The effect of supplementation with *Scutellaria baicalensis* on hepatic function

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**ABSTRACT**

The dried root of the angiosperm *Scutellaria baicalensis*, also known as Chinese skullcap or Baikal skullcap, is widely used in traditional Chinese medicine, Korean traditional medicine and as a nutritional supplement; several studies have indicated that both the supplement and some of its ingredients may have clinically beneficial actions. However, the National Institutes of Health official guidance states that the use of *Scutellaria* “has been implicated in rare instances of clinically apparent liver injury” and that “the onset of symptoms and jaundice occurred within 6–24 weeks of starting skullcap, and the serum enzyme pattern was typically hepatocellular”, with marked increases in serum alanine transaminase, aspartate transaminase, alkaline phosphatase and bilirubin levels. Careful perusal of all such published case reports showed that in each case the patient was concurrently taking at least one other supplement which had an established association with hepatic dysfunction. The authors hypothesised that long-term supplementation with *Scutellaria baicalensis* does not lead to hepatic dysfunction. The aim of this study was to test this hypothesis by assessing liver function before and after starting supplementation with *Scutellaria baicalensis*. Pre- and post-supplementation serum assays of alanine transaminase, aspartate transaminase, alkaline phosphatase and bilirubin were carried out in 17 patients (16 female) of average age 38.6 (standard error 4.4) years who had each taken 1335 mg dried root daily for an average of 444 (71) days. The mean baseline versus follow-up values for each liver function test were: alanine transaminase: 25.7 (2.6) IU/L v. 25.1 (1.7) IU/L; aspartate transaminase: 22.1 (1.1) IU/L v. 23.5 (1.3) IU/L; alkaline phosphatase: 63.7 (4.6) IU/L v. 63.3 (3.9) IU/L; and bilirubin: 6.1 (0.6) μM v. 6.0 (0.7) μM. None of these changes was statistically significant; indeed, three of the four parameters showed a non-significant decrease over time. Furthermore, none manifested clinical symptoms or signs of hepatic dysfunction during *Scutellaria* supplementation. These results suggest that daily intake of a relatively high level of *Scutellaria baicalensis* for over a year is not associated with any biochemical or clinical evidence of hepatic dysfunction. Indeed, *Scutellaria baicalensis* has been shown in murine experiments to have hepatoprotective actions.

**Introduction and background**

Over 350 species have been identified in the genus *Scutellaria* of the Lamiaceae family, of the order Lamiales of Angiospermae; while many of these species appear to have medicinally useful properties, one species in particular, namely *Scutellaria baicalensis*, is widely used in traditional Chinese medicine, Korean traditional medicine and as a nutritional supplement [13,42]. This species is particularly found in China, the Korean peninsula, Mongolia and parts of Russia [45,22,40,17]. Dried extracts of the root of *Scutellaria baicalensis*, also known as Chinese skullcap or Baikal skullcap, have been found to enhance functioning of the immune system [20,38]; have anti-androgenic and growth-inhibitory actions in prostate cancer [5]; have anti-proliferative and apoptotic activity in acute lymphocytic leukaemia, lymphoma and myeloma cell lines [27]; induce cell cycle arrest and apoptosis in human lung cancer cells [19]; reduce gingivitis and dental plaque [3]; reduce body mass and blood triglycerides in diabetic mice [39]; and have been used for many other conditions, such as the treatment of diarrhoea, dysentery, hypertension, insomnia and respiratory infections [46]. Many active flavonoids have been discovered in the dried root extract of *Scutellaria baicalensis* including baicalein (5,6,7-trihydroxyflavone), wogonin (5,7-dihydroxy-8-methoxyflavone), norwogonin (5,7,8-trihydroxyflavone), baicalin and oroxylin A (5,7-dihydroxy-6-methoxy-2-phenylchromen-4-one) [26,36,43,11].

The United States National Institutes of Health (NIH) has reported that the use of *Scutellaria* “has been implicated in rare instances of clinically apparent liver injury” and that “the onset of symptoms and jaundice occurred within 6 to 24 weeks of starting skullcap, and the serum enzyme pattern was typically hepatocellular” (https://livertox.nih.gov/Skullcap.htm). The NIH web-site quotes in detail a case report published in 1994 in which a 53-year-old woman, with no previous history of hepatic disease and no history of alcohol abuse or viral hepatitis risk factors, developed insomnia, anxiety and jaundice four weeks after starting to take an herbal sleep preparation which contained *Scutellaria* [7]. Her serum liver function tests were markedly elevated, as follows. Serum alanine transaminase (ALT): 1208 IU/L; aspartate transaminase (AST): 25.7 IU/L; alkaline phosphatase: 298 IU/L; and bilirubin: 9.0 mg/dL (normal range < 1.2 mg/dL). Within four weeks of stopping the herbal supplementation, the jaundice had resolved and the serum bilirubin was in...
the normal range and by 12 weeks her serum ALT and alkaline phosphatase concentrations were also in their respective normal ranges.

There have been several more recent similar case reports. A 78-year-old woman presented with acute painless jaundice three weeks after starting a supplement containing *Scutellaria baicalensis*, and her liver function tests were also markedly elevated: serum ALT 1626 IU/L; aspartate transaminase (AST) 1053 IU/L (normal range 15–59 IU/L); alkaline phosphatase: 354 IU/L; and bilirubin: 7.2 mg/dL. Liver biopsy findings were consistent with acute drug-induced hepatitis. Four weeks after stopping the supplement her liver function tests had improved, with the serum alkaline phosphatase and bilirubin levels already normalised.

Chalasani and colleagues reported a series of four female patients, average age 61 years, who developed acute hepatic injury which was thought to be caused by taking flavocoxid, a proprietary blend of bioflavonoids, including baicalin, for osteoarthritis. The mean time to onset after starting flavocoxid was 11.2 weeks, and the mean liver function test findings were: ALT 1268 IU/L; alkaline phosphatase: 510 IU/L; and bilirubin: 9.4 mg/dL. Between three and 12 weeks after stopping flavocoxid their liver function test results had normalised and none of the patients showed evidence of chronic hepatic injury. A similar case report has been published in respect of the over-the-counter arthritis supplement Move Free®, which contains *Scutellaria baicalensis* and regarding a supplement containing *Scutellaria baicalensis* taken for joint pain.

Each of these cases was pursed in detail by the one of authors (BKP). In the case reported by Caldwell et al., the patient had taken an herbal preparation containing both *Scutellaria* and valerian root (*Valeriana officinalis*) to help alleviate her worsening insomnia. An *in vitro* study on human hepatic microsomes has shown that valerian and valerian-containing products inhibit glucuronidation and so are likely to interfere with the metabolism of xeno- and endobiotics. A case of valerian-associated hepatotoxicity has been described, as has a case of valerian-associated hepatitis which responded to steroids.

Interestingly, in the original case report by Caldwell et al., the patient also regularly drank herbal tea containing chaparral leaf (*Larrea tridentata*); this herb, too, has been associated with liver toxicity in many published case reports.

Regarding the case described by Yang et al., the Chinese skullcap-containing supplement taken by the patient, namely Move Free Advanced®, also contained glucosamine and chondroitin. Supplementation with the combination of glucosamine and chondroitin is associated with acute liver injury. Indeed, in their study of 151 patients with chronic liver disease, Cerda et al. concluded that the consumption of products containing glucosamine and/or chondroitin is frequent among patients with chronic liver diseases and should be taken into account on the appearance of alterations in liver function tests not explained by the underlying disease.

In the case series described by Chalasani et al., the acute hepatic injury was attributed to flavocoxid. In addition to baicalin, this also contains the flavan flavonoid catechin derived from *Acacia catechu*. As Chalasani et al. pointed out, ‘The hepatotoxic potential of the green tea extracts that contain catechins in humans is well recognized...’ Two catechins contained within the green tea are epigallocatechin gallate (EGCG) and epicatechin gallate (ECG), and it is generally believed that EGCG is responsible for the hepatotoxicity due to green tea extracts. It is interesting that epicatechin is the flavonoid in that is common to both green tea and flavocoxid, raising the suspicion if it is the culprit ingredient for causing liver injury.’ It is also possible that hypersensitivity may have contributed since ‘immunoallergic features occurred in some patients and flavocoxid is also associated with a hypersensitivity pneumonitis’.

The patient described by Dhaneasekar et al. had been taking the supplement Move Free® which, like Move Free Advanced® (see above), also contained glucosamine and chondroitin. Thus the above comments relating to the association of glucosamine and chondroitin supplementation with acute liver injury apply here also.

Finally, the preparation taken by the patient described by Papafragkakis et al. also contained black catechu, which is derived from *Acacia catechu*. Therefore the above comments relating to catechins also apply here.

The hypothesis

In light of the above evidence, the authors hypothesised that long-term supplementation with *Scutellaria baicalensis* does not lead to hepatic dysfunction.

Evaluation of the hypothesis

This hypothesis was tested by assessing liver function tests in patients before and after starting supplementation with *Scutellaria baicalensis*, in line with the above case reports. It should be noted that the above-mentioned liver function tests are sensitive indicators of hepatic dysfunction, with ALT and AST indexing hepatic necroinflammation, alkaline phosphatase indexing cholestatic biliary tract dysfunction and bilirubin measuring hepatic excretory function.

The hypothesis was tested by assessing liver function tests in patients before and after starting supplementation with *Scutellaria baicalensis*. The study sample of 17 consecutive patients attending the Breakspear Medical Group who had started long-term supplementation with *Scutellaria baicalensis* in 2016–2018. The study had research ethics committee approval and was carried out in accordance with the Declaration of Helsinki. Each patient took three capsules of *Scutellaria* Vegetable (*Scutellaria baicalensis*) (Solgar, Leonia, NJ, USA) daily. Each capsule provided 370 mg raw *Scutellaria* root powder and 75 mg *Scutellaria baicalensis* root extract; the other ingredients were hydroxypropyl methylcellulose (or hypromellose) for the vegetable capsule shell and magnesium stearate as an anti-caking agent.

The study sample of 17 patients consisted of one male and 16 female subjects, with a mean (standard error) age of 38.6 (4.4) years. Each took 1335 mg dried root supplementation daily for an average of 444 (71) days. None of the patients manifested clinical symptoms or signs of hepatic dysfunction, were recorded. From venous blood samples taken prior to starting the supplement and again at least 24 weeks after starting, pre- and post-supplementation serum assays of ALT, AST, alkaline phosphatase and bilirubin were carried out at The Doctors Laboratory (London, UK).

After checking the data distributions for normality using the Shapiro-Wilk test, the changes in liver function tests (post-supplementation versus pre-supplementation) were assessed using the two-tailed paired t-test. The software package used for the statistical analyses was R version 3.4.2, running on an x86_64-w64-mingw32/x64 (64-bit) platform.

The study sample of 17 patients consisted of one male and 16 female subjects, with a mean (standard error) age of 38.6 (4.4) years. Each took 1335 mg dried root supplementation daily for an average of 444 (71) days. None of the patients manifested clinical symptoms or signs of hepatic dysfunction during *Scutellaria* supplementation.

The pre- and post-supplementation mean values of each of the liver function tests, together with their associated t-test statistics, are shown in Table 1 and Figs. 1–4. None of the corresponding Shapiro-Wilk tests showed any evidence of deviation from normality. It should be noted that the units for bilirubin concentrations are given as μM, which is the unit most commonly used in the UK for this assay, in contrast to mg/dL, which is the unit of choice in the USA. The laboratory normal ranges for these four assays were as follows: ALT 10–35 IU/L; AST < 31 IU/L; alkaline phosphatase 35–104 IU/L; and bilirubin < 20 μM (equivalent to approximately 1.17 mg/dL).

Discussion

In the present study, all the baseline values of the four liver function tests were within their respective normal ranges. They all remained
normal following an average of 444 days' supplementation with a relatively high daily intake of 1335 mg dried *Scutellaria baicalensis* root. Not only was none of the changes in each of these four tests statistically significant, but three of the four assays showed a non-significant decrease over time, corresponding to a non-significant improvement in hepatic function while taking this supplement.

Table 1
Pre- and post-supplementation liver function test results. Standard errors are given in parentheses. The corresponding Shapiro-Wilk tests showed no evidence of deviation from normality.

<table>
<thead>
<tr>
<th>Serum assay</th>
<th>Mean pre-supplementation concentration</th>
<th>Mean post-supplementation concentration</th>
<th>Paired t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Mean (SE))</td>
<td>(Mean (SE))</td>
<td>t</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>25.76 (2.62)</td>
<td>25.06 (1.75)</td>
<td>0.30599</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>22.06 (1.99)</td>
<td>23.50 (1.25)</td>
<td>1.0790</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/L)</td>
<td>63.71 (4.56)</td>
<td>63.29 (3.93)</td>
<td>0.14026</td>
</tr>
<tr>
<td>Bilirubin (μM)</td>
<td>6.12 (0.59)</td>
<td>6.00 (0.66)</td>
<td>0.2120</td>
</tr>
</tbody>
</table>

Fig. 1. Boxplots showing pre- and post-supplementation ALT concentrations.

Fig. 2. Boxplots showing pre- and post-supplementation AST concentrations.

Fig. 3. Boxplots showing pre- and post-supplementation alkaline phosphatase concentrations.

Fig. 4. Boxplots showing pre- and post-supplementation bilirubin concentrations.

In attempting to reconcile the present results with the case report findings detailed above, it is noteworthy that, in all the case reports, the patients had taken a combination of supplements rather than a supplement consisting of just *Scutellaria baicalensis* (as in the present case).
study. As mentioned above, in each case at least one of these supplement ingredients is known to cause liver damage.

Thus, it is possible that the acute liver injury reported in the above case reports. Furthermore, far from a mechanism of hepatotoxicity having been found, *Scutellaria baicalensis* has actually been shown to have hepatoprotective actions. For example, in a rat model, *Scutellaria baicalensis* has been reported to inhibit hepatic fibrosis induced by carbon tetrachloride or bile duct ligation [31]. In another rat experiment, *Scutellaria baicalensis* was found to protect against aflatoxin-B1-induced hepatic mutagenesis [14]. Again, a study in mice has shown that *Scutellaria baicalensis* protects against alcohol-induced acute liver injury, possibly by downregulating a marker of endoplasmic reticulum stress [16]. Indeed, skullcapflavone I derived from *Scutellaria baicalensis* may potentially be able to reverse liver fibrosis [33]. It has also been found that baikalin, baicain and wogonin, derived from *Scutellaria baicalensis* inhibit hemin-nitrite-hydrogen peroxide-induced hepatic injury; this appears to be dose-dependent and mediated by the inhibition of certain nitro-oxidative reactions [47]. Low-dose baikalin has been shown to upregulate the expression of multiple angiogenic genes to increase cell proliferation in developing blood vessels, while high-dose baikalin inhibits angiogenesis by inducing cell death, suggesting dose-dependent dual effects; the compound baikalin has been found to exhibit only inhibitory effects [48].

It is germane to draw attention to the detailed review of herbal and dietary supplement hepatotoxicity by Bucherntavakul and Reddy [6], who point out that ‘Currently, there is no gold standard, even with a liver biopsy, for the diagnosis of herbal hepatotoxicity. The diagnosis, therefore, depends greatly on the exclusion of other causes of liver disease by a thorough clinical assessment, as well as laboratory testing. The possibility of herbal hepatotoxicity superimposed on pre-existing liver disease should also be considered, especially because many herbal remedies are used by patients with chronic liver diseases, and in this situation, it is more challenging to make a clear-cut diagnosis.’ They point out, for example, that acute hepatitis E has been found to be responsible for some suspected cases of drug-induced hepatic injury. Therefore, in cases of elevated liver function test results in patients taking supplements, it is important to check for other causes including various types of infectious hepatitis, α1-antitrypsin deficiency, chemically induced hepatitis, haemochromatosis, Wilson’s disease, non-alcoholic steatohepatitis and tick-borne illnesses such as chronic Q-fever. Indeed, it is noteworthy that not all the above case reports point to a possible association between *Scutellaria* supplementation and hepatotoxicity involved a comprehensive search for other causes of liver toxicity.

In sum, the present study provides no evidence that *Scutellaria baicalensis* supplementation is associated with liver damage. In clinical practice it should be noted that baikalin may increase the risk of bruising and bleeding, especially if a patient is taking anticoagulant medication [28]. It may also decrease statin levels; it is metabolised by the cytochrome P450 system and so may potentially lead to increased side-effects of other prescribed drugs [18]. Sixteen of the 17 participants in the present study were female, and the average age of all the participants was in the 30s; therefore, without further testing of more male participants or of those of more advanced age, caution must be exercised in concluding that *Scutellaria* will not lead to hepatic dysfunction in patients.

Finally, it is noteworthy that, in general, γ-glutamyl transpeptidase (GGT) levels were not reported in the studies mentioned above. This is in spite of the fact that the GGT level is a highly sensitive and non-specific test of hepatic function; its level usually rises before the levels of other liver function test enzymes when the bile ducts become obstructed and it is a particularly sensitive liver enzyme for detecting bile duct problems. It is therefore recommended that the GGT level be included in future studies of this herb. In the cohort described in the present study, pre- and post-supplementation GGT levels were available for 15 out of the 17 patients and showed a non-significant decrease. The mean pre-supplementation GGT level was 15.13 (2.75) IU/L, while the mean post-supplementation level was 13.80 (1.30) IU/L (normal range 6–42 IU/L; t = 0.4987, df = 14, p = 0.6258; LibreOffice Calc v. 6.0.7, build ID: 1:6.0.7-0ubuntu0.18.04.9, OS: Linux 4.15). Again, these findings are in line with our hypothesis.

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**Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**References**


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