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# 22 Popular Herbal Medicines Having Effects on the Central Nervous System

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## 22.1 INTRODUCTION

According to the World Health Organization (WHO), ca. 80% of the world's population uses herbal medicines as its primary source of health care (Evans, 1998). In developing countries traditional herbal remedies have not yet been replaced by modern drugs, and in developed countries herbal medicine is experiencing a remarkable comeback (Eisenberg, 1998; Ernst and White, 2000). Many herbs have effects on the central nervous system (CNS), and some are specifically promoted for their CNS effects.

This chapter discusses herbal medicines that have been extensively researched for their CNS effects and are in popular use for such indications. In doing so, it briefly describes the mechanisms of action as well as summarizes the existing evidence on clinical efficacy and safety. To minimize random and selection biases, I refer (where possible) to systematic reviews of the published literature.

## **22.2 ST. JOHN'S WORT (*HYPERICUM PERFORATUM*)**

### **22.2.1 MECHANISM OF ACTION**

Tinctures or extracts of St. John's wort (SJW) applied topically or systemically have a wide range of traditional uses: for bronchitis, burns, cancer, enuresis, gastritis, hemorrhoids, hypothyroidism, insect bites, insomnia, kidney disease, scabies, and wound healing (Ernst et al., 2001). At present, SJW is employed almost exclusively to treat mild to moderate depression.

The constituents of SJW include anthraquinone derivatives (naphthodianthrones), including hypericin and pseudohypericin, flavonoids, prenylated phloroglucinols such as hyperforin and tautins, other phenols, and volatile oils (Barnes et al., 2002). Hypericin and hyperforin are prime candidates for the major pharmacologically active constituents but our knowledge on them is incomplete. The antidepressant mechanism of action has previously been assumed to consist of monoamine oxidase (MAO) inhibition (Blandt and Wagner, 1994). It is now believed to lie in a selective inhibition of serotonin, dopamine, and norepheniphrine reuptake in the CNS (Singer et al., 1999).

### **22.2.2 EFFICACY**

A metaanalysis of good methodological quality included 27 double-blind randomized controlled trials (RCTs; Linde, 2000). The authors used the Jadad score (Jadad et al., 1996) for evaluating the methodological quality of the primary studies and found their average quality to be good. Seventeen RCTs were placebo-controlled and demonstrated efficacy in mild to moderate depression. Ten studies compared SJW extracts with standard reference medications and showed apparent equivalence to maprotiline, imipramine, bromazepam, amitriptyline, and diazepam. Two high-quality reviews applied stricter inclusion criteria (Gaster and Hoiroyd, 2000; Kim, 1999). Thus, only eight (Gaster and Hoiroyd, 2000) and six (Kim, 1999) double-blind RCTs were summarized. No formal assessment of the methodological quality of the primary studies was performed in either of these reviews. Their results confirmed that SJW is more effective than placebo in treating mild to moderate depression and similarly zaazin is as effective as low-dose tricyclic anti-depressants. The most critical metaanalysis (Williams et al., 2000) included only 14 RCTs. The authors made no formal assessment of trial quality. They confirmed that SJW extracts were significantly more effective to treat mild to moderate depression than was placebo (relative benefit 1.9, 95% CI: 1.2 to 2.8) and equivalent to tricyclic antidepressants (relative benefit 1.2, 95% CI: 1.0 to 1.4). There was some evidence of publication bias, which may have led to an overestimation of the effect.

Three recent three-armed RCTs (Philipp et al., 1999; Shelton et al., 2001; Hypericum Depression Trial Group, 2002) were not included in the reviews discussed previously. In Philipp et al. (1999), 263 patients with moderate depression received daily doses of 1050 mg standardized SJW extract or 100 mg imipramine or placebo for 8 weeks. The results show that SJW was more effective than placebo and equivalent to imipramine in reducing symptoms of depression as verified by Hamilton depression scores. The other two studies failed to demonstrate an antidepressant effect of SJW over and above that of placebo (Shelton et al., 2001; Hypericum Depression Trial Group, 2002). Both trials included patients with major depression. The most reasonable conclusion from data available to date is therefore that SJW is an effective treatment for mild to moderate but not for major or severe depression.

### **22.2.3 SAFETY**

Taken as a monotherapy, SJW has an excellent safety profile that is clearly superior to that of conventional antidepressants (Ernst et al. 2001; Stevinson, 1999). The only potentially serious adverse effects relate to photosensitization, a complication of high-dose therapy that is extremely rare, and to the possibility that SJW might induce manic symptoms in predisposed patients (Schulz,

2000). Problems may, however, arise when patients take SJW with other medications. SJW acts as a hepatic enzyme inducer by activating the cytochrome P450 system (Ernst, 1999). In addition, it activates the transporter protein P-glycoprotein, which further increases the elimination of synthetic drugs (Drewe, 2000). Through these mechanisms, it can decrease the plasma level of a range of prescribed drugs (e.g., anticoagulants, oral contraceptives, and antiviral agents). This interaction can have major clinical consequences (Piscitelli et al., 2000; Ruschitzka et al., 2000; Yue and Bergquist, 2000), of which endangering the success of organ transplantation through a lowering of plasma cyclosporine levels is perhaps the most serious (Ernst, 2002). Finally there is evidence that the combination of SJW with selective serotonin reuptake inhibitors can lead to serotonin overload or serotonin syndrome, particularly in elderly patients (Ernst, 1999).

## **22.3 GINKGO (*GINKGO BILOBA*)**

### **22.3.1 MECHANISM OF ACTION**

Various parts of the ginkgo tree have been used in traditional Chinese medicine for millennia, for example, for asthma and chilblains. At present, the ginkgo leaf is mostly used for medicinal purposes. It contains flavonoids and terpene lactones (ginkgolides and bilobalides), which are associated with diverse pharmacological actions. *In vitro* and *in vivo* experiments suggest that ginkgo has antiedema, antihypoxic, free radical-scavenging, antioxidant, metabolic, antiplatelet, hemorrhheological, and microcirculatory actions (De Feudis, 1991; Johns and Cupp, 2000). Ginkgo extracts have been used experimentally for a wide range of indications: asthma, brain trauma, cochlea deafness, depression, free-radical damage to the retina, male impotence, reduction of myocardial reperfusion injury, and vertigo (Boon and Smith, 1999). In clinical practice, it is employed mostly for memory impairment, dementia, tinnitus, and intermittent claudication. In some European countries it is registered for these indications, whereas in the U.S. (like all other herbal medicines discussed in this chapter) it is marketed as a dietary supplement.

### **22.3.2 EFFICACY**

A systematic review of high methodological quality included 40 controlled clinical trials of ginkgo for cerebral insufficiency, that is, memory impairment but not dementia (Kleijnen and Knipschild, 1992). The authors used their own score to assess the methodological quality of the primary studies and only eight were judged to be rigorous. All but one of these eight showed positive effects of ginkgo on cognitive functions compared with placebo. In terms of global effectiveness ratings as well as single symptoms (e.g., forgetfulness, lack of concentration), the evidence was clearly in favor of ginkgo compared with placebo. However, the authors suspected publication bias because “there were no negative results reported in many trials of low quality” (Kleijnen and Knipschild, 1992). A further less rigorous metaanalysis focussed on one particular standardized extract (Lichtwer, Germany; Hopfenmüller, 1994). The author included no formal assessment of the methodological quality of the primary studies. Five of the 11 RCTs had not been included in the Kleijnen and Knipschild (1992) article. Again, the overall conclusions were positive.

Our recent systematic review addressed a slightly different research question: does ginkgo improve normal cognitive function in healthy volunteers below the age of 60 years free from any medical condition (Canter and Ernst, 2002)? Nine RCTs met our inclusion criteria. Their methodological quality was on average good, but none of the trials was entirely devoid of limitations. Collectively, the results of these studies did not show a consistent positive effect of ginkgo on any objective measure of cognitive function.

A further systematic review (Ernst and Pittler, 1999) included nine placebo-controlled double-blind RCTs of ginkgo for dementia. The methodological quality of the primary studies was assessed by the Jadad score (Jadad et al., 1996), and three of these studies achieved the highest possible

rating. All these three and eight of the total nine studies suggested that ginkgo is significantly more effective than placebo in delaying the cognitive deterioration in dementia. By using stricter entry criteria, Oken et al. (1998) conducted a metaanalysis of high methodological quality of four placebo-controlled double-blind RCTs of ginkgo for Alzheimer's disease. All these studies were included in our (Ernst and Pittler, 1999) analysis. No formal assessment of the methodological quality of the primary studies was made. Again, the overall result was positive. The pooled effect size in terms of cognitive function was moderate and translated into 3% difference in the Alzheimer's Disease Assessment Scale — cognitive subtest. Thus the average size of the therapeutic effect associated with ginkgo seems to be modest but clinically relevant.

### **22.3.3 SAFETY**

Adverse effects of ginkgo are usually mild, transient, and reversible. Potentially serious adverse effects are bleeding (e.g., subdural hematoma; De Feudis, 1991; Johns and Cupp, 2000) and seizures observed in children after excessive ingestion of seeds (Fetrow and Avila, 1999). Because of the antiplatelet activity of ginkgo (De Feudis, 1991) the possibility exists of interactions with anticoagulants (Ernst, 2000a, 2000b). Several such cases have been reported in the medical literature (Ernst, 2000b). In view of these findings, it might be wise to discontinue ginkgo several days before surgery.

## **22.4 KAVA (*PIPER METHYSTICUM*)**

### **22.4.1 MECHANISM OF ACTION**

Kava is made from the dried rhizome of the kava plant. It is traditionally used in the South Sea as a recreational drink. Kava has also been employed experimentally to attenuate seizures and to treat psychotic states (Fetrow and Avila, 1999). At present, it is mostly used for its anxiolytic effects (Ernst et al., 2001).

The active principle is constituted by a family of four pyrones (kavapyrones). Their main pharmacological properties include central muscle-relaxing and anticonvulsant actions (Schulz, 1999). The mechanism of the anxiolytic effect is still controversial; one theory is that kava pyrones enhance GABA binding in the amygdala without acting as direct antagonists at GABA receptors (Jussofie et al., 1994). Kava pyrones also are powerful strychnine antagonists (Schulz, 1999).

### **22.4.2 EFFICACY**

A recent systematic review and metaanalysis (Pitter and Ernst, 2002) included seven placebo-controlled double-blind RCTs. The methodological quality of the primary studies was assessed by the Jadad score and found to be variable but good on average; four of the studies scored the maximum of 5 points on this scale. Three of the trials could be submitted to a metaanalysis. Its results demonstrated a reduction of the Hamilton Anxiety Score (HAS) in favor of kava with a weighted mean difference of 9.7 HAS units (95% CI: 3.5 to 15.8). One trial, not included in the analysis, compared kava with oxazepam (Lindenberg et al., 1990). Its results suggest that both medications are similarly efficacious anxiolytics. Collectively, these data leave little doubt that short-term administration of kava is efficacious in reducing anxiety in patients suffering from this condition.

### **22.4.3 SAFETY**

In the previously mentioned RCTs, the incidence of adverse effects was similar in the experimental and placebo groups (Pittler and Ernst, 2000, 2002). Two postmarketing surveillance studies involving more than 6000 patients found adverse effects in 2.3 and 1.5% of patients taking 120 to 240

mg standardized kava extracts (Hofmann and Winter, 1996; Siegers et al., 1992). Several (in August 2002 the count was 68 worldwide) cases of toxic liver damage have been associated with kava (e.g., Stoller, 2000). So far the underlying mechanism is unclear.

These case reports are difficult to evaluate conclusively; in the vast majority of instances causality is a matter of debate not least because of concomitantly administered drugs, uncertainty of viral liver damage, and the role of alcohol abuse. Nevertheless, these cases were considered serious enough to warrant withdrawal of kava products from the markets of several countries.

When taken concomitantly with other medication acting on the CNS or with alcohol, there is a danger that the effects may be potentiated, leading to a temporal state of impaired vigilance or reduce consciousness. One such case report is on record (Almeida and Grimsley, 1996).

Long-term use of kava at high doses is associated with flaky, dry, and yellowish discoloring of the skin; ataxia; hair loss; partial loss of hearing; loss of appetite; and body weight reduction. The dermatological signs of kava abuse are known as kava dermopathy or kavatism (Norton and Ruse, 1994); usually they are reversible on discontinuation (Jappe et al., 1998). These phenomena have so far only been observed in inhabitants of the South Sea who took doses over prolonged periods of time, which were considerably higher than those recommended for therapeutic use (Schulz, 1999).

## 22.5 OTHER HERBAL MEDICINES

Numerous other herbal medicines have effects on the CNS. In many cases, they have not been studied in depth. [Table 22.1](#) provides a list of some of these herbs based on data extracted from Ernst and White (2000) and Barnes et al. (2002).

## 22.6 COMMENTS

This brief overview is based (wherever possible) on systematic reviews of the literature. This approach minimized selection and random biases but is by no means free from drawbacks. The two main limitations are publication bias (i.e., the tendency for negative studies to remain unpublished) and the often low quality of the primary data that may render the conclusions of systematic reviews less convincing than one would hope. In addition, two further points are important for interpreting systematic reviews of herbal medicines. First, much of the (older) trial data were published in German or other non-English languages. It is thus important that systematic reviews (not only) in this area apply no language restrictions. Second, herbal medicinal products of one plant may vary hugely in terms of their chemical composition. Systematic reviews often pool data from extracts which differ significantly; for example, some may be of inferior quality. This creates the danger of generating false negative overall results with systematic reviews and stresses the importance of adequately standardizing and describing the extracts, particularly for clinical trials.

The evidence discussed previously demonstrates that many herbal medicines have CNS effects that differ in nature much as CNS effects of synthetic drugs would obviously differ. The important point is that generalizations across all herbal medicines, as they are often published in the lay press, are clearly nonsensical.

This overview also shows that herbal medicines have the potential to both benefit and harm patients, again much like synthetic drugs. One could argue therefore that they should be regulated in the same way as conventional medicines. In the current regulatory framework herbal medicines in the U.S. and U.K. are marketed as dietary supplements, and this is not in the best interests of consumer safety. Finally, if herbal and synthetic medicines are similar in crucial respects, they should be researched with the same rigor and this research should be funded with the same generosity.

**TABLE 22.1**  
**Examples of Other Herbal Medicines with Effects on the Central Nervous System**

Latin (Common) Name	Main Constituents	Relevant Mechanism of Action	Efficacy/Indication <sup>a</sup> (Level of Evidence)	Major Safety Concerns	Comment
<i>Acorus calamus</i> (calamus)	Volatile oil	MAO inhibition, sedation	Sedation (+)	Genotoxic	May potentiate effects of barbiturates
<i>Apium graveolens</i> (celery)	Furanocoumarins	Sedation	Rheumatism, sedation, diuretic (+)	Photosensitivity	Fruits are used for medical purposes, stems for food
Calanitida (cola)	Caffeine	CNS stimulant	Depression, diuretic (+)	Sleeplessness, anxiety	Not for cardiovascular patients
<i>Chamaemelum nobile</i> (Roman chamomile)	Apigenin	Acts on central benzodiazepine receptors	Carminative, antiemetic (–)	Allergy	Should be avoided in hypersensitive individuals
<i>Cinnamomum cassia</i> (cassia)	Volatile oil	CNS stimulant	Range of gastrointestinal symptoms (+)	Allergy	Sometimes used as a substitute for true cinnamon
Crataegus (hawthorn)	Glycosides	CNS depressant	Congestive heart failure (+++)	Nausea, bradycardia	May potentiate action of other cardiac glycosides
<i>Eleutherococcus senticosus</i> (Siberian ginseng)	Eleutherosides	Sedation, CNS stimulant	General tonic (++)	Nerve irritation (prolonged use)	CNS stimulation/depression seem to depend on type of animal model
<i>Ephedra sinica</i> (ephedra/Ma huang)	Ephedrine	Sympathomimetic	Asthma (++)	Tachycardia, anxiety	Also promoted for weight reduction
<i>Fumaria officinalis</i> (fumitory)	Protopine (isoquinoline alkaloid)	Sedation	Diuretic, laxative (+)	Increase of intraocular pressure	Not for glaucoma or hypertensive patients
<i>Humulus lupulus</i> (hop)	Humulones, lupulones (deco-resin)	Sedation	Insomnia (+)	Allergy	Not for patients with depression
<i>Inula helenium</i> (elecampane)	Inulin	Sedation	Expectorant (+)	Allergy	None
<i>Lobelia inflata</i> (lobelia)	Lobeline (alkaloid)	CNS stimulant	Asthma (+)	Nausea, diarrhea	Actions are similar to those of nicotine
<i>Matricaria recurita</i> (German chamomile)	Apigenin	Acts on central benzodiazepine receptors	Wound healing (external use) (++)	Allergy	Should be avoided by hypersensitive individuals
<i>Melissa officinalis</i> (lemon balm)	Volatile oil	Sedation	Antiviral (++)	None reported	Cream against herpes labialis commercially available

Panax ginseng (American/Korean ginseng)	Ginsenoides	Inhibition of uptake of a range of neurotransmitters	Various, e.g., tonic, hypoglycemic (++)	Hypertension, diarrhea, insomnia	May potentiate action of MAO inhibitors
<i>Passiflora incarnata</i> (passionflower)	Harman	Sedation	Insomnia (+)	None reported	None
<i>Pimpinella anisum</i> (aniseed)	Transanethole (volatile oil)	Increases GABA in brain tissue of animals	Dyspepsia, catarrh (+)	Dermatitis, nausea vomiting	Traditionally used mostly for dyspepsia
<i>Polygala senega</i> (snake root)	Saponins	CNS depressant	Expectorant (+)	Gastric irritation	None
<i>Salvia officinalis</i> (sage)	Volatile oil	Anticholinesterase activity	Dyspepsia, pharyngitis (+)	Convulsions	Presently investigated as an antimentia agent
<i>Sarothamum scoparius</i> (broom)	Sparteine	CNS stimulant	Heart weakness, diuretic (+)	Bradycardia, respiratory arrest	Medical use not recommended
<i>Scutellaria laterifolia</i> (skullcap)	Scutellarin (glucoside)	Anticonvulsant, sedative	Epilepsy (+)	Hepatotoxicity	Medical use not recommended
<i>Urtica dioica</i> (stinging nettle)	Ligans	CNS depressant	Arthritis, benign prostatic hyperplasia (++)	Gastric irritation	Interactions with antidiabetic and antihypertensive drugs conceivable
<i>Valeriana officinalis</i> (valerian)	Valtrates	Affects GABA receptors	Insomnia (+++)	Hangover	May potentiate CNS depressants
<i>Vitex agnus castus</i> (chastbury)	Alkaloids (viticin)	Acts at dopamine D <sub>2</sub> receptors and affects prolactine release	Mastodynia, premenstrual syndrome (++)	Only minor adverse effects on record	Mostly used for its estrogenic effects

Note: + = mostly anecdotal evidence; ++ = several positive clinical trials; +++ = systematic review.

<sup>a</sup> Examples only.

Source: Extracted from Ernst, E. et al. (2001) *The Desktop Guide to Alternative and Complementary Medicine*, Mosby, Edinburgh, and Barnes et al. (2002) *Herbal Medicines: A Guide for Healthcare Professionals*, 2nd ed., Pharmaceutical Press, London. With permission.

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