. chinensis* reduced the hepatotoxic effect of these agents in a non-selective manner (Tables 2 and 3) [57]. In fact, pre-treatment with a lignan enriched extract of *S. chinensis* fruit stimulated the hepatic antioxidant/detoxification system, as shown by increased hepatic GSH levels as well as hepatic GRD and GST activities in rats [57].

Some comparative studies in female Balb/c mice have shown that schisandrin B (12 mg/kg per day, p.o. for 3 days) increased the hepatic mitochondrial-GSH level, whereas butylated hydroxytoluene (BHT) decreased it. However, both schisandrin B and BHT increased, albeit to a different extent, the activity of mitochondrial GRD, particularly after CCl₄ challenge [58]. Pre-treatment with schisandrin B (12 mg/kg/day, p.o. for 3 days) sustained the hepatic mitochondrial GSH level in CCl₄-intoxicated mice and protected against CCl₄-induced hepatotoxicity, while BHT pre-treatment did not. Moreover, while both schisandrin B and BHT increased hepatic ascorbic acid (vitamin C) level in control animals, only schisandrin B pre-treatment sustained a high hepatic vitamin C level in CCl₄-intoxicated mice. Also, schisandrin B pre-treatment prevented the CCl₄-induced decrease in the hepatic vitamin E level. However, schisandrin B inhibited NADPH oxidation in mouse liver microsomes incubated with CCl₄ (10 mM) in vitro, whereas, BHT stimulated this oxidation. The ability to sustain the hepatic mitochondrial GSH level and the hepatic vitamin C and vitamin E levels may represent a crucial
Table 2
The effect of *S. chinensis* and vitamin E treatment on aflatoxin B$_1$ (A-B$_1$)-induced hepatotoxicity in rats$^a$

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hepatic tissue</th>
<th>Plasma GOT (U/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Malondialdehyde (nmol/mg wet tissue)</td>
<td>GSH (mg/mg wet tissue)</td>
</tr>
<tr>
<td>--------------------</td>
<td>----------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Control</td>
<td>0.037 ± 0.002</td>
<td>5.89 ± 0.14</td>
</tr>
<tr>
<td>A-B$_1$</td>
<td>0.048 ± 0.003$^3$</td>
<td>5.62 ± 0.15</td>
</tr>
<tr>
<td><em>S. chinensis</em> + A-B$_1$</td>
<td>0.038 ± 0.001$^5$</td>
<td>7.45 ± 0.42$^{5,c}$</td>
</tr>
<tr>
<td>Vit.E + A-B$_1$</td>
<td>0.047 ± 0.003$^3$</td>
<td>6.08 ± 0.19$^5$</td>
</tr>
</tbody>
</table>

$^a$Values are mean ± S.E.M., n = 5; $^b$P < 0.05 vs. control; $^c$P < 0.05 vs. A-B$_1$; $^d$P < 0.05 vs. *S. chinensis* + A-B$_1$. One-way ANOVA followed by Duncan's multiple range test. (Reproduced with permission of *Pharmacology and Toxicology* [57]).
Table 3  
The effect of *S. chinensis* and vitamin E pre-treatment on Cd-induced hepatotoxicity in rats

<table>
<thead>
<tr>
<th></th>
<th>Hepatic tissue</th>
<th>Plasma GOT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Malondialdehyde (nmol/mg wet tissue)</td>
<td>GSH (umol/L)</td>
</tr>
<tr>
<td>Control</td>
<td>0.044 ± 0.002</td>
<td>7.04 ± 0.22</td>
</tr>
<tr>
<td>Cd</td>
<td>0.054 ± 0.005</td>
<td>6.55 ± 0.24</td>
</tr>
<tr>
<td>+ <em>S. chinensis</em></td>
<td>0.042 ± 0.003</td>
<td>7.07 ± 0.48</td>
</tr>
<tr>
<td>Vit. E + Cd</td>
<td>0.049 ± 0.003</td>
<td>6.03 ± 0.59</td>
</tr>
</tbody>
</table>

Values are mean ± S.E.M., n = 5; 1P < 0.05 vs. control; 2P < 0.05 vs. Cd; 3P < 0.05 vs. *S. chinensis* + Cd. Data were analysed using one-way ANOVA followed by Duncan’s multiple range test. (Reproduced from Ip S.P. et al. [57], with permission of Pharmacology and Toxicology).

The scavenging effects of different structures and configurations of schisandrins on active oxygen radicals have been demonstrated using active oxygen radicals from human polymorphonuclear leukocytes stimulated with phorbol myristate acetate. The scavenging effects of schisandrins depend on the stereoconfigurations, the effect of *S*-(−)-schisandrin B being stronger than that of *R*-(+)-schisandrin and that of schisandrin C stronger than that of schisandrin B [60]. This difference may be explained by the dioxymethyl group that captures electrons facilitating radical attack [60,61]. Surprisingly, the scavenging effect of *S,R* (±)-schisandrin B was stronger than that of either *S*-(−)- or *R*-(+)-schisandrin B. The reason for this effect is unknown [61].

Another lignan, schisanhenol (1 mmol/l) was able to scavenge oxygen radicals produced by human neutrophils stimulated by tetradecanoylphorbol acetate. In Fenton reaction system, the inhibitory rate of hydroxyl radical by schisanhenol was 34.4%. In xanthine–xanthine oxidase and UV-irradiation of riboflavin systems, antioxidant property of schisandrin B in protection against CCl₄ hepatotoxicity [58].

The effects of schisandrin B and vitamin E have been compared on ferric chloride (Fe³⁺)-induced oxidation of erythrocyte membrane lipids in vitro and CCl₄-induced lipid peroxidation in vivo. Vitamin E produced a pro-oxidant effect at 110 μM and a biphasic effect at 1.0 mM on the Fe³⁺-induced TBARS (thiobarbituric acid reactive substances) in human erythrocyte membranes; the pro-oxidant effect, lasting 20 min, was followed by a complete suppression of TBARS antioxidant effect. Schisandrin B (110 μM) was capable to inhibit TBARS formation [59]. Pre-treatment with vitamin E (3 mmol/kg per day, p.o. for 3 days) did not protect against CCl₄-induced lipid peroxidation and hepatocellular damage in mice, whereas schisandrin B pre-treatment (0.3–3.0 mmol/kg/day, equivalent to 1.2–12 mg/kg per day, p.o. for 3 days) produced a dose-dependent protective effect on the CCl₄-induced hepatotoxicity (Table 4) [59].
Table 4  
Effects of Schisandrin B (S-B) and vitamin E pre-treatment on CCl₄-induced hepatotoxicity in mice

<table>
<thead>
<tr>
<th></th>
<th>MDA (pmol/mg tissue)</th>
<th>Plasma ALT (U/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>60 ± 1</td>
<td>14.4 ± 0.7</td>
</tr>
<tr>
<td>CCl₄</td>
<td>87 ± 6ᵇ</td>
<td>12526 ± 796ᶜ</td>
</tr>
<tr>
<td>S-B + CCl₄</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 mmol/kg</td>
<td>68 ± 3ᵈ</td>
<td>1008.4 ± 447.4 (92ᶠ)</td>
</tr>
<tr>
<td>3.0 mmol/kg</td>
<td>56 ± 2ᵈ</td>
<td>24.1 ± 4.6 (99ᶠ)</td>
</tr>
<tr>
<td>Vit. E + CCl₄</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.0 mmol/kg</td>
<td>89 ± 9</td>
<td>12 904 ± 873</td>
</tr>
</tbody>
</table>

ᵃValues are mean ± S.E.M., n = 5;ᵇP < 0.05;ᶜP < 0.001 vs. control;ᵈP < 0.05;ᵉP < 0.001 vs. CCl₄ Student's t-test. The italic number in parentheses is the percent of protection. (Reproduced from [59], with permission of Molecular and Cellular Biochemistry).

schisanhenol scavenged superoxide anion radical by 26.1% and 21.9%, respectively. In all these systems, schisanhenol was more potent than vitamin E [55].

3.3. Anticarcinogenic effect

Benzo[a]pyrenes (BPs) are well known carcinogens, widely distributed in the environment [62,63]. The elimination of these polycyclic aromatic hydrocarbons from the body requires their conversion to water-soluble metabolites [64]. Some of the enzymes involved in BP metabolism, such as cytochrome P-450, epoxide hydratase (EH), and arylhydrocarbonhydroxylase (AHH) are induced by various substances found in edible plants. There is some evidence that consumption of vegetables like sprouts, cabbages, broccoli, alfalfa and fibres may reduce the incidence of stomach and colon cancers [65,66].

The effect of deoxyschisandrin, γ-schisandrin, schisandrin C, gomisin A, B and C orally given (100–200 mg/kg per day for 3 days) to male rats has been studied in vitro on liver microsomal monooxygenases and epoxide hydrolase. Among these compounds, schisandrin B, schisandrin C, gomisin A and biphenyl dimethyl dicarboxylate (BDD), a synthetic derivative of gomisin C, significantly increased rat liver cytochrome P-450 concentration, NADPH-cytochrome C reductase, benzophenamine and aminopyrene demethylase activities. Four compounds (γ-schizandrin, schizandrin C, gomisin A and BDD) also markedly stimulated proliferation of smooth endoplasmic reticulum of liver cells from rats treated with schisandrin B [32].

It is known that phenobarbital (PB; 80–100 mg/kg, p.o. for 3 days)-induced microsomal monoxygenase activities are preferentially inhibited by metyrapone, an enzymatic inhibitor of cytochrome P-450 enzymes involved in the synthesis of adrenocorticosteroids. Schisandrin B, schisandrin C, gomisin A, and BDD inhibited
aminopyrene demethylase activity of liver microsomes in a similar manner. Dual induction by gomisin A (100–200 mg/kg, p.o.) and PB decreased the mutagenicity of BP via a decreased covalent binding of BP metabolites to DNA. Gomisin A also decreased the capacity of BP-induced rat microsomes to activate BP to its mutagenic metabolites [31,32].

Using male mice of the strain C57Bl6 that responded with a marked induction of hepatic microsomal benzopyrene hydroxylase activity, S. chinensis (fructus fine powder, 5% in diet for 14 days) induced a threefold increase in cytochrome P-450. EH was stimulated significantly by S. chinensis. It is known that the addition of purified EH to the Salmonella mutagenicity Ames test reduces BP mutagenicity by 30–50%. Total BP metabolism was significantly increased (1.6-fold) in the S. chinensis (1 mg/ml) group. Phenol II formation relative to total metabolites was significantly increased in the S. chinensis group as compared to the control group [67]. Both 7-ethoxycoumarin O-de-ethylase (ECD) and aryl hydrocarbon hydroxylase (AHH) activities were also increased significantly [68]. The binding of aflatoxin to DNA was diminished by S. chinensis [68].

The effect of gomisin A on hepatocarcinogenesis caused by 3′-methyl-4-dimethylaminoazobenzene (3′-MeDAB) in male Donryu rats has been investigated. Gomisin A (30 mg/kg per day, p.o. for 5 weeks) significantly inhibited the appearance in the liver of foci for glutathione-S-transferase placental form (GST-P), a marker enzyme of preneoplasm. Gomisin A decreased the number of hepatic altered foci such as the clear cell and basophilic cell type foci in the early stages [69,70]. Gomisin A (30 mg/kg per day, p.o.) decreased the concentration of 3′-MeDAB-related azo dyes in the liver, and increased their excretion in the bile. After the withdrawal of 3′-MeDAB, carcinogen related azo dyes were not detected either in the liver or the bile, but the proportion of diploid nuclei, though diminished, remained high. It seems that gomisin A improved liver function by reversing abnormal ploidization [71].

Gomisin A (0.03% in diet for 10 weeks) inhibited the development of preneoplastic liver lesions. In fact, gomisin A inhibited the level of GST-P, and the number and size of GST-P positive foci increased in the liver after treatment with 3′-MeDAB. Moreover, although the population of diploid nuclei was increased and that of tetraploid nuclei was decreased by pre-treatment with 3′-MeDAB, gomisin A reverted this effect to near the normal ploidy pattern [71]. This suggests that gomisin A may inhibit the hepatocarcinogenesis induced by 3′-MeDAB by enhancing the excretion of the carcinogen from the liver and by reversing the normal cytokinesis [72].

Gomisin A (30 mg/kg, p.o. daily for 5 weeks) inhibited the increase in serum bile acid concentration induced by the administration of other tumour promoters such as deoxycholic acid (DCA) [73]. Although hepatocarcinogenesis has been reported to be promoted by exogenous administration of bile acids, the relation of endogenous bile acids to hepatocarcinogenesis is not completely understood [74,75]. The oral administration of gomisin A (30 mg/kg) significantly inhibited the increase of serum bile acids, especially DCA, and the appearance of preneoplastic lesions (number and area of GST-P-positive foci in the liver), induced by 3′-
Fig. 1. Inhibitory effect of gomisin A on the promotion of skin papillomas by 12-O-tetradecanoylphorbol-13-acetate (TPA) in DMBA-initiated mice. From 1 week after initiation by a topical application of 50 μg of DMBA, 2.5 μg of TPA was applied twice weekly. Topical application of gomisin A (5 μmol) and vehicle was performed 30 min before each TPA treatment. Data are expressed as percentage of mice bearing papillomas (A) and average number of papillomas per mouse (B). (Reproduced from Yasukawa K. et al. [77] with permission of S. Karger AG, Basel).

MeDAB. These results confirm that DCA is an endogenous risk factor for hepatocarcinogenesis and suggest that the anticarcinogenic effect of gomisin A may be based on improving metabolism of bile acids [76].

Application (1 μg/ear) of 12-O-tetradecanoylphorbol-13-acetate (TPA), a tumour-promoting agent, to mice induces inflammation. Local application (0.6 mg/ear) of gomisin A inhibited TPA-induced inflammation in mice. Also gomisin J and schisandrin C inhibited the inflammation induced by TPA in mice. The ED$_{50}$ of these compounds ranged between 1.4 and 4.4 μmol, gomisin A showing the strongest inhibitory effect. Furthermore, at 5 μmol/mouse, it markedly suppressed the promotion effect of TPA (2.5 μg/mouse) on skin tumour formation in mice following initiation with 7,12-dimethylbenz[a]anthracene (50 μg/mouse) [77] (Fig. 1).

3.4. Effects on physical performance

A number of Russian reports indicate that _S. chinensis_ is able to counteract the effect of fatigue, increase endurance, and improve the physical performance of sportsmen [78], but no controlled studies were done in the western world until the late 1980s. To validate the hypothesis that this plant can improve the physical recovery, in a first series of trials, 50 g of _S. chinensis fructus_ dried extract were administered to thoroughbred horses prior to a 800-m race at maximum speed, and to polo horses submitted to a 12-min gallop at a speed of 400 m/min, or a 5-min gallop at a speed of 700 m/min [79]. _S. chinensis_ counteracted significantly the anticipatory respiratory and cardiac frequency as compared to the control group.
Fig. 2. Effect of *S. chinensis* treatment on lactate (a) and glucose (b) plasmatic profile in race horses subjected to effort. Arrows represent the first record after the exercise (7 min). Values are mean ± S.E.M., n = 5; * P < 0.05; ** P < 0.01 vs. control (saline); Student’s *t*- test. (Reproduced with permission of *Fitoterapia* [80]).

Also, the seric lactic acid was reduced and the plasmatic glucose increased in *S. chinensis* treated horses. Interestingly, the horses treated with *S. chinensis* were able to complete the race at an average of 1.8 s faster, indicating an improvement in the physical performance of the horses [79–81]. On a second series of studies, the effect *S. chinensis fructus* dried extract (single dose of 6 g, p.o.) was studied in race and spring horses in order to assess whether the type and intensity of the exercise is critical for the effect [80]. *S. chinensis* was capable of reducing significantly the heart rate and respiratory frequency at different time intervals after the trial, particularly in race horses. Plasmatic glucose concentration increased significantly in both types of exercise. The plasmatic concentration of lactic acid was reduced in *S. chinensis* treated horses as compared to the controls, this decrease being again more evident in race horses [80] (Fig. 2).

The liver accomplishes important functions in the metabolisation of lactic acid, and its functionality determines to a great extent the performance level of horses. Accordingly, an increase of the transaminase activity results in an impairment of the horses’ physical performance [82]. As it is known that *S. chinensis* decreases the hepatic transaminases activity [20,21], the hypothesis was made that *S. chinensis* could lower the seric levels of transaminases and, thus, reverse the impaired performance of horses [83]. Indeed, an association between poor performance and high seric levels of hepatic enzymes in sport horses was shown [82]. Moreover, training leads to an increment of creatinine phosphokinase (CPK) [82], an enzyme present in the striated and heart muscle, and intense anaerobic exercise can lead to
muscle skeletal damage, with increase in seric level of CPK and transaminases. Poorly performing sport horses with long lasting high levels of γ-glutamyltransferase (GGT), GOT and CPK were orally administered 3 g of *S. chinensis* dried extract, during 14 days. *S. chinensis* reduced the levels of GGT and GOT in the serum at day 7 and 14 after administration [83]. Surprisingly, the CPK levels were also reduced by day 7 and 14 after administration indicating that these animals presented a muscular damage that could be reverted with *S. chinensis* [83]. Simultaneously, Ko et al. [84] reported a protective effect against physical exercise-induced muscle damage and a myocardial protective effect in rats pretreated with a lignan enriched extract of *S. chinensis* fruit (0.8 g/kg day, p.o for 3 days) [85]. Protection was associated with a significant enhancement in the hepatic antioxidant status, as assessed by GSH and MDA concentrations [84–87]. Fig. 4 summarises the possible effects of *S. chinensis* on the metabolic pathways during maximum physical effort. *S. chinensis* reduced the hepatic damage leading to a decrease in transaminases (GOT, GGT). As a consequence, gluconeogenesis characterised by an increase in seric glucose level was improved. On the other hand, *S. chinensis* reduced the striated muscle damage via a decrease of seric CPK level and reduced the seric lactate levels, probably by an antioxidant effect.

3.5. Activity on central nervous system (CNS)

Activation of the CNS by *S. chinensis* has been evidenced during electroencephalographic examination. In particular, *S. chinensis*, antagonised the effect of substances suppressing the CNS such as barbiturates, chloral hydrate, aminazine, and halothane [88,89]. *Schisandra* lignans (1–5 mg/kg, i.p.) antagonised the effect of hexenal and chloral hydrate in rats [88]. The CNS activating effect of *S. chinensis* was observed even under the presence of antagonist to dopamine receptors DA₂.
Fig. 4. Antioxidant effect of *S. chinensis* on liver and striated muscle during exercise.

[88]. However, potentiation of phenobarbital sleeping time [90] would indicate that *S. chinensis* has a depressing action on the CNS. This could be explained by the presence in the tested extracts of different concentrations of schisandrol A which is known to prolonge the sleeping time induced by phenobarbital and decrease the spontaneous motor activity in mice [91].

The cholinergic system is also significantly influenced by *S. chinensis*. A crude petrol ether fruit extract (10–30 mg/kg, p.o.) decreased the convulsant threshold and potentiated the antidiuretic action of nicotine and potentiated the excitatory action of carbachol on the intestine in rats. This petrol ether extract potentiated the action of reserpine only at higher doses (1.5 g/kg) [92,93]. This extract affected mostly the cholinergic system, with a biphasic response. At dose of 280 mg/kg p.o., it showed an indirect nicotinomimetic action potentiating the carbachol intestinal motility, whereas, a higher dose (840 mg/kg, p.o.) had a cholinolytic effect [93].

Schisanhenol and schisandrin B have been shown to protect peroxidative damage of aging and ischemic rat brain [94]. Schisanhenol and schisandrin (10^−4 M) completely inhibited the swelling and disintegration of brain mitochondria, as well as the reduction of brain membrane fluidity induced by Fe^{2+}/cysteine [94]. In vitro experiments on mitochondria and membrane from ischemic and reperfusion brain indicate that both lignans significantly inhibited production of MDA and loss of ATPase activity induced by reoxygenation following anoxia. Oral administration (150 mg/kg) of schisanhenol or schisandrin B induced increase of cytosol glutathione-peroxidase of brain in mice under the condition of reoxygenation following anoxia [94].

Human intellectual activity can be enhanced by *S. chinensis* so that work efficiency is also increased. Schisandrin (5–10 mg/day, p.o.) improved certain activities requiring concentration, fine coordination, sensitivity and endurance, as
demonstrated in healthy young male adults in the following experiments: insertion of thread into needle within 5 min; error rate in telegraphist reception and transmission; running marathon. *S. chinensis* seed powder (3 g daily, p.o.) could improve vision, enlarge the visual field, improve hearing power, and increase the discriminating ability of skin receptors [95].

3.6. Pharmacokinetics and metabolism

Until now, there are no reports on the pharmacokinetics of *S. chinensis* extracts. After oral administration to healthy male subjects of 15 mg of schisandrin the mean value of maximum plasma concentration was 96.1 ± 14.1 ng/ml [96]. Schisandrin was metabolised by rat liver microsomes to give three main first phase metabolites. Several oxidation routes appear to be involved: hydroxylation of an alkyl substituent at first and then demethylation of the -OCH₃ groups on the aromatic rings. The metabolites were found in urine and bile of rats [97].

After oral administration of 10 mg/kg to rats, the maximum serum concentration of gomisin A (1446.1 ± 131.8 ng/ml) was reached at 15–30 min, over 80% being bound to serum proteins [98–100]. The rapid metabolisation of gomisin A, has been attributed to a first pass effect, producing demethylated metabolites [98] and glucuronic and arylsulfate conjugates [101].

After oral administration to rats of schisandrol A, this compound was absorbed from the gastrointestinal tract with a half-life of 58 min. After i.v. injection of schisandrol A, the blood level showed a biphasic decline, with a half-life of the elimination phase of 42 min. Schisandrol A was detected in urine 1 h after oral administration [10]. Five minutes after i.v. administration, high levels of schisandrol A were found in the lungs, moderate amounts in the liver, heart, brain, and kidneys and low amounts in the ileum and spleen. In the brain, the higher amounts were found in the hypothalamus, corpus striatum and hippocampus, and moderate amounts in the cerebral cortex and cerebellum. These differences may be relevant to the neuroleptic and anticonvulsant properties of schisandrol A [102].

3.7. Toxicology

The acute toxicity for *S. chinensis* fructus dried extract (4:1), standardised to a concentration of 2% of schisandrin was low (LD₅₀ > 21 g/kg, p.o.) in rats [103]. Other authors reported the absence of lethal effects following intragastric administration of 5 g/kg to mice [95]. The oral and i.p. LD₅₀ values in mice for a petroleum ether extract of *S. chinensis* fruit (10% schisandrins) were 10.5 and 4.4 g/kg, respectively. The oral LD₅₀ of a petroleum ether extract standardised to 40% of schisandrins was 2.8 g/kg in mice [93].

An ethanol extract of *S. chinensis* orally given to mice at doses of 0.6 and 1.2 g/kg for 10 days resulted in only mild toxic effects, such as decrease in activity, piloerection and apathy, while body weight increase, blood picture and main organs were not significantly altered [95].

The p.o. toxicity of *S. chinensis* fructus dried extract standardised to a minimum
of 2% of schisandrin was studied in Landrace piglets for 90 days at daily doses of 0.07, 0.36 and 0.72 g/kg. The body weight and food intake, were not affected during the whole experimental period. No changes in the red blood cells, white blood cells, haemoglobin and hematocrit were found. The glycemia, urea and protein concentrations did not show any significant variations with respect to the control. Triglycerides, GOT and GGT were also not modified by S. chinensis administration. In the tissues examined (liver, heart, kidneys, intestine, lungs, spleen and gonads) no toxic effect was observed [103].

In other studies [103] and using the same standardised dried extract of S. chinensis fruit (0.105–0.5 g/kg per day, p.o.), the potential toxic effects on the reproductive function was studied in rats and mice. No foetotoxicity in these experimental models was found. No changes in the implantation efficiency or other investigated parameters were observed.

Information on the toxicity of S. chinensis lignans is very limited. With schisandrin B, no death was observed following a single intragastric dose of 2 g/kg to rats. Intragastric dosing of 200 mg for 30 days caused no significant effect on body weight, haemoglobin and histology of the major organs in mice [95]. Schisandrin B, given intragastrically to dogs at 10 mg/kg daily for 4 weeks, did not affect appetite, body weight, blood picture, liver and kidney functions, as well as the histology of the liver [95].

4. Conclusions

S. chinensis has been used in traditional Chinese medicine for thousands of years. In the last decades, the pharmacology and chemistry of this drug has been extensively studied. Much evidence shows that S. chinensis and its dibenzoclootene lignans may act on the function of the liver. The findings are useful for further understanding the pharmacological basis of S. chinensis as an antioxidant, anticancer, tonic and antiaging drug. Furthermore, S. chinensis might also be useful in the treatment of other diseases related to oxygen free radical injury and metabolic disturbances, such as radiation injury, inflammations and reperfusion of ischemic organs, as well as in stress conditions and sport medicine.

Schisandra lignans seem also a potential source of new synthetic drugs, as is the case of BDD [104,105]. Recently, halogenated gomisin J derivatives have been shown to possess anti-human immunodeficiency virus (HIV) activities, by inhibiting the activity of the enzyme reverse transcriptase as well as expressing cytoprotective activity in HIV-1-infected H9 cells. [106]

Nevertheless, despite the numerous pharmacological studies available, clinical trials are necessary to support the use of S. chinensis in the medical practice.

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