Monograph of *Scutellaria lateriflora*

by Helen Lowe Metzman

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Botanical nomenclature

Botanical Name: *Scutellaria lateriflora* (Linné.)
Common Name: Mad-dog Skullcap (syn. Scullcap)
Other Common Names:
United States: Virginia Skullcap, Hood-wort, Helmetflower, Blue Pimpernel, Side-flowering Skullcap, Hooded Willow-herb, Mad-weed, Mad-Dog Weed
France: Scutellaire, Toque
Germany: Helmkraut, Sumpfhelmkraut
Italian: Scutellaria
Spanish: Escutelaria
Etymology: *Scutella*, meaning "little dish" or *scutellum* meaning "little shield" both describe the shape of the calyx. *Lateriflora* means that the flowers on the racemes are turned to one side. In the 1700s the Genus was *Cassida*, which meant "helmet," referring to the upper part of the calyx (Leonard, 1927, 704).
Botanical Family: Lamiaceae (old family name: Labiatae)

Definition

Skullcap consists of the above ground (leaf, stem and flower) or aerial parts, which are collected when the plant is in flower between July and September (British Herbal Pharmacopoeia, 1983). The herb can be fresh, dried, whole, crushed, chopped or pressed (Youngken, 1948).

Marcroscopic identification

Distribution: Skullcap is a perennial indigenous North American herb found growing in moist thickets, woods, fields, and bottomlands throughout the continent. The plant's geographic range extends from Newfoundland to British Columbia and south to Georgia and California. The herb spreads by slender rhizomes and runners (Brown & Brown, 1984) (Gleason & Cronquist, 1963).
Stem: Erect or reclining, 1-8 dm tall with thin glabrous quadrangular stems that are branched or unbranched, width can reach 1-4 mm, lower parts of stem can be yellowish-green and the upper parts a darker green or purplish in color, ridges in upper part covered with white hairs (Brown & Brown, 1984) (Gleason & Cronquist, 1963) (Youngken, 1948).
Leaves: Opposite, thin, mostly glabrous, ovate to lanceovate with serrate or heavily toothed margins, subcordate or rounded at base, pinnately veined, 2.5-10 cm long, upper surface dark green, light green below, and a petiole of 5-25 mm long (Brown & Brown, 1984) (Gleason & Cronquist, 1963) (Youngken, 1948).
Inflorescence: Narrow spikelike one-sided racemes 3-10 cm in many of the leaf axils and occasionally one terminal, raceme subtended by large leaves (Brown & Brown, 1984).
Flowers: Solitary in leaf axils, or in one-sided racemes. Irregular, slender, tubular, two lipped corolla, 6-10 mm blue, violet or white, hairy, 4 stamens under the upper lip, bearded filaments (Brown & Brown, 1984).
Calyx: 2-lipped of similar length, 3-4 mm bell shaped, rounded without teeth at tips, upper lip cap-like or saucer like protuberance near center, pubescent (Brown & Brown, 1984) (Gleason & Cronquist, 1963).
Nutlets: 1.4-1.7 mm, pale, on a short stalk above receptacle (Brown & Brown, 1984, 796-7)

Adulterants

Skullcap has a reputation for being substituted and adulterated with other members of the mint family (Lamiaceae) (British Herbal Pharmacopeia, 1983). The 22nd edition of the *US Dispensatory* described

Scutellaria as "one of the most substituted and adulterated plants in the Materia Medica" (The Dispensatory of the United States of America, 1937). For similar nervine actions, *Scutellaria lateriflora* is often substituted by other species such as *S. galericulata, S. minor, S. integrifolia*, and *S. versicolor, S. hyssopifolia* (Grieve, 1971) *S. canescens*, and *S. cordifolia* (Wolfson & Hoffmann). The 1983 edition of the British Herbal Pharmacopoeia makes note that it was probable that their definition of skullcap was on germander (*Teucrium spp.*), a similar looking member of the Lamiaceae family.

In the late 1980s four cases of hepatotaxicity (hepatocellular jaundice) in Great Britain, three in Edinburough and one in Tyneside, were associated with skullcap consumption (MacGregor, Abernethy, Dahabra, Cobden & Hayes, 1989). The first case involved a woman who had been taking a product called Neurelax and the other cases involved Kalms tablets for anxiety. Both products indicated that they contained skullcap, valerian, and other herbs. Other cases of hepatitis and liver damage were reported after skullcap consumption in Australia and Norway (De Smet, 1993). Eventually, it was later thought and finally proved that skullcap had been adulterated with European germander (*Teucrium chamaedrys* L.) and American germander (*Teucrium canadense*) (Gafner et al., 2003) (De Smet, 1993 and 1997). Furthermore, seven reports of hepatotoxicity on individuals taking *Teucrium chamaedrys* for weight loss were reported in the late 1980s through the early 1990s (Larrey D, Vial T, Pauwels A, Castot A, Biour M, David M, et al., 1992). Eventually, 26 cases of acute hepatitis in France and two cases in Canada were associated with *Teucrium chamaedrys* (Liliberte & Villeneuve 1996). American germander, additionally referred to as pink skullcap in wholesale markets, has also been incorrectly marketed as *Scutellaria lateriflora* (Foster & Tyler, 1998) (Duke, 2006).

Due to the adulteration issue, a comparison study was made of *Scutellaria lateriflora*, *Teucrium canadense*, and *Teucrium chamaedrys* to distinguish the species (Gafner, Bergeron, Batch, Angerhofer, Sudberg, & Sudberg, 2003). The study revealed that *S. lateriflora's* predominant constituents are biacalin, lateriflorin, dihydrobaiclain, and baicalein, and none of these constituents were detected in *Teucrium*. Teucrioside is dominant in *T. chamaedrys* and not present in *S. lateriflora*; whereas the phenylpropanoids of verbascoside and teucrioside are most prevalent in *T. canadense*. Other distinguishing microscopic characteristics seen in *T. canadense* include "strap-shaped trichomes on the stem, as well as bristle-like trichomes on the leaf" (Gafner, Bergeron, Batch, Angerhofer, Sudberg, & Sudberg, 2003, 453). Microscopic magnification (400x) reveals that *T. chamaedrys* contains a waxy cuticle with stomata and glandular scales. The hepatotoxicity from *Teucrium spp.* is thought to be due to diterpenes with an oxidized

Scutellaria lateriflora (skullcap)

furane ring and according to the study, the extracts of *S. lateriflora* did not contain this moiety.

HPLC comparisons: To distinguish *S. lateriflora* and *S. galericulata* from *Teucrium chamaedrys*, chromatography indicated the presence of 6-hydroxy flavones without B ring substituents were only present in *Scutellaria spp.* (Peck, Rowe and Harkliss, 1993). A study on the adulteration of *Scutellaria lateriflora* found that *S. galericulata's* major constituent is 2'-methoxychrysin and not present in *S. lateriflora* (Gafner, Bergeron, Batch, Angerhofer, Sudberg, & Sudberg (2003).

Taste/Odor/Energetics

Taste: Bitter (British Herbal Pharmacopoeia, 1996), (The Dispensatory of the United States of America, 1937).

Odor: Not aromatic (Cook, 1869) or a slight odor (British Herbal Pharmacopoeia, 1996) (The Dispensatory of the United States of America, 1937).

Energetics: Not mentioned in traditional authoritative literature, but a recent book on the energetics of western herbs states that skullcap is cool and dry (Holmes, 1998).

Summary of physiological actions:

Neurotrophorestorative, anxiolytic, nerve tonic, antispasmodic, sedative, slightly astringent, analgesic, anticonvulsive, anti-seizure.

Key constituents

The flavonoids baicalin and baicalein are thought to be main active constituents in *S. lateriflora*. Recent research shows that baicalin and baicalein are in greater concentrations than scutellarin, which was once thought to be the prominent constituent. (Bergeron et al, 2005) (Lehmann, 2000).

Flavonoid glycosides – baicalin; dihydrobaicalin; lateriflorin; scutellarin; 7-glucuronyloxy-5,6,2'-trihydroxyflavone-glycoside (ikonnikoside I); oroxylin A-7-O-glucuronide (Bergeron, et al, 2005) (Gafner, Bergeron, Batch, Angerhofer, Sudberg, & Sudberg (2003).

Flavonoid aglycones – baicalein; oroxylin A; wogonin; 5,6,7-trihydroxy-2' methoxyflavone (Bergeron, et al., 2005)

Note: Another study of the flavonoids in three different *S. lateriflora* extracts did not detect p-coumaric acid, ikonnikoside I and 5,6,7-trihydroxy-2'-methylflavone-7-0 glucoronide (Awad et al., 2003).

Fig 1: Scutellarin

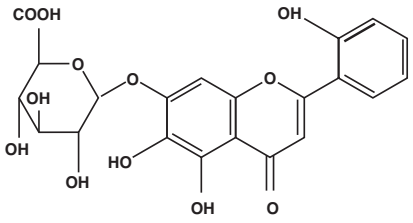


Fig 2: Baicalin

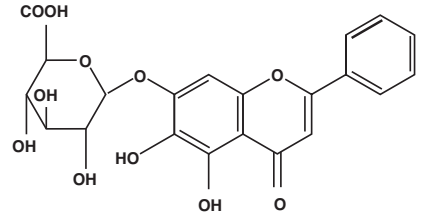


Fig 3: Baicalein

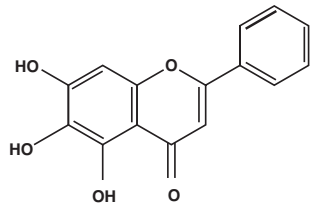
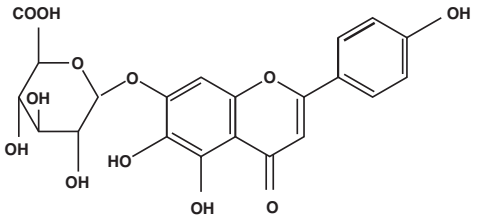


Fig 4: Ikonnikoside I



Amino acids – Glutamine (HPLC testing showed 31.2 mg/g of aqueous solution); glutamate, β-alanine, hypotaurine, taurine, and GABA (HPLC testing indicated that all of these amino acids were less than 5 mg/g extract) (Awad et al, 2003). Another study by Bergeron et al (2005) states that GABA is the dominant amino acid (approximately 0.55%), glutamine (0.34%) and in quantities of less than 0.1% are tryptophan,

phenylalanine, praline, gluamic acid, arginine, asparagines, aspatric acid, tyrosine, isoleucine, leucine, and valine (Bergeron et al., 2005, p. 3079).

Iridoids – catalpol (Yaghmai, 1988)

Volatile oil and waxes – 9 monoterpenes with β-pinene and camphene (Yaghmai, 1988) and diterpenes – limonene and caryophyllene (Wohlmuth, 2002). Sesquiterpenes are 78.3% of the essential oil including δ-cadinene (27%), calamenene (15.2%), β-elemene (9.2%) (Yaghmai, 1988)

Comparisons of baicalin and baicalein in *S.lateriflora, S. baicalensis,* and other Scutellaria species:

In *S. lateriflora*, baicalin has been shown to vary between 0.84 – 5.85% while baicalein varies between 0.021 – 0.494% (Gafner, 2006). Studies of *S. baicalensis* have shown that baicalin, depending on the source, varies between 4.3% – 17% (Gafner, 2006). The ratio of baicalin (40 mg/g) to baicalein (21 mg/g) in *Scutellaria lateriflora* in a 50% ethanol extract was approximately 2:1. However, a 95% ethanol extract yielded more baicalein than baicalin. The roots of *S. baicalensis* in a 50% ethanol extract yielded four and six times the amount of baicalin to baicalein (Awad et al., 2003, p.648). Additionally, the roots of nine species of *Scutellaria* were tested and compared to the leaves and stems for flavonoid concentrations. The roots were determined to have greater concentrations of baicalin to baicalein (Awad et al., 2003). Further research on root extracts of *S. lateriflora* is necessary to test for flavonoid concentrations.

Pharmacology

Pharmacodynamics of whole herb

Anxiolytic effects: An *in vivo* study of behavioral tests on rats using hydroalcoholic extractions of *S. lateriflora* in a milk solution (1 ml of aqueous extract -100 mg extract/ml milk solution) were compared to a control group using only 1 ml milk solutions (Awad et al., 2003). According to the study, rats treated with *S. lateriflora* displayed more risky, less anxious behavior than the control rats.

Cytochrome P450 3A4 enzyme inhibition(CYP 3A4): A study that measured three commercially prepared and different concentrations of hydroalcoholic, glycerin, and glycerin-ethanol tinctures as well as two crude extracts of *S. lateriflora* demonstrated that all of the samples *in vitro* inhibit CYP 3A4 at least by 84% (Awad et al., 2003). The potential for CYP 3A4 inhibition suggests that there may be a herb-drug interaction when taking *S. lateriflora* with pharmaceuticals. It is interesting to note that many *in vitro* research studies show similar results of other medicinal plants inhibiting CYP 3A4. *In vivo* research is necessary to support these findings.

Prevention of seizures: Researchers gave rats that had been induced with lithium/pilocarpine seizures different preparations traditionally used for the prevention of seizures and anticonvulsant. A combination of *Gelsemium sempervirens, Datura stramonium,* and *Scutellaria lateriflora* was given for 30 days and compared to rats given only tap water, Kombucha tea, colloidal metals, and a larger cocktail of herbs that also contained *Gelsemium sempervirens, Datura stramonium,* and *Scutellaria lateriflora*. The rats that received only the herbal treatment of *Gelsemium, Datura*, and *Scutellaria* displayed no seizures during the 30 days; whereas, the herbal cocktail only "attenuated the numbers of seizures, but did not eliminate them" as was originally anticipated due to the synergistic effect from the combination of herbs (Peredery & Persinger, 2004, 702). None of the other treatment groups showed any reduction in the number of seizures. The seizures resumed after the herbal treatment of *Gelsemium, Datura*, and *Scutellaria* was removed (Peredery & Persinger, 2004)

Anti-inflammatory evaluation: *S. lateriflora* whole herb, hot water and alcohol extracts were tested *in vitro* for the inhibition of COX-1 and COX-2 inflammatory responses (Gafner, et al.). The study was performed on cell-free enzyme inhibition assays. Interestingly, the hot water extraction, which had a fewer total flavonoid content, was more effective than the alcohol extraction with greater quantities of flavonoids. Although both extraction methods demonstrated anti-inflammatory responses, the authors speculate that constituents other than flavonoids also contribute to the anti-inflammatory effect.

Pharmacology of constituents found in *S. lateriflora*

Note: The anxiolytic and neurotorophorestorative actions of *S. lateriflora* have only been recently studied and there are only a few peer-reviewed studies which attempt to explain its nervine activity. Due to the lack of scientific studies, researchers are attempting to draw pharmacological comparisons of *S. lateriflora* from Baical

skullcap (*S. baicalensis*) since the two species share similar constituents. *S. baicalensis*, a popular herb from China commonly referred to as *huang-qin*, is used for chronic inflammatory conditions such as allergies, asthma, arthritis, infections, fevers, and as an antioxidant. *S. baicalensis* has been extensively studied with research on whole plant as well as individual constituents. Many of the studies have been on baicalin, baicalein, and wogonin, all of which are present in *S. lateriflora*, although not in the same concentrations as in *S. baicalensis*. The potential that *S. lateriflora* may also share the same pharmacological actions with *S. baicalensis* exists and further research is necessary to substantiate these assumptions.

Anxiolytic effects

$GABA_A$ receptor binding: Gamma-aminobutyric acid (GABA) is an inhibitory amino acid neurotransmitter aiding to induce relaxation and sleep and to balance the excitatory activity of the brain (Germann & Stanfield, 2002). $GABA_A$ receptor agonists typically produce anxiolytic or sedative hypnotic effects. Pharmaceuticals such as benzodiazepines, e.g. Diazepam (Valium), exhibit anxiolytic activity since they help to induce GABA binding. In studies of *S. baicalensis*, two constituents, baicalin and its aglycone baicalein, both of which are also found in *S. lateriflora*, demonstrated *in vitro* binding to the benzodiazepine site of a $GABA_A$ receptor (Awad et al., 2003). Another study of the flavonoids in *S. baicalensis* demonstrated the constituents, baicalein, baicalin, scutellarein, oroxylin A, and wogonin (all present in *S. lateriflora*) had affinities as ligands for the benzodiazepine binding site of $GABA_A$ receptor complex (Wang, Hui, Chen, Xu, Wong, & Xue, 2002). Wogonin, in a separate study, demonstrated *in vitro* interactions with the $GABA_A$ receptor and *in vivo* anxiolytic effects without myorelaxant effects in mice (Hui, Huen, Wang, Zheng, Sigel, Baur, et al.,2002). It is important to note, however, that wogonin is only 0.02% in *S. lateriflora* as opposed to 0.2% in *S. baicalensis* (Hui et al., 2002) (Bergeron et al, 2005). In a Vogel conflict test, mice treated with baicalin and baicalein displayed anxiolytic effects and compared to the benzodiazepine receptor agonist, chlordiazeposide and a $5\text{-}AT_{1A}$ receptor agonist (Liao, Hung, & Chen, 2003). Higher doses of baicalein (10 mg/kg – i.p.) and baicalin (20. mg/kg), but not lower doses of baicalein (5.0 mg/kg) nor baicalin (5.0 and 10.0 mg/kg), increased the number of shocks in a lick shock paradigm. Since baicalein and baicalin were antagonized by a benzodiazepine receptor antagonist, flumazenil, but not a $5\text{-}HT_{1A}$ receptor antagonist, the authors speculate that the anxiolytic effects of the constituents are due to their affinity to the benzodiazepine sites of $GABA_A$ receptors (Liao, Hung, & Chen, 2003).

Baicalin Demonstrates Anxiolytic Effects Without Motor Depression or Myorelaxation: Mice treated with baicalin (7.5-30mg/kg) in an elevated plus-maze (EPM) displayed an increase in percentage of open arm entries as well as time spent in the open arms without any obvious change to locomotor activity (Xu, Wang, Tsang, Ho, Zheng, Yuen, et al., 2005). This study suggests that baicalin might activate benzodiazepine binding sites of the $GABA_A$ receptor, creating an anti-anxiety effect on the mice. Furthermore, in a hole-board test, there were not any significant changes in head dips for mice treated with baicalin in comparison to control mice solely treated with water. These observations imply that the baicalin, with its anxiolytic effects, does not necessarily affect motor control of the mice.

Comparisons of amino acid concentrations as possible contributors to sedative/anxiolytic effects: There is speculation that the amino acid content of *S. lateriflora* contributes to the plant's anxiolytic properties. HPLC was conducted on different *S. lateriflora* extracts to determine the plant's dominant amino acids (Awad et al, 2003). These amino acids were then compared to the amino acid compositions of two other "anxiolytic" plants, *Valeriana officinalis* and *Passiflora incarnata* and to three "non-anxiolytic" plants, *Oxytenantera abyssinica, Echinacea pallida*, and *Echinacea purpurea* (Awad et al, 2003). According to the study, the GABA concentrations in *S. lateriflora* (1.53 mg/g aqueous extract/ 1.65 mg/g alcoholic extract) were not as high as in *P. incarnata* (3.4 mg/g) but higher than in *V. officinalis* (exact concentration not given in study). The authors suggest that glutamine, the amino acid of highest concentration in *S. lateriflora* (31.2mg/g of aqueous extract) and *V. officinalis* (24.6 mg/g extract) and of second highest concentration in *P. incarnata* (2.6 mg/g), may furthermore contribute to the herbs' anxiolytic properties. Glutamine has the capability to cross the brain-blood barrier where GABAnergic

neurons metabolize it to GABA (Awad et al, 2003). Interestingly, however, of the three "non-anxiolytic" plants, *O. abyssinica* had "higher amounts of all amino acids compared to the other plant samples" (Awad et al, 2003, 648). The extracts of both species of *Echinacea* revealed low concentrations of the tested amino acids. The data from *O. abyssinica* contradicts what the authors had hypothesized, since the plant had more than double the amount of GABA and half the concentration of glutamine found in *S. lateriflora*. Further research is necessary to determine whether amino acid concentrations contribute to anxiolytic properties of *S. lateriflora*.

Inhibition of [^{3}H]-LSD Binding to Serotonin-7(5-HT$_7$) receptors: Serotonin-7 receptor ligands may be involved in the nervine tonic activities of *S. lateriflora* (Gafner, Bergeron, Batcha, Reich, Arnason, Burdette, et al., 2003). A HPLC study was made to isolate constituents from a hot aqueous extract (1:20) and a 70% ethanol extract (1:10) of *S. lateriflora*. All of the dominant isolated flavonoid constituents, baicalein, baicalin, scutellarin, wogonin, 7-glucoronyloxy-5,6,2'-trihydroxylavone (ikonnikoside 1) and dihydrobaicalin had the capacity to inhibit [^{3}H]-LSD binding and bind to the 5-HT$_7$ receptor. The authors speculate that these constituents contribute to the binding activity of *S. laterflora* extracts to the 5-HT$_7$ receptors. The study also suggests that flavone glucuronides had a greater affinity than the non-glycosylated compounds to bind to the receptors. There is still uncertainty as to whether these ligands act as agonists or antagonists, are specific for the 5-HT$_7$ receptor, and/or bind to other serotonin receptors (Gafner, Bergeron, Batcha, Reich, Arnason, Burdette, et al., 2003).

Potential for an anti-inflammatory effect

The flavonoids, baicalin, baicalein and wogonin, have been shown to "inhibit [the inflammatory processes promoted by] LPS-induced NO production and iNOS gene expression, as well as the increase in TNFα levels by RAW 264.7 cells" (Calixto, Campos, Otuki & Santos, 2004, 95). Other studies suggest that baicalein in approximate IC$_{50}$ value of 1.8μ/mL prevents eotaxin production (Calixto, et al., 2004, p. 95). Eotaxins are specific chemokines that select and attract eosinophils to an inflammatory site. Cytokines also influence the expression of genes responsible for maintaining the inflammatory processes, and baicalin (IC$_{50}$ value of 3 to 50 μ/mL) has been demonstrated to inhibit the expression of "IL-1β, IL-6, TNFα, INFγ, MIP-α/β" *in vitro* (Calixto et al., 2004, 95).

Another research study showed that when baicalin was injected into rat skin with IL-8, a pro-inflammatory cytokine, it resulted in "significantly inhibited IL-8 elicited neutrophil infiltration" (Li, Fu, Gong, Dunlop, Kung, Yan et al., 2000, 295). The authors conclude that baicalin was able to influence the inflammatory process by interfering with the chemokine receptor binding complex due to a reduction of chemotaxis from chemokine ligands *in vitro* and suppressed inflammatory capability of IL-8 *in vivo*.

Baicalein inhibited the production of interleukin-12 (IL-12), an inflammatory agent, in lipopolysaccharide (LPS)-stimulated primary mouse macrophages through the inhibition of transcription factors NF-κB and the binding to the NF-κB sequence of the IL-12 site (Kang, Chang, Kim, Cho & Kim, 2003).

Endothelial leukocyte adhesion molecule-1 (ELAM-1) and intercellular adhesion molecule-1 (ICAM-1) are found to be expressed in inflammatory conditions such as asthma, rheumatoid arthritis, and atherosclerosis. Inflammation development involves the "adhesion of activating leukocytes to the vascular endothelium" (Kiruma, Matsushita & Hayashi, 2001, p. 332). *In vitro* research demonstrated that baicalin inhibited ELAM-1 and ICAM-1 induced by thrombin and thrombin receptor agonist peptide, therefore suppressing the inflammatory response (Kiruma, Matsushita & Hayashi, 2001).

Antioxidant activities

Both baicalin and baicalein, which were isolated from *Scutellaria rivularis*, a species used in folk medicine in Tawain, displayed antioxidant activities (Shieh D, Liu L, & Lin C, 2000). Baicalin displayed an ability to scavenge superoxide free radicals, while baicalein inhibited xanthine oxidase, a flavoprotein enzyme which catalyzes xanthine to uric acid yielding "superoxide anions" (Shieh et al, 2000, p. 2862).

Potential hepatoprotection

Baicalin and baicalein and to a lesser amount wogonin, were shown *in vitro* to influence metabolic activity in

mitochondria potentially effecting apoptosis in human hepatoma cell lines Hep G2 and SK-Hep1 with a slight influence in Hep 3B cell lines (Chang, Chen, & Lu, 2001).

Pharmacokinetics

Research on flavonoid glycosides metabolism indicates that intestinal bacteria *E. coli HGU* and *Bacteroides J-37* transform baicalin to its aglycone baicalein (Kim D, Jung E, Sohng I, Han J, Kim T & Han M, 1997). The baicalein is then conjugated back to bioavailable baicalin "by glucuronidation in the body, intestine and liver" (Akao T, Kawabata K, Yanagisawa E, Ishihara K, Mizuhara Y, Wakui Y, et al., 2000, 1564). In a study using rats, orally administered baicalin was detected in the plasma of rats with intestinal bacteria in their gut, but not baicalein, and only a trace of baicalin was recovered in rats that had the intestinal bacteria removed (Akao et al., 2000). These results further suggest that baicalin is poorly absorbed until it is hydrolyzed by intestinal bacteria to baicalein and then reconjugated by intestinal and hepatic microsomes back to baicalin.

In a study on the pharmacokinetics of baicalin, there is a suggestion that the flavonoid might be metabolized by a CPY450 catalysis and "goes through hepatobiliary excretion against a concentration gradient" (Tsai and Tsai, 2004). Furthermore, further analysis in the study from a microdialysis probe inserted into rat striatum after *i.v.* administration of baicalin did not show an increase in the concentration of the constituent, suggesting that it may not cross the blood brain barrier, although baicalein may do so.

Scutellaria lateriflora (skullcap)

Clinical trials

To date, there has only been one clinical trial on skullcap (Wolfson and Hoffmann, 2003). In an effort to analyze the anxiolytic properties of *Scutellaria lateriflora*, Wolfson and Hoffmann, performed a double blind, placebo controlled crossover designed study of 19 volunteers consisting of 15 women and 4 men between the ages of 20-70 years old. Each volunteer received separate and coded packets of: two capsules of a placebo (**A**), one 350-mg capsule of freeze-dried skullcap by Eclectic Institute (**B**), one 100-mg capsule of freeze-dried skullcap extract by Phytos (**C**), and two capsules with each containing 100-mg of freeze-dried skullcap extract by Phytos (**D**). These standardized extracts and the method of preparing the extracts of *S. lateriflora* are patented in *U. S. Patent 6,740,343 B2*. As a part of the trial, the volunteers subjectively evaluated the factors of energy, cognition, and anxiety over time at baseline and at 30, 60, 90, and 120 minutes. The results indicated that the effect on anxiety was most significant since all of the skullcap capsules rated higher than placebo in this category. Of the skullcap capsules, **D** with the 2-100 mg

capsules from Phytos scored the highest. **B** and **C** scored similar effects on anxiety. The study suggests that the total of 200-mg in the extract had a greater effect than the 350-mg of the skullcap which was not extracted. **D**, however, had the most influence on cognition and energy suggesting that there is a sedative effect with the greater dose, but with **B** and **C** there was only a mild change. Discussion regarding the efficacy of skullcap and method of preparation and harvesting conditions is mentioned in the article with concern about the variability in potency.

This study is limited by a small population size with only 19 volunteers all of whom rated the effects subjectively. The volunteers did not take the herbs under the observation of clinical trial investigators and the results are based on assuming the volunteers accurately followed the directions regarding administration of the herb. Additional limitations are due to the skullcap being manufactured by two different herbal companies suggesting the potential for a difference in the potency of the original plant material and extraction techniques. Further clinical studies are necessary to substantiate the validity of this research.

Extrapolations from pharmacology

Scutellaria lateriflora has been traditionally used for its anxiolytic and neurotrophorestorative actions. However, since *S. lateriflora* shares similar constituents to *S. baicalensis*, the plant should be considered for potential actions such as antinflammatory, antiallergic, antioxidant, and hepatoprotective. Additionally, further study of seizure prevention by *S. lateriflora* should be considered since $GABA_A$ receptor agonists are modulated by benzodiazepines (e.g. diazepam) and the constituents baicalin and baicalein have been shown to modulate $GABA_A$ receptors, and since there is historical use of the plant for this purpose.

History

J. P. Tournefort (1656 – 1708) first described the genus of skullcap as *Cassida*. In 1753, Rivin proposed to Linnaeus to change the genus to *Scutellaria* and at that time 12 species worldwide were named with *S. lateriflora* as one of the species listed (Leonard, 1927). Presently, the genus *Scutellaria* is circumglobal with over 360 species (Chemesova, 1993).

Traditional use

Native American uses

Skullcap is an indigenous North American species and was utilized by the Cherokee and Iroquois tribes. The Cherokees made a decoction consisting of "*S. lateriflora, S. elliptica, Hypericum spp.* and *Stylosanthes spp.* [pencil flower] to promote suppressed menstruation" and as a "wash to counteract the ill effects of eating food prepared by a woman in the menstrual condition, or when such a woman by chance comes into a sick room or house under taboo" (Mooney, 1885) (Banks, 2004, 97). A decoction of the root was used for diarrhea, breast pains, and the expelling of afterbirth (Banks, 2004). The Cherokee also created a root compound from the herb to aid the kidneys (Moerman, 1998). The Iroquois made an infusion from powdering the roots for the prevention of smallpox and for cleaning the throat (Moerman, 1998).

Uses for hydrophobia or rabies

In 1772 skullcap was introduced into the medical field as a prophylactic and treatment for rabies after Dr. Lawrence Van Derveer discovered its "powers" to cure mad-dog disease (Webster, 1898, 200). The name "Mad-Dog Skullcap" was derived from this alleged cure associated with the plant. Testimonies abound in the early 1800s confirming skullcap's use for rabies and brought a reputation to Dr. Lawrence Van Derveer as the doctor who cured rabies.

On September 14, 1819 Lyman Spalding MD read "*A History of the Introduction and Use of Scutellaria lateriflora, (Scullcap,) as a Remedy for Preventing and Curing Hydrophobia*" before the New York Historical Society (Spalding, 1819). The presentation included excerpts from Lawrence Van Derveer's use of the plant. Included in the reading was a recipe for the bite of mad dog after a Mr. Daniel Lewis was bitten:

> Take the plant call scull-cap, gathered either before dog-days begin, or after they are over (that is, before the 30th of July and after the 10th of September,) and cure it in the shade. Cut it fine, and bottle it up close. Of this powder make a decoction as strong as common tea, and give it to an adult, half pint night and morning fasting; to a child of three years old, one gill; to a child of eight years, one and a half gill; to a child of twelve years; two gills.
>
> The patient on every third day, during the period

> of taking the decoction, must miss taking it, and instead of it, must take two teaspoons of powdered roll of brimstone, with molasses, or sufficient to procure a free passage. Continue this course for forty days.
>
> The patient must abstain from butter or milk, or anything of greasy nature in his diet, and wholly from spirituous liquors. It is important also that he should not wet his feet (Spalding, 1819, 12).

By the time of his death in 1815, Dr. Van Derveer was claimed to have successfully used skullcap as a cure for "the bites of mad dogs" and is thought to have cured "four thousand persons and one thousand cattle from becoming affected with the disease" (Beach, 1869, 765). However, numbers have a way of becoming distorted throughout history since in another writing, Constantine Raphinesque states that the plant "prevented 400 persons and 1000 cattle from becoming hydrophobus, after being bitten by mad dogs" (Erichsen-Brown, 1979, 291). Also noteworthy is that Dr. Van Derveer's son, Henry Van Derveer, was said to have cured forty more cases in three years (Millspaugh, 1892).

The New York Evening Post, dated July 16, 1819, reported on a case in which James Cann was bit deep in the hand by Peter Fish on June 10, 1819 (Spalding, 1819). The formula for *Scutellaria lateriflora* as a treatment in this incident is as follows:

> "…obtained three ounces of dried herb, finely cut up, with direction to put a tea-spoon full and a half of it in a quart of warm water and to drink half a pint of this infusion, morning and night for two successive days, and on the third to omit it, and take a tea-spoonful of flowers of sulphur. In this manner, Williams directed the skullcap and sulphur to be alternatively used for forty days, during which time, exercise avoided, and an abstentious diet observed." He followed the direction and remained free of complaint until Thursday the 17th and fluctuated on and off again with spasms until the 22nd and he had no spasms and then continued scullcap 3-4 weeks longer (Spalding, 1819, 21-30).

Despite its reputation for curing rabies as promoted by Dr. Van Derveer, many members of the medical community questioned the herb's legitimacy for this indication since the formulas did not work for them. However, Dr. S. W. Williams, who was usually skeptical of anyone who might be considered to be a "charlatan" or a "quack," had confidence in the virtues of skullcap, and a veterinary surgeon, Mr. Youatt, also supported the plant as a possible cure for hydrophobia (Millspaugh, 1892).

Skullcap's use during the mid 1800s to present

In 1824 Cadet de Gassicourt analyzed skullcap for its active chemical principles in Paris and concluded that it contained a bitter principle, volatile and a yellow fixed oil, tannin, mucilage, and gum sugar (Felter & Lloyd, 1898) (Myers & Gillispie, 1889).

Despite the fact that debate continued into the 1800s regarding skullcap's ability to cure hydrophobia, the plant started to gain a reputation for more specific nervous indications. Skullcap began to be used for nervous diseases such as "…convulsions, tetanus, St. Vitus' dance, tremors, &c" (Erichsen-Brown, 1979, 291 – as quoted from Raphinesque, 1830 – see references). From 1859-1861 skullcap became a "valuable tonic nervine and antispasmodic" and was combined with lady slipper root. During this period, the plant was also combined with diaphoretic herbs such as catnip, sage, pennyroyal, or pleurisy root, and was used for fevers and taken as a hot or cold infusion (Erichsen-Brown, 1979 – as quoted from Gunn, 1861 – see references).

From the mid to late 1880s and into the early 1900s, skullcap continued to be recommended for its use as a nervous system tonic and was recommended by the physiomedicalists and eclectic practitioners for insomnia, neuralgia, irritability, chorea, twitchings, and women's menstrual pains (see indication section). In the early 1900s, skullcap when combined with passionflower was documented to treat an opium addict of almost twenty years and recommended as a spring or fall tonic (Finley, 1919).

Skullcap was listed in the US Pharmacopoeia from 1863 to 1916 and in the National Formulary from 1916 to 1947. The US Dispensatory, in its 22nd edition (1937), made the claim that skullcap was "as destitute of medicinal properties as a plant may be, not even being aromatic. When taken internally, it produces no very obvious effects, and probably is of no remedial value…" (U.S. Dispensatory, 1937, 968) (note: this is also in The Dispensatory of the United States of America Twentieth

Edition (1918) Edited by Joseph P. Remington, Horatio C. Woods and others.) Skullcap was removed from the National Formulary in 1947.

From 1935-7, the National Association of Medical Herbalists of Great Britain's publications of *The Medical Herbalist* mention use of skullcap in combinations with other herbs such as valerian, hops, mistletoe, vervain and lady slipper for nervous twitchings, St. Vitus Dance, headaches, epilepsy, nervous debility, and nervous conditions during a woman's change of life (Yemm, 1935-7).

In 1939, Jethro Kloss wrote in *Back to Eden* that skullcap "is one of the best nerve tonics…very quieting and soothing to the nerves of people who are easily excited…good in neuralgia, aches and pains…useful in St. Vitus's dance, shaking palsy, convulsions, fits, rheumatism, hydrophobia, epilepsy, and bites of poisonous insects and snakes…to suppress undue sexual desire…[and as a] substitute for quinine" (Kloss, 1939, 313).

Although skullcap was removed from the National Formulary in 1947, its reputation as a nervine continued into the later part of the 20th century. The British Herbal Pharmacopeia in 1983 still recognized skullcap for its anti-convulsive and sedative actions and for indications such as epilepsy, chorea, hysteria, and nervous tension states. The 1996 British Pharmacopeia states skullcap's action as a "mild sedative" (British Herbal Medicine Association, 1996, 172).

In 1989 four cases of hepatoxicity were reported from the supposed use of skullcap in England, which later were found to be due to an adulteration with germander (see adulteration and safety sections). Skullcap was found to be extensively adulterated with germander in Europe and the United States, which later resulted in detailed macroscopic and microscopic identification to decipher the two species. In the 1998 edition of *Tyler's Honest Herbal* by Steven Foster and Varro E. Tyler, the authors warn against the use of the plant as they conclude that "deficiencies in activity, safety, and quality all make skullcap a good herb to avoid" (Foster and Tyler, 1998, 350). Foster and Tyler suggested caution with skullcap due to its history of adulterations with germander, substitutions with other species, and because there were no definitive research studies validating the plant's therapeutic activity at the time of the book's publication.

Skullcap's reputation appears to be improving as contemporary herbalists once again tout its actions on the nervous system. Skullcap is used as a tonic "take the edge off," specific for the "frazzled" individual of today's fast paced industrial society and to reduce anxiety (Upton, 2005) (7Song, 2005). It is also indicated and may be useful for petite mal seizures, epilepsy, and premenstrual symptoms of psychological dysphoria or Premenstrual Dysphoric Disorder (Hoffmann, 2005).

Specific indications

Physiomedicalists and Eclectics

Physiomedicalist William Cook recommends skullcap for restless and wakeful conditions with feebleness, chronic wakefulness, even from the sleeplessness that occurs from withdrawal of opium. In addition, according to Cook, skullcap is a very reliable and prompt acting herb which tones and soothes the nervous system allowing for a "quiet sleep" without a feeling of being drugged, "excitement, sensitiveness, nor languor." He also uses the herb for cases of "uterine sufferings, nervous headache, aching through the bowels, and neuralgia," and skullcap is recommended when there is "feebleness with agitation, but not connected with acute or sub-acute inflammatory excitement." (Cook, 1869)

King's American Dispensatory indicates skullcap is "…useful in chorea, convulsions, tremors, intermittent fever, neuralgia, and all nervous affections" (Felter & Lloyd, 1898). The Dispensatory mentions that the herb was specific for nervous excitability accompanied by or after acute or chronic diseases, from physical or mental overwork, teething, hysteria, or from a difficulty in controlling voluntary muscles.

Finley Ellingwood's use of skullcap was indicated when there was either irritability of the nervous system, irritability from insomnia, restlessness, or nervous excitability; and in nervous cases of "irregular muscular action twitching, tremors and restlessness, with or without incoordination" (Ellingwood, 1919).

Harvey Felter had faith in skullcap to calm the nervous and muscular system, for chorea (Huntington's Disease), when combined with macrotys (black cohosh) and valerian, when used for restlessness after a prolonged sickness, for functional heart disorders caused by nervousness, and with an intermittent pulse accompanied by hysteria. He also had trust in the use of

skullcap with insomnia when it was due to worry, nervous irritability or exhaustion. He felt that skullcap could be effective during subsultus tendinum (lock jaw) when there are "grave prostrating fevers" (Felter, 1922). Felter questioned skullcap's use in delirium tremens, epilepsy, and paralysis agitans (Parkinson's disease). He felt that its reputation for a cure for these diseases was overstated. He wrote that skullcap's reputation for treating rabies did not stand the test of time and was completely invalidated.

Priest and Priest wrote that skullcap is indicated for "irritation of the cerebrospinal nervous system….functional nervous exhaustion, post febrile nervous weakness, chorea, hysteria, agitation and epileptiform convulsions, insomnia, nightmares, restless sleep" (Priest & Priest, 1982, p. 80-1)

Safety issues

Since the adulteration of skullcap with germander resulted in hepatotoxicity for some individuals, it is imperative that manufacturers and consumers be vigilant regarding the source of the plant material. *Consumer Reports* in their May 2004 issue listed skullcap under the category of "LIKELY HAZARDOUS Adverse-event reports or theoretical risks" with a danger of "abnormal liver function or damage" (*Consumer Reports*, 2004). In response to this warning by *Consumer Reports*, the American Herbal Products Association (AHPA) contested the statement and replied in a letter to the editor of *Consumer Reports* that the article failed to mention that skullcap had been misidentified and adulterated with germander (McGuffin, 2004). Due to the publicity regarding the adulteration of skullcap with germander, manufactures must perform HPLC to distinguish and ensure accurate species identification (see adulteration section). Consumers also need to be educated about reliable and reputable manufactures or growers to buy their products from.

In view of the fact that some of skullcap's constituents have been shown *in vitro* to be GABA ligands (see pharmacology section), there is the possibility that the herb can potentiate sedative, tranquilizing, hypnotic, or depressant medicines. However, no research has been performed to substantiate this safety issue. Further research is necessary to determine if skullcap demonstrates any interaction with sedative pharmaceuticals.

The potential for CYP 3A4 inhibition (see pharmacology section) suggests that there may be a drug-herb interaction when taking skullcap with pharmaceuticals (Awad et al, 2003). Again, further research is required prior to establishing any claim to this hypothesis.

Contraindications: None known.
Use in pregnancy: Considered safe.
Use in breastfeeding: Considered safe.
Use for children: Considered safe when taken within the correct dosage.
Overdose: "of the tincture can cause giddiness, stupor, confusion of mind, twitching of the limbs, intermission of the pulse, and other symptoms of epilepsy, for which in diluted strength and small doses it has been successfully given" (Grieve, 1971, 725).

Dosages and preparations

Dosage

The following dose and preparation is from The 1983 British Herbal Pharmacopoeia. Be aware that the book suggests the "commercial material described in the present monograph is probably derived from a species of Teucrium" (BHP, 1983, 194):
"Dried plant. Dose 1-2 g or by infusion. [T.I.D]
Liquid Extract 1:1 in 25% alcohol Dose 2-4 ml [T.I.D]
Tincture 1:5 in 45% alcohol. Dose 1-2 ml [T.I.D]" (BHP, 1983, p. 194)

Preparations

Tincture: of fresh plant 1:2 (75% EtOH: 25% water)
of dried plant 1:5 (50% EtOH: 50% water) (Cech, 2000)
of fresh plant 1:2 95% EtOH (7Song)

Hot Infusion: "Pour 1 cup of boiling water over 1-2 teaspoons of dried herb and infuse for 10 to 15 minutes...[drink] three times a day or as needed." (Hoffmann, 2003)

Historical preparations and doses

Tincture: 4 oz finely crushed scutellaria, pack in percolator, treat with diluted alcohol until a quart is obtained. 1 drachm at "suitable intervals" (Cook, 1869)
1 fluid drachm = 3.69 cc or ml

Fluid Extract Dose: "from five to thirty minims" (Ellingwood, 1919)

Note: 1 minim=.06 cc or ml This is the equivalent of .3 ml to 1.8 ml

Infusion: "half an ounce of the recently dried leaves or herb, to ½ pint of boiling water, will make a very strong infusion. Dose of specific scutellaria, 1 to 30 drops…fluid extract, 1-60 drops." (Felter & Lloyd, 1898)

The US Pharmacopoeia of 1890 recommends the following formula for making an extract of skullcap:

EXTRACTUM SCUTELLARIÆ FLUIDUM

Fluid extract of Scutellaria

Scutellaria, in No. 40 powder,	
one thousand grammes	1000 Gm.
Diluted Alcohol, *a sufficient quantity*,	
To make *one thousand cubic centimeters*	1000 Cc.

Moisten the powder with *three hundred and fifty (350) cubic centimeters* of Diluted Alcohol, and pack it firmly in a cylindrical percolator; then add enough Diluted Alcohol to saturate the powder and leave a stratum above it. When the liquid begins to drop from the percolator, close the lower orifice, and, having closely covered the percolator, macerate for forty-eight hours. Then allow the percolation to proceed, gradually adding Diluted Alcohol, until the Scutellaria is exhausted. Reserve the first *eight hundred (800) cubic centimeters* of the percolate, and evaporate the remainder, at a temperature not exceeding 50° C. (122° F.), to a soft extract; dissolve this in the reserved portion, and add enough Diluted Alcohol to make the Fluid Extract measure *one thousand (1000) cubic centimeters*. (United States Pharmacopoeia Convention (USPC) p. 168)

Commercial studies on extraction methods

A study by the Australian Government showed that the greatest flavonoid (70%) content of dried skullcap was best extracted with 40-60% EtOH.

Glycerin skullcap extracts were compared by Tom's of Maine for flavonoid content. The hot water extract showed 24% total flavonoids with 13.5% baiclain compared to the 70% alcohol extract with 37% flavonoids and 17% baicalin (Gafner et al., 2000.). Other research by the same company indicates that flavonoids extract better using dried plant rather than fresh plant material (Russell et al, 2003). Heating at 70°C significantly improved flavonoid extraction rather than using no heat at all. Regardless of whether the extract was heated or not, the flavonoid stability was poor over a six month period with a 30-66.4 % loss of total flavonoids. The greatest stability of flavonoids was maintained with 70°C extraction and the addition of the anti-oxidants ascorbic acid and citric/ascorbic acid combination.

Baicalein, is better extracted with a super critical fluid extraction (SFE) using CO_2 and 10% (v/v) ethanol (EtOH)- 0.293% at 40°C or high temperatures of ASE between 150-190°C – 0.263% at 190°C (Bergeron et al, 2005).

With an accelerated solvent extraction (ACE) at 85°C with water, the percentages of extraction are as follows: Baicalin – 13.%; baicalein – 0.13%; wogonin – 0.02%; dihydrobaicalin – 4.27%; lateriflorin – 2.53%; ikonnikoside I – 1.44%; scutellarin – 1.44% and oroxylin A-7-0 glucuronide – 0.62% (Bergeron et al, 2005).

Conclusion

Scutellaria lateriflora is a herb that has been traditionally used for centuries as a nervine and neurotrophorestorative for anxiety, PMS, epilepsy, and sleep. Recent discoveries of some of the plant's constituents could lead to new uses for skullcap as an antiallergenic, antioxidant, and for hepatoprotection. In the past decade, research has aided in substantiating skullcap's traditional uses. Due to its unfortunate history concerning adulteration with germander, skullcap was and is still is under scrutiny for its safety and efficacy. Microscopic analysis is essential to clarify the authenticity of the plant. Hopefully, current research will prove that an abundance in activity, safety, and quality all make skullcap a good herb to try.

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