MEDI HERB
a phytotherapist's perspective
Not for Public Distribution. For Professional Use Only.
No. 63 September 2015

Herbs with Nervine Activity

Saffron

The stigma (female reproductive organ) of *Crocus sativus* has a long history of culinary, medicinal, dyeing and ceremonial applications. It is the world's most expensive spice (by weight) and is frequently adulterated. Saffron has colourful autumn flowers (usually lilac-purple, 3.5–5 cm long), containing several bright orange-red threadlike stigmas.

Saffron has been used in many traditions. The major indications include menstrual disorders, fever, colds, depression and general weakness.[1-5] One of the most well known effects of Saffron recorded in traditional Islamic medicine is mood enhancing. It is stated that "... its action on enlivening the essence of the spirit and inducing happiness is great".[6] It has also been used to calm the nerves,[3] for impotence and reduced fertility in men.[1,5] In Ayurveda, Saffron is said to support the tonic action of other herbs, particularly those acting on the female reproductive system. Its nourishing effects support the nervous and reproductive tissues, so in addition to depression, it is used for general nervous debility.[7,8]

A number of randomised, double-blind clinical trials have been conducted in Iran. These trials evaluated a concentrated extract of Saffron. The extract strength is not defined, but is likely to be about 6:1, and with a prescribed dosage of 30 mg/day of extract, this corresponds to about 180 mg/day of dried stigma. In patients with mild to moderate **depression**, Saffron extract was a significantly better treatment than placebo[9] and had similar efficacy to that of fluoxetine[10] and imipramine.[11] The beneficial outcome was demonstrated by improvement in the Hamilton rating scale for depression. *See Table 1 for more details*.

Two randomised, placebo-controlled trials assessed the effect of saffron on sexual impairment caused as a side effect of treatment with fluoxetine for depression.[12,13] The same extract and dosage as described above, was administered to men and to women for 4 weeks. Patients with major depression had been receiving treatment with the drug for 6 weeks and baseline scores of the Hamilton rating scale for depression were about 9 for all patients. Saffron significantly improved erectile function and intercourse satisfaction in men, and significantly improved scores for the sexual arousal, lubrication and pain domains of the Female Sexual Function Index in women. Frequency of side effects were similar in both groups (on this basis, saffron could be safety taken with fluoxetine – *see also Safety section*).[12,13] Although mixed results have been observed in otherwise healthy, (nondepressed) men with erectile dysfunction.[14,15]

The same extract and dosage taken over 2 cycles, improved Hamilton Depression Rating Scale scores and other symptoms of premenstrual syndrome in a placebo-controlled trial.[16]

Skullcap

Scutellaria lateriflora aerial parts have been traditionally used to treat nervous tension and epilepsy.[17] It was also used by Eclectic physicians for nervousness with fatigue or depression. Skullcap is described as tonic and antispasmodic, acting through the nervous system,[18] and is of benefit for nervous disorders characterised by irregular muscular action such as twitching, tremors and restlessness.[2] A contemporary view supports the use of Skullcap for nervous tension due to chronic stress, illness or exhaustion; for neuralgia, insomnia as well as depression.[19]

Control	Results	Refs
placebo	• significant decrease in HAM-D scores from baseline after 6 weeks: 12.2 for the saffron group, 5.1 for placebo ($p < 0.0001$)	9
fluoxetine	• both groups showed a significant improvement over the 6 weeks of treatment	10
imipramine	• similar improvement demonstrated in the decrease in HAM-D scores from baseline: 12.2 for the saffron group, 15.0 for drug group	11

Table 1. Randomised, double-blind trials of 6 weeks' treatment with Saffron extract in mild to moderate depression.

Note: Patients had a baseline Hamilton rating scale for depression (HAM-D 17-item) score of at least 18.

Historically herbal products containing Skullcap have been found to be adulterated, sometimes with the potentially toxic germander (e.g. *Teucrium chamaedrys, T. canadense*). In addition, until about 2002 there was very little reliable information available about its constituents. Analytical methods have been developed and the characteristic phytochemical profile is now known.[20,21]

Preliminary results from two studies show Skullcap had a mild antianxiety effect in healthy volunteers.[22,23] Mood was also enhanced.[22]

Schisandra

Schisandra chinensis (*Schizandra chinensis*) fruit is indicated in traditional Chinese medicine (TCM) for a wide variety of conditions. It **quiets the spirit** while calming and containing the *Heart qi*, hence is used to treat irritability, palpitations, dream-disturbed sleep and insomnia. It is also used in this tradition for neurasthenia and general fatigue.[3,24,25] Schisandra has been used in the Soviet Far East as a tonic, particularly in fatigue. Indigenous Siberians used dried Schisandra berries to combat fatigue during their hunting trips. Often the hunters roamed for days subsisting on nothing but the fresh or dried berries, and showed no signs of fatigue.[26-28]

Preparations of both the fruit and the seed of Schisandra have been investigated in research conducted in the former USSR.[29] The following studies evaluated preparations that used the fruit or were undefined.

In mostly uncontrolled clinical studies, administration of Schisandra:

- demonstrated tonic and adaptogenic effects in workers and patients with nervous disorders;[30,31]
- improved mental performance in healthy volunteers and workers;[30]
- was beneficial for patients with general asthenia, exhaustion and reduced physical and mental performance;[29]
- had a beneficial effect in patients with **stress-induced, mild depression**;[30]
- provided a stimulant effect, improved mood and reduced hallucinations in some patients with paranoid or catatonic schizophrenia but may not be useful in other forms of the disease or chronic disease.[29]

St John's Wort

Hypericum perforatum aerial parts have been used in western herbal medicine primarily for the nervous system.

The herb has been used traditionally throughout Europe for symptoms of nervous tension, such as, insomnia, cramps, intestinal colic, dysmenorrhoea, bed wetting and anxiety. Its restorative action has been traditionally utilised for the treatment of melancholic conditions, depression and convalescence following concussion and other trauma. The combination of traditional restorative and relaxant actions supports the treatment of conditions where **tension and exhaustion combine**. The original rationale behind the traditional use of St John's Wort in menopause was to support this body change as symptoms of debility (rather than hormonal).[32] Other specific traditional indications include disorders of the spine such as neuralgia, sciatica and wounds where nerves are involved.[17,33,34]

Systematic review and meta-analysis of the results of randomised clinical trials suggests that standardised extracts of St John's Wort may be effective for treating depression. The first meta-analysis published in 2005,[35] was updated in 2008,[36] to include trials of patients with moderate to severe depression as well as of mild to moderate severity. The 2008 analysis also excluded some of the former trials due to more rigorous diagnostic criteria. The meta-analyses found that extracts of St John's Wort demonstrate greater efficacy than placebo, similar efficacy as standard antidepressants and have fewer side effects than antidepressant drugs. Side effects from St John's Wort were minor and uncommon. The most commonly prescribed daily dosage was standardised extract corresponding to about 4 g of dried herb, although higher doses were also prescribed, for example, if there was insufficient clinical response.[35,36] Another analysis of two of these trials (major depression) suggests that if no clinical response occurs within one month of treatment with St John's Wort it is unlikely that the individual will respond to the herb and alteration of the treatment strategy is required.[37] (Although St John's Wort was found to be beneficial in the more major forms of depression, its use is best confined to **mild to moderate depression**.)

A 2010 placebo-controlled trial found St John's Wort extract (equivalent to about 2.7 g/day of dried herb) was beneficial for the treatment of atypical depression, particularly for the symptom hypersomnia (excessive sleepiness).[38]

St John's Wort extract has also shown clinical benefit in other conditions involving the nervous system including:

- somatoform disorders – improvement was independent of the presence or absence of depression, and as well as clinical improvement in symptoms, an **antianxiety effect** was observed (randomised controlled trials; dose: about 3.3 g/day of dried herb);[39,40]
- **fatigue** (uncontrolled, pilot study and nearly half the participants were depressed at the start of the trial; dose: about 3.8 g/day of dried herb);[41]
- restless legs syndrome (uncontrolled study; extract undefined).[42]

Safety

Saffron has reportedly been used as an abortifacient at doses of 10 g. Daily doses of up to 1.5 g are thought to be safe. Descriptions of adverse effects for doses of 1.2–4 g/day are mostly found the older literature (prior to 1925), and bear little relationship to dosage (i.e. reported adverse effects were not dependent upon dose). It is possible that the correct botanical species was not identified, and the more toxic plant, meadow saffron (*Colchicum autumnale*), was responsible.[43] Islamic traditional medicine ascribes Saffron with oxytocic activity and it is recommended to facilitate difficult labour, but the prescribed doses are high: 3.5–7 g.[6] Traditional Chinese medicine advises against the use of Saffron in pregnancy with a caution (dose: 3–9 g)[3] and contraindication (dose: 1.5–6 g)[24] noted.

Two double-blind, placebo-controlled trials investigated the effect of Saffron taken for 7 days on coagulation parameters in healthy volunteers. No significant effect was observed in the larger trial (n = 60).[44,45] Minor effects on bleeding time and international normalised ratio (INR) were observed in the smaller trial (n = 30) for those receiving Saffron (200 mg/day dried stigma). However, the changes were within the normal range and not considered clinically important. In addition, there was no effect at the higher dose of 400 mg/day. One female volunteer in each group of 5 women receiving Saffron showed abnormal uterine bleeding.[45]

A preliminary study investigated the safety of concomitant use of Saffron in 20 patients taking selective serotonin reuptake inhibitors. Saffron extract taken for 4 weeks had no significant effect on a wide range of laboratory parameters such as liver function, renal function (including blood urea nitrogen and creatinine) and coagulation factors including prothrombin time and INR. (The extract was the same as that described in the depression trials above, so probably corresponded to about 180 mg/day of dried stigma.)[46] Saffron (400 mg/day dried stigma, for 7 days) in healthy volunteers increased blood urea nitrogen and creatinine. No effect was observed at 200 mg/day.[45]

Allergy or sensitization to Saffron occurs rarely.[47,48]

Schisandra is contraindicated in pregnancy, except at birth. According to TCM Schisandra is contraindicated in the early stages of cough or rash and in excess heat patterns.

St John's Wort may cause hyperaesthesia in some sensitive individuals especially when combined with a high exposure to sunlight or artificial UVA light. St John's Wort is known to interact with many drugs.

Supportive Formulation

These herbs complement each other to support the nervous system with major nervine, but also, restorative and relaxant actions.

Indications

- Nervous exhaustion, fatigue.
- Mild to moderate depression, where additional nervous system support is required.
- To relieve mild anxiety, sleeplessness and insomnia.
- Part of a treatment regimen for premenstrual syndrome.

REFERENCES

[1] Nadkarni AK. *Dr. K.M. Nadkarni's Indian Materia Medica*, 3rd Edn, Vol 1. First published 1954, reprinted Popular Prakashan, Bombay, 1976. [2] Ellingwood F, Lloyd JU. *American Materia Medica, Therapeutics and Pharmacognosy*. 11th Edn. First published 1898, reprinted Eclectic Medical Publications, Portland, 1983. [3] *Pharmacopoeia of the People's Republic of China*, English Edn. Beijing: Chemical Industry Press, 1997. [4] Bharatiya Vidya Bhavan's Swami Prakashananda Ayurveda Research Centre. *Selected Medicinal Plants of India*. Chemexcil, Bombay, 1992. [5] Afifi FU, Abu-Irmaileh B. *J Ethnopharmacol* 2000; **72**: 101 [6] Javadi B et al. *Iran J Basic Med Sci* 2013; **16**: 1 [7] Frawley D, Lad V. *The Yoga of Herbs: An Ayurvedic Guide to Herbal Medicine*, 2nd Edition. Lotus Press, Santa Fe, 1988. [8] Pole S. *Ayurvedic Medicine: The Principles of Traditional Practice*. Singing Dragon, London, 2013. [9] Akhondzadeh S et al. *Phytother Res* 2005; **19**: 148 [10] Noorbala AA et al. *J Ethnopharmacol* 2005; **97**: 281 [11] Akhondzadeh S et al. *BMC Complement Altern Med* 2004; **4**: 12 [12] Modabbernia A et al. *Psychopharmacology* 2012; **223**: 381 [13] Kashani L et al. *Hum Psychopharmacol* 2013; **28**: 54 [14] Shamsa A et al. *Phytomedicine* 2009; **16**: 690 [15] Safarinejad MR et al. *Int J Impot Res* 2010; **22**: 240 [16] Agha-Hosseini M et al. *BJOG* 2008; **115**: 515 [17] *British Herbal Pharmacopoeia*. BHMA, Bournemouth, 1983. [18] Cook WH. *The Physio-medical Dispensatory*. First published 1869, reprinted Eclectic Medical Publications, Portland, 1985. [19] Holmes P. *The Energetics of Western Herbs: Treatment Strategies Integrating Western and Oriental Herbal Medicine*, Revised 3rd Edn. Snow Lotus Press, Boulder, 1998. [20] Bone K. *Clinical Guide to Blending Liquid Herbs. Herbal Formulations for the Individual Patient*. Churchill Livingstone, USA, 2003. [21] Gafner S et al. *J AOAC Int* 2003; **86**: 453 [22] Wolfson P, Hoffmann DL. *Altern Ther Health Med* 2003; **9**: 74 [23] Brock C et al. *Phytother Res* 2014; **28**: 692 [24] Bensky D, Clavey S, Stoger E. *Chinese Herbal Medicine: Materia Medica*, 3rd Edn. Eastland Press, Seattle, 2004. [25] World Health Organization. *Medicinal Plants in China*. WHO Regional Office for the Western Pacific, Manilla, 1989. [26] Hancke JL et al. *Fitoterapia* 1999; **70**: 451 [27] Moskalenko SA. *J Ethnopharmacol* 1987; **21**: 231 [28] Kourennoff PM, St George G. *Russian Folk Medicine*. London & New York, WH Allen, 1970. [29] Panossian A, Wikman G. *J Ethnopharmacol* 2008; **118**: 183 [30] Panossian A, Wikman G. *Pharmaceuticals* 2010; **3**: 188 [31] American Herbal Pharmacopoeia. *Schisandra Berry – Schisandra chinensis: Analytical, Quality Control, and Therapeutic Monograph*. American Herbal Pharmacopoeia, Santa Cruz, October 1999. [32] Mills SY. *The Essential Book of Herbal Medicine*. Penguin Arkana (Penguin), London, 1991. [33] Felter HW, Lloyd JU. *King's American Dispensatory*. 18th Edn, 3rd revision. First published 1898-1900, reprinted Eclectic Medical Publications, Portland, 1983. [34] Millspaugh CF. *American Medicinal Plants: An Illustrated and Descriptive Guide to Plants Indigenous to and Naturalized in the United States Which Are Used in Medicine*. First published 1892, reprinted Dover Publications, New York, 1974. [35] Linde K et al. *Cochrane Database Syst Rev* 2005; (2): CD000448 [36] Linde K et al. *Cochrane Database Syst Rev* 2008; (4):CD000448 [37] Sarris J et al. *Aust J Herbal Med* 2012; **24**: 118 [38] Mannel M et al. *J Psychiatr Res* 2010; **44**: 760 [39] Muller T et al. *Psychosom Med* 2004; **66**: 538 [40] Volz HP et al. *Psychopharmacol* 2002; **164**: 294 [41] Stevinson C et al. *Phytomedicine* 1998; **5**: 443 [42] Pereira Jr JC et al. *Clinics* 2013; **68**: 469 [43] Schmidt M et al. *Wien Med Wochenschr* 2007; **157**: 315 [44] Ayatollahi H et al. *Phytother Res* 2014; **28**: 539 [45] Modaghegh MH et al. *Phytomedicine*

2008; **15**: 1032 [46] Mansoori P et al. *J Med Plants* 2011; **10**: 121 [47] Moneret-Vautrin DA et al. *Allerg Immunol* 2002; **34**: 135 [48] Lucas CD et al. *Adv Food Nutr Res* 2001; **43**: 195

Author: Michelle Morgan