American skullcap (Scutellaria lateriflora): an ancient remedy for today's anxiety?

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American skullcap (*Scutellaria lateriflor*a): an ancient remedy for today's anxiety?

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Abstract

Anxiety is a common but potentially serious disorder as it can lead to somatic and social dysfunction. Orthodox anxiolytics are associated with unpleasant side-effects and dependency. American skullcap (*Scutellaria lateriflora*) is a popular herb in traditional medicine systems and the western materia medica for anxiety and related disorders. Preliminary clinical and in vitro research provides encouraging support for its potential as a safe, well-tolerated and effective alternative.

Key points

- Research has demonstrated the capacity of American skullcap's flavonoids to bind to brain receptors implicated in modulation of anxiety
- In one year up to one in six UK adults in the UK may suffer from an unexplained psychological disorder, the most common being anxiety
- Anxiety and stress are common reasons for visits to herbal medicine practitioners.
- An initial survey of UK and Ireland herbal medicine practitioners indicated American skullcap as their treatment of choice for anxiety and related disorders
- Quality control of the raw herb and its commercial products is important.

Key words: Anxiety, Stress, Herbal Medicine, Flavonoids

Introduction

Anxiety is 'an unpleasant emotional state ranging from mild unease to intense fear' (B.M.A., 2002). Although anxiety is a normal response to stressful situations it can be seen as a chronic manifestation of a modern lifestyle that includes repeated daily stressors (Pavlovich, 1999). It is a potentially serious disorder as it can precipitate a number of health problems and difficulties in social and occupational functioning (Fricchione, 2004).

Physical symptoms of anxiety include pallor, sweating, hyperventilation, diarrhoea, irritable bowel, flushing, dysphagia, palpitations, nausea and muscle tension (B.M.A., 2002). Furthermore, Pitsavos *et al.* (2006) found strong evidence for a positive association between severity of state anxiety in both men and women and increased levels of plasma pro-inflammatory cytokines, coagulation factors, C-reactive protein and white blood cells. Alleviation of these adverse effects on health is important.

Many orthodox anxiolytic treatments can have unwanted side-effects. Benzodiazepines, for example, have been linked to muscle weakness, amnesia, headaches, vertigo, urinary retention, slurred speech and gastro-intestinal disturbances. They may lead to tolerance and physical and psychological dependence and are considered to be dangerous to use long-term (BNF, 2008). The side effects of antipsychotics, sometimes prescribed in the short-term for severe anxiety, include tremor, abnormal face and body movements and restlessness (BNF, 2008). Beta-blockers may be prescribed for relief of physical symptoms, such as tremors and palpitations, associated with anxiety. However, side-effects are similar to those of benzodiazepines and may additionally include bradycardia, vasoconstriction and heart failure (BNF, 2008). There is therefore a need for safe alternatives, without unwanted side-effects.

American skullcap (*Scutellaria lateriflora*) (Figure 1) is one of the most commonly used herbs by western medical herbalists, particularly for anxiety and related conditions (Bergner, 2002-2003). This article discusses its clinical application, and reviews both scientific and anecdotal evidence in support of its traditional use for anxiety.

American skullcap (*Scutellaria lateriflora* L)

Scutellaria lateriflora is a perennial herb belonging to the *Lamiaceae* (mint) family and is one of 360 known skullcap species worldwide (Malikov and Yuldashev, 2002). It grows on wetlands and is indigenous to North America and Canada where it is widely distributed (U.S.D.A.). It also grows on riverbanks and marshes in northern Iran (Yaghmai, 1988) and is grown commercially worldwide (Wills and Stuart, 2004).

It was an important North American ethnobotanical medicine for use in anxiety, hysteria, phobias, panic attacks, tension, sleep disorders and stress (Felter and Lloyd, 1898; Joshee *et al.*, 2002). It has also been used for centuries in both Persian and Cherokee folk medicine for nervous disorders of the digestive tract (Khosh, 2000) and Native American women traditionally used it for premenstrual tension (Indiana Medical History Museum, undated). The herb is also used extensively and highly valued in traditional western herbal medicine. It was mentioned in the first American *materia medica* in 1785 but had been in longstanding use as a home remedy before then (Lloyd 1911).

In modern western herbal medicine it is used most commonly for insomnia, nervous disorders and digestive disturbances (Greenfield and Davis (2004). Bergner (2002-2003) proposes its action is primarily as a trophorestorative on the central nervous system, allowing relaxation following nervous exhaustion. It is also used for barbiturate and tranquiliser withdrawal symptoms (Joshee *et al.*, 2002), fibromyalgia, anorexia nervosa, post-stroke paralysis, atherosclerosis, hyperlipidaemia, allergies, skin conditions and inflammation (Natural Medicines Comprehensive Database., 2008).

Figure 1: *Scutellaria lateriflora* L.

Following reports of liver damage from use of *S. lateriflora* products there was a decline in its popularity in the1970s and 1980s (McCaleb, 2004). The cause of the hepatotoxicity was likely to be due to contamination with Germander (*Teucrium*) *species* (De Smet, 1999) which contain pyrrolizidine alkaloids (McCaleb, 2004). *S. lateriflora* is not associated with hepatotoxicity.

Since 2002 there has been a sharp increase in demand for *S. lateriflora* , possibly due to it being favoured as an anxiolytic alternative to the previously popular *Piper methysticum* (kava kava), which, due to toxicity fears, is no longer widely prescribed by herbalists in Europe (Greenfield and Davis, 2004).

Scutellaria baicalensis (Georgi) (Baikal skullcap) root is extensively prescribed in traditional Chinese and Japanese (kampo) medicines, particularly to treat inflammatory diseases, and has been widely researched in relation to its efficacy and pharmacological properties. Although *S. lateriflora* is a popular herb in western herbal medicine and contained in many herbal formulations (Joshee *et al.*, 2002), particularly for anxiety and stress, relatively few scientific studies of this herb exist (Cole *et al.*, 2008).

S lateriflora is the practitioner's choice for treating anxiety

Results of a survey conducted by the authors amongst herbal medicine practitioners in the UK and Ireland indicate that *S. lateriflora* is considered to be an effective intervention for anxiety and stress and is commonly prescribed for these conditions and related co-morbidities.

The survey aimed to gather information on the extent of, and indications for, current use of *S. lateriflora*, its perceived effectiveness and safety. Herbal medicine practitioners were selected from the membership list of the National Institute of Medical Herbalists (NIMH). All members with identifiable email addresses were contacted (n = 377) and responses were received from 62 (a 16% response rate).

Results indicate primary use of *S. lateriflora* for relief of anxiety, stress or associated symptoms with 84% of respondents saying they would prescribe it for specific anxiety disorders and 100% for anxiety-related co-morbidities. Twenty five respondents said it is their preferred herb for anxiety (Figure 2). One respondent indicated their preferred anxiolytic as being *S. baicalensis*. In common with many other *Scutellaria* species, *S. lateriflora* and *S. baicalensis* have similar phytochemical constituents, although in different ratios and quantities, which may explain the differing traditional uses amongst *Scutellaria* species. For instance, *S. baicalensis* contains 800 times more scutellarin than *S. lateriflora* (Cole *et al.*, 2008). Although *S. baicalensis* is most commonly used for inflammation (Joshee *et al.*, 2002) both *S. lateriflora* and *S. baicalensis* have been found to inhibit cyclooexgenases *in vitro* (Gafner *et al.*, 2004; Jia *et al.*, 2007). *S. lateriflora* is reported to have been traditionally used for inflammation. The Iroquai tribe, for example, used it 'to keep the throat clear' (Joshee *et al.*, 2002). Conversely, *S. baicalensis* root is reported to have been used as a sedative (Liao *et al.*, 1998).

All respondents who regularly prescribe *S. lateriflora* (92%) identified use for anxiety as distinct from depression and whilst some reported it useful in depression (16%) also, several respondents reported it as unsuitable for significant depression.

Use for insomnia and sleep-related disorders was specifically reported by 57% of respondents. Other conditions for which it was used include fear and panic states, migraine and other headaches, muscular tension, physical and mental exhaustion and post viral fatigue. It was also reported by 3 practitioners as useful in emotional disturbance in menopause and in premenstrual syndrome.

The survey respondents reported the herb as being used over a range of time periods from immediate short term use to several years, with positive response expected to be experienced by the patient within the first two weeks and persisting throughout the period of use.

The benefits most often reported by patients to their practitioners were feeling calmer, improved sleep patterns and quality, and better able to cope in stressful situations. Other positive effects were mood elevation, increased energy, being more focused and feeling generally more relaxed.

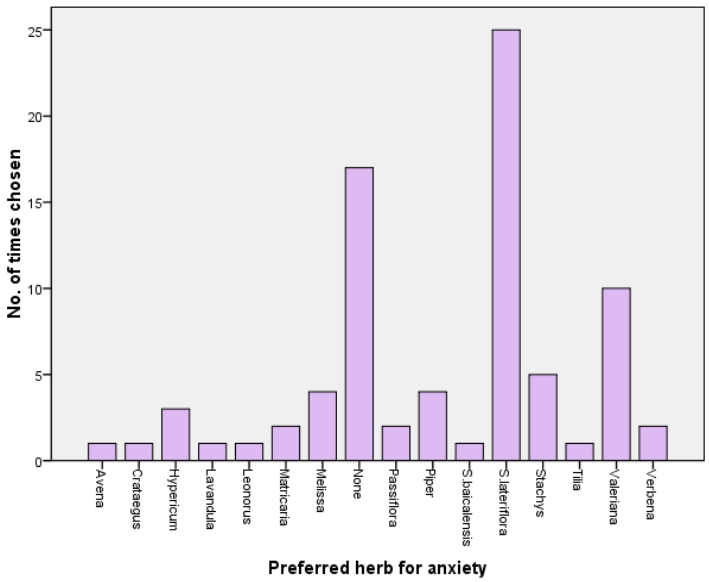

Figure 2: Anxiolytic herbs as preferred by survey respondents

Key: Avena = *A. sativa* (oats); Crataegus = *Crataegus* spp. (hawthorn); Hypericum = *H. perforatum* (St John's wort); Lavandula = *Lavandula* spp. (lavender); Leonorus = *L. cardiaca* (motherwort); Matricaria = *M. recutita* (German chamomile); Melissa = *M. officinalis* (balm); None = no preference; Passiflora = *P. incarnata* (passion flower); Piper = *Piper methysticum* (kava-kava); *S. baicalensis* (baikal skullcap); *S. lateriflora* (American skullcap); Stachys = *S. betonica* (wood betony); Tilia = *Tilia* spp (linden); Valeriana = *Valeriana officinalis* (valerian); Verbena = *Verbena officinalis* (vervain).

Tinctures made from either fresh or dried organic and non-organic herb are the preferred mode of administration by respondents. The main reason is a belief that tinctures are more effective and they are better for patient compliance and generally more convenient than dried herb. Many (63%) said they prefer to use organic *S. lateriflora* and 42% prefer tinctures made from the fresh herb, believing this to be the most effective.

All respondents prescribe the herb in combination with other herbs. Only 9% of the respondents regularly prescribed *S. lateriflora* as a single herb so it is difficult to draw conclusions about the perceived actions of *S. lateriflora* used on its own. Nevertheless the practitioners appear to be confident in attributing specific actions and responses to *S. lateriflora* as distinct from other herbs in a mixture in having the anxiolytic actions. Furthermore, respondents prescribing it as a single herb reported positive feedback from their patients such as reduced anxiety, fewer and less intense panic attacks, feeling of well-being, feeling more positive, more able to cope. Interestingly, one practitioner prescribing the herb in combination reported a relapse in symptoms of anxiety in some patients whenever it was removed from the mix.

The herb was reported as being well tolerated with no reports of toxicity and only minor and infrequent side effects (reported by 7 users), including daytime drowsiness, mild digestive upset and vivid dreaming. It is uncertain whether any of these side effects were in fact due to *S. lateriflora*.

It is recognised that the response rate (16%) was low and survey respondents include only those replying to email contact and therefore may not be representative of all UK

and Ireland herbal practitioners. The poor response rate and the propensity of respondents to administer *S. lateriflora* in combination with other herbs make it impossible to rely on evidence regarding the efficacy of the herb from the practitioner survey alone. A future survey could include herbal practitioners from other professional bodies such as the Council of Practitioners of Phytotherapy. In addition contact with herbalists internationally may provide a more useful indication of the benefits of the herb.

Preparations and dosages used.

Preparations of *S. lateriflora* are made from the aerial parts and are sold in the form of tinctures, teas and tablets; and capsules containing powders, liquids or freeze-dried material. Dosages vary according to extraction, marc: menstrum ratio, practitioner preference and preparations used but average at around I g equivalent dry weight per dose three times daily (Natural Medicines Comprehensive Database., 2008). Preparations from fresh herb are thought to be most effective (Felter and Lloyd, 1898; Kuhn and Winston, 2001; Yarnell and Abascal, 2001).

Contraindications and side-effects

Due to its potential sedative action (Greenfield and Davis, 2004) it may be advisable to refrain from using *S. lateriflora* in combination with other sedatives, including alcohol and benzodiazepines. It is not possible to comment on the safety of its use in pregnancy.

Anxiety: the demand for herbal treatment

In one year up to one in six adults in Great Britain may suffer from a medically unexplained psychological disorder, the most common being anxiety (men 4%; women 5%), depression (men 2%; women 3%) or both experienced at the same time (men 7%; women 11%). These figures indicate that anxiety and depression are more prevalent in women than in men (Office for National Statistics, 2006). Herbal medicine is used more frequently by women than by men (Gunther *et al.*, 2004) and, according to a survey in the United States (del Mundo *et al.*, 2002) around 30% of visits to a complementary and alternative medicine (CAM) practitioner were for anxiety and/or stress. Of 664 respondents (74% of whom were females) only back pain was a more common reason for CAM visits. As chiropractors were the most visited CAM therapists, with medical herbalists a close second, it may be deduced that since the chiropractors are more likely to treat back pain, the majority of visits to herbal medicine practitioners were by women with anxiety and stress (del Mundo *et al.*, 2002).

The potential efficacy of *S. lateriflora* in treating anxiety

Chemistry

S. lateriflora is rich in flavonoids, a group of phenolic compounds that are highly active physiologically, and have been attributed with its anxiolytic effects. Baicalin, its aglycone baicalein, wogonin and lateriflorin are the major flavonoids in *S. lateriflora* (Nishikawa *et al.*, 1999; Gafner *et al.*, 2000; Gafner *et al.*, 2004).

It also contains gamma - aminobutyric acid (GABA), an inhibitory neurotransmitter that modulates anxiety, sleep, convulsions and mood (Rabow *et al.*, 1995), and markedly high levels of glutamine, a non-essential amino acid that plays an important role in immune function – particularly in response to stress (Bergeron *et al.*, 2005). Although GABA does not readily cross the blood-brain barrier (Spinella, 2002), glutamine can and may be biosynthesised to GABA by GABA-ergic neurons. The presence of glutamine in the herb may therefore contribute to its anxiolytic activity by increasing the availability of GABA in the central nervous system (Bergeron *et al.*, 2005).

***In vitro* studies**

Benzodiazepines are allosteric ligands for the $GABA_A$ receptor, a chloride channel that is gated by GABA. They bind to the benzodiazepine site of the $GABA_A$ receptor, thus increasing the affinity of the inhibitory neurotransmitter GABA for the GABA site of the $GABA_A$ receptor, decreasing the likelihood of action potentials by excitatory neurotransmitters (Rabow *et al.*, 1995). A study (Liao *et al.*, 1998), indicated oroxylin A, baicalein and wogonin, which are flavonoids found in *S. lateriflora,* had weak affinities for the benzodiazepine site of $GABA_A$ receptors in mouse cerebral cortex *in vitro*. In another study Hui *et al.* (2000) tested the capacity of baicalin, baicalein, scutellarein and wogonin to bind to the benzodiazepine site of the $GABA_A$ receptor in homogenised rat brain. Affinity to the benzodiazepine site for scutellarein was moderate and weak for baicalin. Contrary to results of the earlier study (Liao *et al.*, 1998) the binding affinities of wogonin and baicalein were strong. The authors suggested the discrepancy may be due to differences in species and assay models used (Hui *et al.*, 2000).

The ability of the skullcap flavonoids to bind to the benzodiazepine site of the $GABA_A$ receptor suggests an anxiolytic effect for *S. lateriflora* but studies on human tissue of neuronal origin are needed to verify results.

Gafner *et al*. (2003) found extracts of dried *S. lateriflora* aerial parts and its flavonoids baicalin, scutellarin, wogonin, lateriflorein, ikonnikoside I and dihydrobaicalin, had high affinity for the serotonin$_7$ (5-HT_7) receptor in human 5-HT_7 - transfected Chinese hamster ovary cell lines. It was not known whether these extracts and flavonoids were agonists or antagonists (Gafner *et al.*, 2003) but 5-HT_7 receptor antagonists and inverse agonists are known to be useful in the treatment of premenstrual syndrome, sleep disorders, appetite disorders, anxiety, phobias, panic, and stress-related disorders (Bright *et al.*, 2004); these are also conditions for which *S. lateriflora* is traditionally used (Joshee *et al.*, 2002; Greenfield and Davis, 2004).

Human clinical trials

To date only one clinical trial has been published on *S. lateriflora.* Wolfson and Hoffmann (2003) assessed its short-term anxiolytic properties in a double-blind, placebo-controlled crossover study of 19 healthy volunteers. Participants took either two placebo capsules, one capsule containing 100 mg of organic freeze-dried *S. lateriflora,* two capsules of these, or one capsule of 350 mg organic freeze-dried *S. lateriflora*. Participants' energy, cognition and anxiety were self-rated at various time points up to 2 hours following administration. All three herb tests had notable effects on subjective anxiety scores when compared to placebo. There was only a very mild

decline in cognition and energy with the herbs, with no adverse reactions or side-effects, suggesting that *S. lateriflora* could be a valuable anxiolytic (Wolfson and Hoffmann, 2003).

More research needs to be conducted in order to assess long-term effects. Furthermore, the authors acknowledge that the use of validated psychometric tests is needed to determine the herb's clinical anxiolytic effects.

Summary and evaluation of experimental results

The receptor binding affinities of flavonoids present in *S. lateriflora,* including baicalein, baicalin, wogonin and scutellarein, to $GABA_A$-BDZ receptor sites *in vitro* (Liao *et al.*, 1998; Hui *et al.*, 2000) indicates a possible anxiolytic action for the herb as does the presence of glutamine and the ability of certain *S. lateriflora* flavonoids to bind to $5HT_7$ receptors *in vitro* (Gafner *et al.*, 2003). The results of a survey amongst herbal medicine practitioners on their use of the herb and of a clinical study lend further support to its effectiveness as an anxiolytic.

The majority of *in vitro* findings are as a result of research conducted using individual phytochemicals of *S. lateriflora.* Whilst orthodox medicine tends to employ isolated phytochemicals, herbal medicine uses whole plant parts in the belief that there are synergistic benefits of the multiple active constituents in a single herb (Spinella 2002). It is likely that the efficacy of *S. lateriflora* is due to its multiple constituents acting in synergy rather than to the summative activities of the constituent phytochemicals. There is still a need for more research into the pharmacology of extracts from whole aerial parts of the herb and the variability which may arise from the herb sourced from different geographical regions.

Conclusions

The traditional therapeutic uses of *S. lateriflora* are supported by evidence from research. A positive therapeutic benefit of the herb for anxiety is indicated by the results of a survey conducted amongst herbal medicine practitioners; *in vitro* and chemical studies; and a clinical trial, which supports its reputation for safety as well as its efficacy as an anxiolytic.

As with all studies of herbal medicines important considerations, which may impact upon findings are the variations in quality and quantity of any given herbal preparation as well as the effects of other herbs in a mixture. Commercial herbal products have been found to contain significant variations in phytochemical profile within a species. Such variation may be according to geographic region, biodiversity, ecological variations, cultivation, seasonality, harvesting, processing method, marc to menstrum ratio and alcohol concentration, and storage time affecting stability, (Ciddi, 2006; Gao *et al.*, 2008). Stability of a herbal product is important with regard to efficacy and safety and may be affected by various factors, such as pH, light, enzymatic degradation (for example due to harvesting stress, heat or insects) and temperature (Gafner and Bergeron 2005).

Furthermore, quality control of *S. lateriflora* is important to not only ensure high standards of efficacy but also for reasons of safety. It is frequently adulterated with

germander species or other skullcap species, both deliberately (germander has a heavier dry weight) and due to misidentification of the large number of skullcap species (Gorman, 2008) . High Performance Liquid Chromatography (HPLC) methods can be used for verifying its purity and quality. A characteristic profile of the HPLC chromatogram or 'fingerprint', which is altered by adulteration, can be used for accurate identification of the herb. The pattern's relative percentage of flavonoids is the key point to ascertain the quality and identity of *S. lateriflora* (Wills and Stuart, 2004).

While the results of the *in vitro* and chemical studies are interesting and provide clues to the pharmacological action of *S. lateriflora,* more clinical studies are required to provide better evidence of the therapeutic value of *Scutellaria lateriflora* as an effective agent for anxiety and stress. It has the potential to be as important for the treatment of anxiety as St John's Wort has been found to be for depression. Ultimately it may emerge as a useful and cost-effective agent to rival currently used anxiolytic pharmaceuticals.

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