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REVIEW

Herbal medicine for depression, anxiety and insomnia: A review of psychopharmacology and clinical evidence

Jerome Sarris[a,b,*], Alexander Panossian[c], Isaac Schweitzer[a], Con Stough[b], Andrew Scholey[b]

[a] The University of Melbourne, Faculty of Medicine, Department of Psychiatry, Australia
[b] Swinburne University of Technology, Centre for Human Psychopharmacology, Australia
[c] Swedish Herbal Institute Research & Development, Sweden

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Kava

Abstract

Research in the area of herbal psychopharmacology has increased markedly over the past decades. To date however, a comprehensive review of herbal antidepressant, anxiolytic and hypnotic psychopharmacology and applications in depression, anxiety and insomnia has been absent. A search of MEDLINE (PubMed), CINAHL, PsycINFO, and the Cochrane Library databases was conducted (up to February 21st 2011) on commonly used psychotropic herbal medicines. A review of the literature was conducted to ascertain mechanisms of action of these botanicals, in addition to a systematic review of controlled clinical trials for treatment of mood, anxiety and sleep disorders, which are common comorbid psychiatric disorders. Specific emphasis was given to emerging phytomedicines. Analysis of evidence levels was conducted, as were effect sizes (Cohen's d) where data were available. Results provided evidence of a range of neurochemical, endocrinological, and epigenetic effects for 21 individual phytomedicines, which are detailed in this paper. Sixty six controlled studies were located involving eleven phytomedicines. Several of these provide a high level of evidence, such as *Hypericum perforatum* for major depression, and *Piper methysticum* for anxiety disorders. Several human clinical trials provide preliminary positive evidence of antidepressant effects (*Echium amoenum*, *Crocus sativus*, and *Rhodiola rosea*) and anxiolytic activity (*Matricaria recutita*, *Ginkgo biloba*, *Passiflora incanata*, *E. amoenum*, and *Scutellaria lateriflora*). Caution should however be taken when interpreting the results as many studies have not been replicated. Several herbal medicines with in vitro and in vivo evidence are currently unexplored in human studies, and along with use of emerging genetic technologies "herbomics", are areas of potential future research.

* Corresponding author at: The University of Melbourne, Department of Psychiatry &The Melbourne Clinic, 2 Salisbury Street Richmond, Victoria 3121, Australia. Tel.: +613 9420 9255; fax: +61 3 9427 7558.
E-mail address: jsarris@unimelb.edu.au (J. Sarris).

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1. Introduction

1.1. Overview of herbal psychopharmacology

Mood, anxiety, and sleep disorders are prevalent and highly comorbid psychiatric conditions (Kessler et al., 2005) that have been treated with botanical medicines since antiquity. Contemporaneously, herbal medicine and Complementary and Alternative Medicine (CAM) use is widespread amongst sufferers of mood and anxiety disorders. Data from a nationally representative sample of 2055 people interviewed during 1997–1998 revealed that 57% of those suffering anxiety attacks, and 54% of those with severe depression reported using herbal medicine and CAM therapies during the previous 12 months to treat their disorder (Kessler et al., 2001). Interviews of 82 psychiatric North American inpatients hospitalised for acute care for various psychiatric disorders revealed that 44% had used herbal medicine (mainly for psychiatric purposes) during the previous 12 months (Elkins et al., 2005).

Scientific understanding of psychoactive plants has significantly advanced over the last two centuries, after the isolation of active constituents, such as morphine from opium poppies (Pengelly, 1997). Modern research on herbal medicine in psychiatry although still in its infancy, has increased in recent years with a 50% increase in the literature over 5 years up to 2008 (García-García et al., 2008). Research into psychoactive plants that may affect the central nervous system (CNS) has flourished, with an abundance of pre-clinical in vitro and in vivo studies validating many phytotherapies as having an array of biopsychological effects (Kumar, 2006). Aside from notable psychoactive constituents isolated from plants (usually containing alkaloids) such as cocaine from *Erythroxylon coca* (coca), morphine from *Papaver somniferum* (opium poppy), or arecoline from *Areca catechu* (betel nut), other less potent plants, such as *Hypericum perforatum* (St John's wort), have developed evidence of beneficial therapeutic activity over the last several decades (Spinella, 2001). Many of these that are available as "over-the-counter" psychotropic herbal medicines are fairly safe, and present with fewer side effects in comparison to conventional pharmacotherapies such as antidepressants (cholinergic symptoms, sexual dysfunction, insomnia, and withdrawal issues) and benzodiazepines (somnolence, dependence and withdrawal issues) (Baldwin et al., 2007; Papakostas, 2008; Schweitzer et al., 2009). Regardless, not all commonly used phytomedicines are safe, for example there are case reports (albeit rare) of *H. perforatum* causing switching to mania in bipolar disorder (Fahmi et al., 2002) and drug interactions (Madabushi et al., 2006), and liver toxicity with *Piper methysticum* (kava) (Teschke, 2010).

Mainstream drug development and, to some degree traditional pharmacognosy (study of nature-derived drugs), often use isolated single active principles from plant material (Heinrich et al., 2004). In some cases this is highly effective, leading for example to the development of aspirin, opiate anaesthetics, digitoxin and taxol. However in certain cases, attempts to isolate the active principles from plant extracts may be ultimately self-defeating since overall biological effects often rely on synergistic and polyvalent interactions between plant components (Williamson, 2001). Thus while in some instances it may be possible to isolate single active principle from plants, it is more common for plant extracts to contain numerous potentially psychoactive components. Presence of several psychoactive compounds in one plant may have a "synergistic" effect, defined as "a working together effect seen by a combination of substances that is greater than would have been expected from a consideration of individual contributions" (Heinrich et al., 2004). The "silver bullet" concept adopted by orthodox Western medicine for the drug discovery over the past 100 years, is now increasingly viewed as inadequate in many clinical situations (Wermuth, 2004). As a result, a cocktail of drugs are now commonly employed against conditions such as HIV infection, cancer or hypertension. These synergistic and polyvalence concepts have been used in traditional medicinal systems (e.g. TCM and Ayurvedic medicine) for millennia (Bensky and Gamble, 1991), and now have become accepted as the practice of polypharmacy. The use of polypharmacy in psychiatry is increasing, with use of combinations of antidepressants (Patten and Beck, 2004) and antipsychotics (Tranulis et al., 2008) being commonly employed. For example Comer et al. (2010) found that across a 12 year period (1996–2007) combination psychotropic treatment in children rose from 14.3% to 20.2% (adjusted OR = 1.89, 95% CI:1.22,2.94; $p<0.01$).

An example of synergy can be found in *Salvia* spp. (sage) which is known to have pro-cognitive and cholinesterase inhibiting properties (Scholey et al., 2008). Savelev et al. (2003) examined the cholinesterase inhibiting properties of components from *Salvia lavandulaefolia* essential oil. Combinations of constituents demonstrated enhanced cholinesterase inhibition via in vitro synergy at levels which would not be predicted from the activities of individual components. Epigenetic studies are already demonstrating that combinations of constituents are not only having an added effect of triggering the expression of genes, they are in fact triggering. An example of this can be found in a study of a multi-compound herbal product Phytodolor which contains three anti-inflammatory herbs. Epigenetic assays showed that the gene expression profile of the whole formula was unique, and did not reflect the effects from the individual herbs (Jordan et al., 2010).

A related concept to synergy is that of "polyvalence" (Houghton, 2009) which, unlike synergy (which strictly speaking refers to single pharmacological effect), describes the range of biological activities that a herbal extract may exhibit which contribute to the overall in vivo or clinical effect. Polyvalence can occur due to a variety of chemicals being present, each having different physiological effects, or to the presence of one particular chemical which has more than one disease-relevant physiological effect (Houghton, 2009). Alternatively an extract may contain compounds which do not directly affect the pathophysiological processes, but which may modify the absorption, distribution, metabolism and excretion of bioactive constituents, or reduce their side-effects (Williamson, 2001). Examples relevant to the current paper include *Valeriana officinalis* (valerian) which contains constituents with a range of properties relevant to anxiolysis, muscle relaxation, and sleep promotion (Patočka and Jakl, 2010). These include γ-aminobutyric acid (GABA)-ergic compounds such as free

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GABA, benzodiazepine receptor-binding flavonoids, the terpenes valerenic acid and valepotriates, which inhibit GABA breakdown and cause smooth muscle relaxation, as well as lignans which inhibit serotonin binding (Benke et al., 2009; Neuhaus et al., 2008). The action of these in concert may underlie behavioural effects. Similarly *H. perforatum* contains at least two widely studied neuro-active components: hyperforin and hypericin (Butterweck and Schmidt, 2007), however research has shown that the presence or absence of a simple flavonoid compound "rutin" significantly modulates the antidepressant effect of the plant (Wurglics and Schubert-Zsilavecz, 2006).

A more relevant issue might be the extent to which botanical extracts used in behavioural research are (or have the potential to be) standardised. Translating and comparing the findings of one study to another without knowledge of any standardisation remains difficult, if not impossible, even when results appear consistent between studies. Even standardisation based on concentrations of one or several psychoactive components does not guarantee that there is batch-to-batch consistency or "phytoequivalence", and this should be borne in mind when examining literature on herbal psychopharmacology (Scholey et al., 2005).

1.2. Herbal psychotropic mechanisms of action

Both at the cellular and whole organism level, a plethora of molecular processes are involved in stress responses mediated by the CNS. Consequently many compounds may be active against a range of targets, all contributing to the observed effect. Given the complexity of psychiatric disorders (e.g. depression, anxiety or insomnia), modulation of single neurotransmitter target may not necessarily treat the patient as successfully as approaches that target multiple neuroendocrine systems. This is evidenced by the growing body of positive studies using adjunctive combinations of interventions to enhance efficacy in mood disorders (Sarris et al., 2010a).

Mechanisms of action for herbal medicines used for treatment of psychiatric disorders primarily involve modulation of neuronal communication, via specific plant metabolites binding to neurotransmitter/neuromodulator receptors (Spinella, 2001), and via alteration of neurotransmitter synthesis and general function (Sarris, 2007). Other actions may involve stimulating or sedating CNS activity, and regulating or supporting the healthy function of the endocrine system (Kumar, 2006; Sarris, 2007; Spinella, 2001). Herbal medicines have a range of psychotherapeutic actions which may include antidepressant, anxiolytic, nootropic (cognitive enhancing), sedative, hypnotic and analgesic effects (Spinella, 2001). Other traditionally viewed effects that may not follow standard terminology include "adaptogenic" and "tonic" actions, which are posited to provide increased adaptation to exogenous stressors via complex effects on neurochemistry and the endocrine system (Panossian and Wikman, 2009). Such actions may be clinically relevant to a range of psychiatric disorders, including mood, anxiety and sleep disorders, which are prevalent conditions (Kessler et al., 2005). Similarly, the mechanisms of action underlying these disorders, while varied, still interface with each other, and often when certain underlying neurological, endocrine or circadian factors are treated, a beneficial effect may be observed in other domains. This may potentially impact the treatment of other comorbid psychiatric disorders e.g. if depression is treated then anxiety may resolve, or if insomnia is addressed then depression may be relieved.

One way to explore the psychopharmacological effects of herbal medicines and to increase their clinical validation is via the use of "omic" genetic technologies (Ulrich-Merzenich et al., 2007). Omics include pharmacogenomics, proteomics (epigenetics), and metabolomics. The use of omic technology in phytotherapy (field of herbal medicine) may be termed "herbomics". Omic technologies may provide answers on pharmacodynamics, toxicity/safety, synergy effects, and clinical efficacy. One such application of omic technology is the testing of epigenetic effects of herbal medicines via proteomic assays. The results of two epigenetic studies conducted in the area of herbal psychopharmacology, reveal interesting effects. Wong et al. (2004) conducted gene expression tests in an animal model comparing 8 weeks of a single daily intravenous dose of imipramine, *H. perforatum*, or saline control. Results showed that the herb differentially regulated 66 genes and expression sequence tags, while imipramine regulated 74. Six common transcripts (concerning synaptic and energy metabolism functions) were expressed by both treatments. Another proteomic animal model study conducted by Pennington et al. (2009) compared genetic protein expression in *H. perforatum* to the antidepressant clomipramine, and traditional Chinese medicine formulation "Xiao-yao-san" (XYS: used for mood disorders in Asia). From the 1616 protein spots analysed, *H. perforatum* was found to differentially express, in HT22 cells derived from mouse rat hippocampal cells, 64 proteins, XYS 40 proteins, and clomipramine 90 proteins. Mass spectrometry revealed that forty-three protein spots were found to have overlapping expressions, with the most affected involving energy metabolism. Western blotting analysis revealed that both the herb and clomipramine increased expression of two forms of DRP-2, a protein involved with axonal outgrowth and regeneration, while heat shock protein 70 (neuronal-protein folding gene) was also found to be increased. The significance of these studies is that they provide evidence that *H. perforatum* not only affects the transcription of many genes, but modulates similar genetic expressions to a conventional antidepressant. Future similar proteomic studies of other herbal psychotropics hold the promise of revealing similar genetic expressions common to conventional pharmacotherapies.

1.3. Aims of review

While other key reviews exist in the area of natural products and psychiatric disorders, these have either focused on an individual disorder e.g. anxiety (Lakhan and Vieira, 2010), a specific plant medicine e.g. *H. perforatum* (Kasper et al., 2010a), or covered the area in a relatively cursory manner (Sarris, 2007). None have provided a review of both the mechanistic underpinnings and clinical applications across a broad range of psychiatric disorders, nor calculated effect sizes for the clinical studies. So while research is increasing in the area of herbal psychopharmacology, to date no comprehensive review exists exploring the use of botanicals in the treatment of unipolar depression, anxiety disorders, and insomnia. These are highly comorbid and have common pathophysiological underpinnings, and as psychotropic herbal medicines exert an

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array of psychopharmacological actions, it is of value to provide a review which encompasses these interrelated areas. Thus, in this novel paper we provide 1) a review of preclinical studies to provide a mechanistic understanding of the activity (or activities) of major psychotropic herbal medicines (to relate this to psychiatric applications), and 2) a systematic review of relevant randomised controlled clinical trials to identify and analyse current evidence (including calculation of effect sizes where possible).

2. Methods

A search of the electronic databases MEDLINE (PubMed), CINAHL, PsycINFO, and The Cochrane Library was conducted up to February 21st 2011 to review the evidence of herbal medicines with anxiolytic, antidepressant and hypnotic activity. Databases were searched firstly for in vitro and in vivo data on the mechanisms of action of major herbal medicines used commonly in modern phytotherapy (Mills and Bone, 2000). Next, a systematic search of controlled clinical trials using the search terms "Depression" OR "Major Depressive Disorder" OR "Anxiety" OR "Generalised Anxiety Disorder" OR "Panic Disorder" OR "Social Anxiety" OR "Post-Traumatic Stress Disorder" OR "Obsessive Compulsive Disorder" OR "Anxiety Disorder" OR "Insomnia" OR "Sleep Disorder" was combined with the search terms "Herbal Medicine" OR "Herb*"OR "Medicinal Plants" OR "Botanical Medicine" in addition to thirty individual herbal medicines (common names and Latin binomial names) e.g. "St John's wort" OR "*Hypericum perforatum*". A forward search of key identified papers was subsequently performed using Web of Science cited reference search, in addition to hand-searching the literature. Papers that met the inclusion criteria for evidence of efficacy were human clinical trials using individual herbal medicines to treat mood, anxiety or sleep disorders. Specific inclusion criteria: 1) randomised and controlled trials (RCTs) i.e. using either an inert placebo or active comparator control (e.g. antidepressant), 2) have a total sample size of >10 (case studies were not included), 3) sufficient data available for analysis, and 4) be written in English. No criteria were set for gender, age, or ethnicity. All other papers that did not meet these criteria were excluded. As *H. perforatum*, *P. methysticum*, and *V. officinalis* have an abundance of studies, meta-analyses were primarily reviewed.

An analysis of the type of evidence in the mechanisms of action tables was formed from review of pre-clinical and clinical evidence in the area, while traditional knowledge was assessed primarily via an established pharmacopoeia: King's Dispensatory (Felter and Lloyd, 2008 (b) (1898)). Analysis of the level of evidence in the clinical studies table was performed by the researchers, with disagreements resolved by mutual consensus. Levels of evidence were defined as: Level A—meta-analyses or replicated RCTs with positive results; Level B—one unreplicated RCT, or studies with mixed but mainly positive results; Level C—one or more clinical trials with poor methodology, or mixed or unsupportive evidence from clinical trials. Where sufficient data of the clinical trials where available, we calculated effect sizes as Cohen's *d* by firstly subtracting the differences in scores between placebo and intervention (between baseline and endpoint), then dividing this by the pooled baseline standard deviation. Post treatment standard deviations were used when baseline data was absent (Cohen, 1988).

3. Results

3.1. Preclinical psychopharmacology

3.1.1. Herbal antidepressants and depression

It is estimated that by the year 2020, depression will result in the second greatest increase in morbidity after cardiovascular disease, presenting a significant socioeconomic burden (WHO, 2006). The pathophysiology of major depressive disorder (MDD) is complex, and it appears that a variety of overlapping biological causations exist (Belmaker and Agam, 2008). In the last several decades, the main premise concerning the biopathophysiology of MDD has focused on monoamine impairment (dysfunction in monoamine expression and receptor activity), lowering of monoamine production, or secondary messenger (e.g. G proteins or cyclic AMP) system malfunction (Hindmarch, 2001; Ressler and Nemeroff, 2000). In recent years, added attention has also focused on the role of neuroendocrinological abnormalities involving cortisol excess and its impeding effects on neurogenesis via reducing brain-derived neurotropic factor, as well as impaired endogenous opioid function, changes in GABAergic and/or glutamatergic transmission, cytokine or steroidal alterations, and abnormal circadian rhythm (Antonijevic, 2006; Hindmarch, 2001; Plotsky et al., 1998; Raison et al., 2006; Ressler and Nemeroff, 2000).

Several herbal medicines revealed an array of pre-clinical antidepressant activity, with seven being detailed in Table 1. Some antidepressant herbal medicines such as *H. perforatum*, *Rhodiola rosea* (roseroot), *Crocus sativus* (saffron) offer promise for the treatment of this disorder via known psychopharmacological actions including inhibition of monoamine re-uptake (such as serotonin, dopamine and noradrenaline), enhanced binding and sensitisation of serotonin receptors, monoamine oxidase inhibition, and neuro-endocrine modulation (Kumar, 2006; Sarris, 2007; Spinella, 2001). Other effects may include GABAergic effects, cytokine modulation (especially in depressive disorders with a comorbid inflammatory condition), and opioid and cannabinoid system effects (Spinella, 2001). In the case of most phytomedicines the antidepressant mechanisms of action are not as clearly defined as with SSRIs, having a multitude of biological effects on reuptake and receptor binding of various monoamines, commonly in addition to endocrine and psychoneuroimmunological modulation (Butterweck and Schmidt, 2007; Sarris and Kavanagh, 2009).

Some herbal medicines with mood elevating effects (such as *R. rosea* and *C. sativus*) also display anxiolytic effects. This may be due to modulation of neurological pathways that have both antidepressant and anxiolytic effects (e.g. GABA, serotonin, and noradrenaline systems), or this may be due to a "halo effect" whereby when depression is effectively treated, anxiety may also be reduced (Brady and Verduin, 2005; Nierenberg, 2001). This was found in the case in a recent RCT involving participants with generalised anxiety, which found that *P. methysticum* (an established anxiolytic) in addition to anxiety reduction, also provided a statistically significant reduction of comorbid depression on the Montgomery–Asberg Depression Rating Scale (Sarris et al., 2009a).

3.1.2. Herbal anxiolytics and anxiety

Anxiety disorders such as generalised anxiety disorder (GAD), social phobia, and post traumatic stress disorder present with a marked element of psychological anxiety and distress (American Psychiatric Association, 2000). The pathophysiology of anxiety disorders is still being unravelled, although current evidence indicates that the neurobiology involves abnormalities of serotonergic, noradrenergic, glutamatergic, and GABA-ergic transmission (Nutt et al., 2002). The involvement of these pathways is reflected in the efficacy of selective serotonin reuptake inhibitors (SSRIs), selective serotonin and noradrenalin reuptake inhibitors (SNRIs), and benzodiazepines (Tyrer and Baldwin, 2006).

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Table 1 Herbal antidepressants: mechanisms of action and clinical applications.

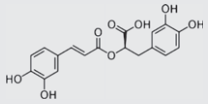
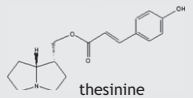
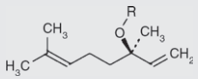
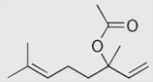
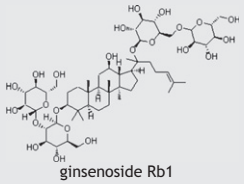
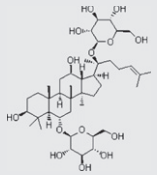
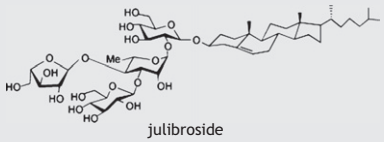
Herbal medicine	Mechanisms of action≠	Type of evidence *			Potential application *	Major active constituents
		Dep	Anx	Ins		
Borage (*Echium amoenum*)	◊ Anxiolysis shown in an animal model (elevated plus maze test) ◊ Antidepressant mechanism currently unknown (Rabbani et al., 2004)	1,2,3	2,3	–	Depression Anxiety	 rosmarinic acid  thesinine
Lavender (*Lavandula* spp.)	◊ GABA modulation (based on volatile constituents) ◊ Anxiolysis shown in animal models (elevated plus maze and open field tests) (Atsumi and Tonosaki, 2007; Bradley et al., 2007; Perry and Perry, 2006; Shaw et al., 2007; Toda and Morimoto, 2008)	1,2,3	2,3	2,3	Depression Anxiety Somatic tension	 linalool  linayl acetate
Korean ginseng (*Panax ginseng*)	◊ HPA-axis modulation ◊ Monoamine modulation (dopamine, serotonin) ◊ Anti-inflammatory and antioxidant effects ◊ Nitric oxide synthase inhibition (Bhattacharya and Mitra, 1991; Chen, 1996; Dang et al., 2009; Joo et al., 2005; Kim et al., 2003; Park et al., 2005)	1,2,3	–	–	Fatigue Depression Poor cognition	 ginsenoside Rb1  ginsenoside Rg1
Mimosa (*Albizia julibrissin*)	◊ 5-HT_{1A} receptor binding affinity ◊ 5-HT_{2c} receptor binding affinity ◊ Antidepressant, anxiolytic effects in animal models (elevated plus maze and tail suspension tests) ◊ Significantly decreased sleep latency and increased sleep duration in pentobarbital-induced sleep (Cao et al., 2010; Cho et al., 2010; Jung et al., 2005; Kim et al., 2007; Kim et al., 2004)	2,3	2,3	2,3	Depression Anxiety Insomnia	 julibroside

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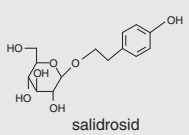
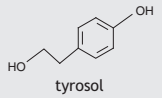
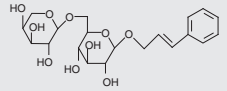
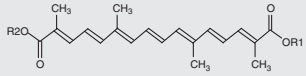
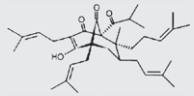
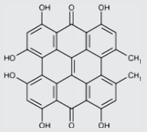
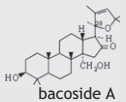
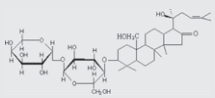
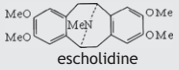
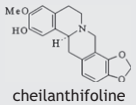
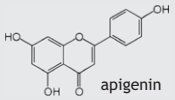
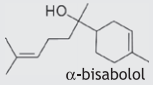
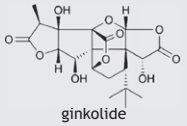
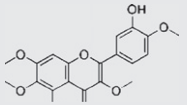
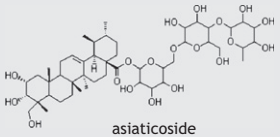
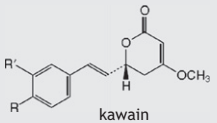
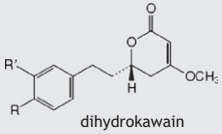
Table 1 (*continued*)

Herbal medicine	Mechanisms of action≠	Type of evidence *			Potential application *	Major active constituents
		Dep	Anx	Ins		
Roseroot (*Rhodiola rosea*)	◊ Neuroendocrine modulation (inhibition of cortisol, stress-induced protein kinases, nitric oxide) ◊ Monoamine oxidase A inhibition ◊ Monoamine modulation ◊ Normalisation of 5-HT and anti-stress effects in animal depression models (Chen et al., 2009; Panossian et al. 2007, Panossian et al. 2008; Mattioli et al., 2009; Perfumi and Mattioli, 2007; van Diermen et al., 2009)	1,2,3	1,2,3	—	Fatigue Cognitive impairment Depression Anxiety	 salidrosid  tyrosol  rosavin
Saffron (*Crocus sativus*)	◊ ↑Re-uptake inhibition of monoamines (dopamine, norepinephrine, serotonin) ◊ NMDA receptor antagonism ◊ GABA-α agonism ◊ Anxiolytic effects in animal models (elevated plus maze and open field test) (Hosseinzadeh and Noraei, 2009; Lechtenberg et al., 2008?; Schmidt et al., 2007)	1,2,3	2,3	—	Depression Anxiety	 crocin  safranal
St John's wort (*Hypericum perforatum*)	◊ Modulation of monoamine transmission via Na+ channel ◊ Nonselective inhibition of re-uptake of serotonin, dopamine, norepinephrine ◊ Decreased degradation of neurochemicals ◊ Increased binding/sensitivity/ density to 5-$HT_{1A,B}$ ◊ Dopaminergic activity (prefrontal cortex) ◊ Inhibited neuronal release of glutamate ◊ Neuroendocrine modulation ◊ Anti-depressant and anxiolytic activity in animal models (Butterweck, 2003; Chang and Wang, 2010; Franklin et al., 2006; Muller and Rossol, 1994; Singer et al., 1999; Yoshitake et al., 2004)	1,2,3	2,3	3	Depression Bipolar depression	 hyperforin  hypericin

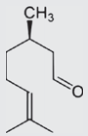
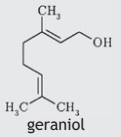
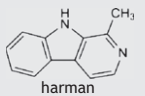
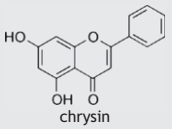
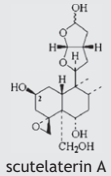
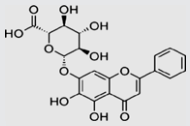
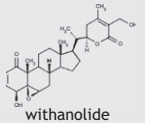
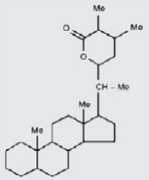
1 Human clinical data, 2 Experimental evidence of activity, 3 Traditional systems of medicine and pharmacopoeias endorse use.
* Dep = Depression, Anx = Anxiety, Ins = Insomnia.

Table 2 Herbal anxiolytics: mechanisms of action and clinical applications.

Herbal medicine	Mechanisms of action	Evidence*			Potential clinical application	Major active constituents	
		Dep	Anx	Ins			
Brahmi (*Bacopa monniera*)	◊ Metal chelation/β-amyloid protection ◊ Cholinesterase inhibition ◊ $5HT_{2c}$ modulation ◊ Antioxidant effects ◊ Antidepressant effects in forced swim and learned helplessness animal models (Krishnakumar et al., 2009; Limpeanchob et al., 2008; Sairam et al., 2002; Stough et al., 2001; Tripathi et al., 1996)	2,3	2,3	3	Cognitive impairment Anxiety Depression Nervous exhaustion	 bacoside A	 bacoside P
California poppy (*Eschscholzia californica*)	◊ Binding affinity with GABA receptors (flumazenil antagonist) ◊ Anxiolysis in animal models (familiar environment and anti-conflict tests) (Hanus et al., 2004; Kleber et al., 1995; Rolland et al., 2001; Rolland et al., 1991; Schafer et al., 1995)	–	2,3	2,3	Anxiety Insomnia Pain	 escholidine	 cheilanthifoline
Chamomile (*Matricaria recutita*)	◊ Binding to GABA receptors ◊ Modulates monoamine neurotransmission ◊ Neuroendocrine modulation (Avallone et al., 2000; Awad et al., 2007; Salgueiro et al., 1997; Viola et al., 1995; Zanoli et al., 2000)	–	1,2,3	3	Anxiety Insomnia Stress	 apigenin	 α-bisabolol
Ginkgo (*Ginkgo biloba*)	◊ Modulation of cholinergic and monoamine pathways ◊ Antioxidant, anti-PAF, anti-inflammatory effects ◊ GABAergic effects ◊ Nitric oxide activity (Di Renzo, 2000; Woelk et al., 2007)	2	1,2	–	Cognitive impairment Anxiety Depression	 ginkolide	 bilobalide
Gotu cola (*Centella asiatica*)	◊ GABA transaminase inhibition ◊ Animal models have shown anxiolytic effects (elevated plus maze, open field, social interaction tests) ◊ Inhibition of acoustic startle response in human RCT (Awad et al., 2007; Bradwejn et al., 2000; Wijeweera et al., 2006)	3	1,2,3	–	Anxiety Stress Cognitive impairment	 asiaticoside	
Kava (*Piper methysticum*)	◊ GABA channel modulation (lipid membrane structure and sodium channel function) ◊ Weak GABA binding (increased synergistic effect of [3H]muscimol binding to GABA-α receptors)	1,2,3	1,2,3	1,2,3	Anxiety Comorbid depression Anxious insomnia ADHD	 kawain	 dihydrokawain

(continued on next page)

Table 2 (*continued*)

Herbal medicine	Mechanisms of action	Evidence*			Potential clinical application	Major active constituents	
		Dep	Anx	Ins			
	◊ β-adrenergic downregulation ◊ MAO-B inhibition ◊ Re-uptake inhibition of norepinephrine in the prefrontal cortex (Boonen and Haberlein, 1998; Davies et al., 1992; Jussofie et al., 1994; Magura et al., 1997; Uebelhack et al., 1998)				Pain		
Lemonbalm (*Melissa officinalis*)	◊ Potent in vitro inhibitor of rat brain GABA transaminase (GABA-T) ◊ MAO-A inhibition ◊ Acute dosing caused a significant increase in self-rated calmness on a human stress tests (Awad et al., 2009; Kennedy et al., 2004; Kennedy et al., 2002; Lopez et al., 2009)	2,3	1,2,3	3	Acute stress Anxiety Depression	 citranellal	 geraniol
Passionflower (*Passiflora* spp.)	◊ GABA-system mediated anxiolysis ◊ Benzodiazepine receptor partial agonist ◊ Animal behavioural models have shown non-sedative anxiolytic effects (elevated-plus maze, light/dark box choice tests) (Dhawan et al., 2001a, b, 2002; Grundmann et al., 2009; Grundmann et al., 2008; Sena et al., 2009)	—	1,2,3	1,3	Anxiety Insomnia	 harman	 chrysin
Scullcap (*Scutellaria lateriflora*)	◊ Posited GABA-α binding affinity ◊ Anxiolysis in animal maze-test model (Awad et al., 2003)	3	1,2,3	3	Anxiety Nervous exhaustion Insomnia	 scutelaterin A	 baicalin
Withania (*Withania somnifera*)	◊ GABA-mimetic activity (enhanced flunitrazepam binding) ◊ Anxiolytic effect comparable to that produced by lorazepam in animal models (elevated plus-maze, social interaction and feeding latency in an unfamiliar environment tests) (Bhattacharya et al., 2000; Bhattacharya and Muruganandam, 2003; Mehta et al., 1991)	2,3	2,3	3	Anxiety Insomnia Fatigue Nervous exhaustion	 withanolide	 withaferin

1 Human clinical data, 2 Experimental evidence of activity, 3 Traditional systems of medicine and pharmacopoeias endorse use.
* Dep = Depression, Anx = Anxiety, Ins = Insomnia.

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In Table 2, ten herbal medicines with known anxiolytic effects are detailed. Phytotherapeutic interventions that may benefit anxiety disorders such as *P. methysticum* are classed as "anxiolytics", and usually have effects on the GABA system, (Sarris, 2007) either via inducing ionic channel transmission by blockage of voltage-gates, or blockage, or through alteration of membrane structures, (Sarris and Kavanagh, 2009) GABA transaminase or glutamic acid decarboxylase inhibition, (Awad et al., 2007) or less commonly via binding with benzodiazepine receptor sites (e.g. the α subunit)(Spinella, 2001). Subsequent increased GABA neurotransmission has a damping effect of stimulatory pathways, which ultimately provides a psychologically calming effect (Baldwin and Polkinghorn, 2005).

A novel study by Awad et al. (2007) was conducted to determine whether several common botanicals directly affected the primary brain enzymes responsible for GABA metabolism. In vitro rat brain homogenate assays revealed that, of the preparations assessed, the aqueous extract of *Melissa officinalis* (lemon balm) exhibited the greatest inhibition of GABA transaminase activity, while *Matricaria recutita* (chamomile) and *Humulus lupulus* (hops) showed significant inhibition of glutamic acid decarboxylase activity.

3.1.3. Herbal hypnotics and insomnia

Insomnia is a common affliction in Western societies, with the prevalence of general sleep disturbance experienced by people over a year is estimated at approximately 85%, while the estimate of diagnosed primary insomnia is estimated at around 10% (Roth and Roehrs, 2003). The pathophysiology behind sleep disorders appears to involve "hyperarousal" of the neuroendocrine system caused by abnormalities in circadian rhythm (involving CLOCK genes, melatonin secretion, and adenosine receptors), GABA pathways, endocrine factors (high cortisol), and excitatory pathways involving glutamate and aspartate (Roth et al., 2007; Sateia and Nowell, 2004).

Herbal hypnotics and sedatives such as *Valeriana* spp. and *H. lupulus* are believed to work via modulation of adenosine receptors (for example antagonising the adenosine blocking effects of caffeine), melatonergic effects, or via GABAergic activity (Sarris, 2007; Sarris and Byrne, 2011; Spinella, 2001). Anxiolysis that occurs from GABA modulation may also have follow-on soporific effects (potentially in stress-induced insomnia) (Sarris et al., 2009a). This may occur due to shared common pathways via a general down-regulation of neurological stimulatory activity. Due to this, plant medicines such as *Zizyphus jujuba* (sour date) and *V. officinalis*, while commonly used in phytotherapy for insomnia, can be both potentially also used to treat anxiety. This is reflected in the continuum that exists with sedating agents. As Spinella (2001) outlines, at one end of the sedation spectrum, substances that act as mild sedatives will cause relaxation and anxiolysis, while as the strength of the down-regulation of biological arousal increases, somnolence occurs, followed by marked sedation, coma and then death. While this continuum may be relevant to plants such as *P. somniferum*, it is not representative of many herbal anxiolytic/hypnotics, which while exerting a dose-dependent response, do not cause pronounced sedation. While only four hypnotic herbal medicines are detailed in Table 3, several other herbal medicines which are potentially beneficial for insomnia also exist, and are detailed in Table 2. These include *Passiflora incanata* (passionflower), *Eschscholzia californica* (California poppy), *P. methysticum*, and *Scutellaria lateriflora* (scullcap).

3.2. Clinical evidence in depression, anxiety, and insomnia

3.2.1. Overview of results

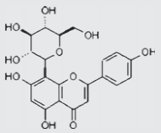
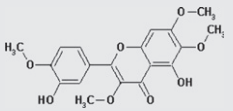
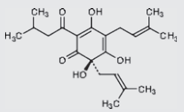
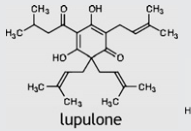
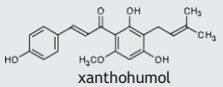
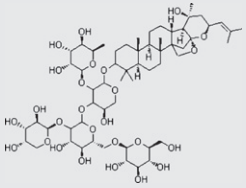
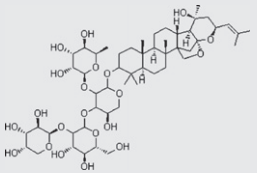
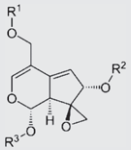
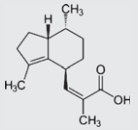
A systematic search of the literature revealed 2975 papers (including preclinical and clinical studies, meta-analyses, reviews, and commentaries), of which 66 relevant RCTs (including studies in meta-analyses) involving eleven individual plant medicines merited final inclusion (Table 4). Clinical study methodology (from controlled trials and meta-analyses) revealed typical treatment durations of between 4 and 8 weeks, and sample sizes of approximately 30–60 participants. Three phytomedicines displayed level A evidence (evidence analysis discussed in methods); *P. methysticum* for generalised anxiety and *H. perforatum* and *C. sativus* for unipolar depression. Meta-analyses and systematic reviews of *P. methysticum* and *H. perforatum* revealed significant effects over placebo and comparable effects to synthetic agents (Linde et al., 2008; Pittler and Ernst, 2003; Sarris and Kavanagh, 2009). The majority of phytomedicines (six) had level B evidence, denoting that many single trials exist but that these are yet to be replicated, thus more RCTs are required to make firm conclusions. Four phytomedicines were found to have level C grade of evidence: *Scutellaria officinalis* for anxiety (positive but poor methodology), *V. officinalis* (mixed evidence) and *P. incanata* (positive result only on one outcome) for insomnia, and *H. perforatum* with no significant effect in obsessive–compulsive disorder (OCD) or social phobia.

3.2.2. Clinical evidence in depression

Several herbal medicines with antidepressant effects in preclinical models have been subjected to clinical trials (see Table 4). A recent meta-analysis of *H. perforatum* RCTs was conducted by Rahimi et al. (2009). Comparison of *H. perforatum* with placebo yielded a significant relative risk (RR) for response in favour of the active of 1.22 (95% CI: 1.03, 1.45) and a weighted mean difference between treatments of 1.33 points (95% CI: 1.15, 1.51) on the Hamilton Depression Rating Scale (HAMD). Comparison with SSRIs yielded a non-significant difference between treatments of 0.32 (95% CI: −1.28, 0.64) for mean reduction in HAMD score from baseline. Importantly, a significant difference in favour of *H. perforatum* over conventional antidepressants for withdrawals due to adverse events was found: RR of 0.53 (95% CI: 0.35, 0.82). The results of this meta-analysis is comparable to the Linde et al. (2008) meta-analysis which provided a RR of 1.48 (95% CI: 1.23, 1.77) from 18 combined studies for response versus placebo, and an equivocal effect with synthetic antidepressants (SSRIs) RR 1.00 (95% CI: 0.90, 1.15). A recent long-term follow-up study involving 426 responders to extract WS 5570 were assessed for remission rates after continuation of 26 weeks of randomised WS 5570 (300 mg three times a day standardised to between 3 and 6% hyperforin and not less than 6% flavonoids) or placebo (Kasper et al., 2008). Results revealed a relapse rate for completers of 18% (51/282) compared to 25.7% (37/144) for placebo. Average relapse time for SJW was 14 days longer compared to placebo, which while statistically significant, is still a modest result. Standardisation and quality is an issue of note with SJW, as extracts show variability of efficacy potentially due to different constituent profiles (Kasper et al., 2010a). Due to this, results using high quality European pharmaceutical grade extracts cannot be transferred to some inferior extracts.

Please cite this article as: Sarris, J., et al., Herbal medicine for depression, anxiety and insomnia: A review of psychopharmacology and clinical evidence, Eur. Neuropsychopharmacol. (2011), doi:10.1016/j.euroneuro.2011.04.002

Table 3 Herbal hypnotics: mechanisms of action and clinical applications.

Herbal medicine	Mechanisms of action	Evidence*			Potential applications	Major active constituents
		Dep	Anx	Ins		
Chaste tree (*Vitex agnus castus*)	◊ Circadian rhythm modulation via increased melatonin secretion (dose-dependent effect that may benefit sleep latency insomnia) (Dericks-Tan et al., 2003)	1,2,3	–	2	Insomnia Dysphoria (menstrual)	 vitexin  casticin
Hops (*Humulus lupulus*)	◊ Melatonin receptor modulation (binding affinity to M_1 and M_2 receptors) ◊ Hypothermic activity (Abourashed et al., 2004; Brattstrom, 2007; Butterweck et al., 2007)	–	2,3	1,2,3	Insomnia	 humulone  lupulone  xanthohumol
Sour date (*Zizyphus jujuba*)	◊ Inhibits glutamate-mediated pathways in the hippocampus ◊ Jujubosides increased total sleep time when given orally in rats ◊ Animal models using suanzaoren (a TCM formula containing *Z. jujuba* as the principle herb) have found modulation of central monoamines and limbic system interaction (Cao et al., 2010; Chen et al., 1985; Hsieh et al., 1986a; Hsieh et al., 1986b; Morishita et al., 1987)	–	2,3	2,3	Insomnia Anxiety	 jujuboside A  jujuboside B
Valerian (*Valeriana spp.*)	◊ Adenosine (A_1 receptor) interactions GABA modulation (increased binding and decreased degradation of GABA) ◊ Valerenic acid from valerian has demonstrated GABA-A receptor (β3 subunit) agonism ◊ 5-HT_{5a} partial agonism ◊ Animal models have shown anxiolytic effects (elevated plus maze) (Benke et al., 2009; Dietz et al., 2005; Murphy et al., 2009; Ortiz et al., 1999; Sichardt et al., 2007; Trauner et al., 2008)	3	2,3	1,2,3	Insomnia Anxiety Somatic tension CNS stimulant withdrawal	 valepotriate  valerenic acid

1 Human clinical data, 2 Experimental evidence of activity, 3 Traditional systems of medicine and pharmacopoeias endorse use.
* Dep = Depression, Anx = Anxiety, Ins = Insomnia.

Table 4 Herbal psychotropics: human clinical studies.

Herbal medicine	First author	Methodology	Results[#]	Evidence level
Borage (*Echium amoenum*)	(Sayyah et al., 2006)	*Depression*: 6-week RCT (n=35) using 375mg of Borage vs. placebo	Statistically significant reduction versus placebo on HAMD at week but this was not maintained at week 6. No significant effect on HAMA	B
	(Sayyah et al., 2009a)	*OCD:* 6-week RCT (n=44) using 500mg/day of Borage vs. placebo	Borage significantly reduced OCD symptoms over placebo on Y-BOCS at endpoint, in addition to significantly reducing HAMA rated anxiety	B
Chamomile (*Matricaria recutita*)	(Amsterdam et al., 2009)	*Anxiety*: 8-week RCT (n=57) using standardised Chamomile extract (220mg-1100mg of titrated, depending on response) vs. placebo tablets	Chamomile significantly reduced participant's anxiety scores on HAMA compared to placebo at the end of eight weeks of treatment	B
Ginkgo (*Ginkgo biloba*)	(Woelk et al., 2007)	*Anxiety*: 4-week RCT (n=107) 240mg, 480mg Ginkgo extract EGb761 vs. placebo	Dose-dependent significant reduction of anxiety over placebo of 2.2 and 6.5 points on HAMA for 480mg and 240mg doses of EGb 761, respectively	B
Kava (*Piper methysticum*)	(Pittler and Ernst, 2003)	*Anxiety*: Review of 11 RCTs (N=645) and a meta-analysis of 6 RCTS (N=345)	Significantly greater anxiolysis from Kava than placebo; 5.0 point reduction over placebo on HAMA (95% CI: 1.1–8.8)	A
	(Witte et al., 2005)	*Anxiety*: Meta-analysis Kava WS1490 extract 6 RCTs included	Odds ratio in favour of Kava= 3.3 (95% CI: 2.09–5.22)	
Lavender (*Lavandula* spp.)	(Akhondzadeh et al., 2003)	*Depression*: 4-week RCT (n=45) using Lavender tincture (1:5 50% alcohol, 60 drops) vs. imipramine, or the combination	Imipramine was more effective than Lavender. The addition of Lavender to imipramine was more effective in reducing HAMD rated depression than imipramine alone, indicating a synergistic effect	B~
Passionflower (*Passiflora incarnata*)	(Akhondzadeh et al., 2001)	*Anxiety*: 4-week RCT (n=36) using 45drops of Passionflower vs. 30mg of oxazepam	Passionflower was as effective (with less side effects) as oxazepam in reducing anxiety	B
	(Movafegh et al., 2008)	*Anxiety:* Acute study RCT (n=60) using 500mg of Passionflower vs. placebo for pre-surgical anxiety	Anxiety scores were significantly lower in the passionflower group than in the control group on a numerical rating scale	
	(Ngan and Conduit, 2011)	*Insomnia*: 3-week RCT^ (n=41) using 2g of Passionflower tea vs. placebo (parsley) tea before sleep	Aside from an improvement between groups on subjective sleep quality, no significant differences were found on other sleep outcomes	C
Roseroot (*Rhodiola rosea*)	(Darbinyan et al., 2007)	*Depression*: 6-week 3-arm RCT (n=89) comparing 340mg vs 680mg of standardised Roseroot vs. placebo	Both Roseroot groups has significant reduction on HAMD significant and on insomnia, somatisation and emotional instability subscale outcome measures	B

(continued on next page)

Table 4 (*continued*)

Herbal medicine	First author	Methodology	Results[#]	Evidence level
Saffron (*Crocus sativus*)	(Akhondzadeh et al., 2005) (Moshiri et al., 2006) (Akhondzadeh et al., 2004)	*Depression*: Five 6-week RCTs: Two trials using 30–90 mg of Saffron vs. placebo;	Significant improvement for depression over placebo on HAMD for Saffron petals and stamen	A
	(Noorbala et al., 2005) (Akhondzadeh et al., 2007)	Three trials using Saffron vs. synthetic antidepressants	An equivalent therapeutic response occurred with Saffron vs. imipramine and fluoxetine on HAMD depression	
Scullcap (*Scutellaria lateriflora*)	(Wolfson and Hoffmann, 2003)	*Anxiety*: Acute cross-over RCT (n=19) using Scullcap vs. placebo	Scullcap dose-dependently reduced symptoms of anxiety and tension after acute administration compared with placebo	C
St John's wort: SJW (*Hypericum perforatum*)	(Rahimi et al., 2009)	*Depression*: Meta-analysis SJW vs. placebo 13 RCTs	RR 1.22 (95% CI: 1.03, 1.45) for clinical response (four studies) Significantly greater reduction over placebo of 1.33 points (95% CI: 1.15, 1.51) on HAMD (three studies) SJW showed an effect comparable to synthetics RR 0.99 (95% CI: 0.91, 1.08) for clinical response	A
	(Linde et al., 2008)	*Depression*: Meta-analyses SJW vs placebo 18 RCTs (N=3064)	SJW showed a significant effect on HAMD vs. placebo RR 1.48 (95% CI: 1.23, 1.77)	
		SJW vs SSRIs SJW vs Tri/tetracyclics 12 RCTs	Comparable to synthetics RR 1.00 (95% CI: 0.90, 1.15)	
	(Kobak et al., 2005a)	*OCD:* 12-week RCT (n=60) comparing SJW (600mg-1800mg) vs. placebo	RR 1.02 (95% CI: 0.90, 1.15) No significant result occurred between treatments on Y-BOCS, nor on response rates	C
	(Kobak et al., 2005b)	*Social Phobia:*12-week RCT (n=40) using SJW (600mg-1800mg) vs. placebo	No significant result occurred between treatments on the Liebowitz Social Anxiety Scale	C
Valerian (*Valeriana spp.*)	(Bent et al., 2006)	*Insomnia*: Systematic review 16 RCTs (N=1093) and meta-analysis. Valerian vs. placebo or vs. active controls	Six studies included in meta-analysis revealed significantly improved quality over placebo on the dichotomous outcome of sleep quality (RR of improved sleep = 1.8, 95% CI: 1.2, 2.9) However the review revealed 9/16 studies revealed no positive outcomes	C
	(Fernandez-San-Martin et al., 2010)	*Insomnia:* Systematic review and meta-analysis of 18 RCTs, Valerian vs. placebo or active controls	Valerian reduced sleep latency over placebo by only 0.70 min (95% CI −3.44, 4.83), with the standardised mean differences between the groups measured being statistically equivocal −0.02 (95% CI −0.35, 0.31)	

Level A: Meta-analyses or replicated RCTs with positive results Level B: One unreplicated RCT, or mixed but mainly positive results Level C: One or more clinical trials with poor methodology, or consistent mixed or unsupportive evidence. RR: relative risk ~Evidence-based on Lavender as an adjuvant rather than as a monotherapy, HAMD: Hamilton Depression Rating Scale, HAMA: Hamilton Anxiety Rating Scale, Y-BOCS: Yale-Brown Obsessive Compulsive Scale.

[#] "Significant" is $p<0.05$.

^ Two 1-week crossover periods, with a 1-week washout between.

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H. perforatum has better tolerability over some conventional antidepressants, as demonstrated by Kasper et al. (2010b) comparative analysis between paroxetine and *Hypericum* extract WS 5570, which revealed 10 to 38 fold higher adverse events rate for the synthetic comparator. While concerns exist over interactions of *H. perforatum* with pharmaceuticals, it should be noted that this mainly concerns high hyperforin extracts (Izzo, 2004). This is reflected in a systematic review of 19 studies that showed that high-dose hyperforin extracts (>10 mg/day) had outcomes consistent with CYP3A induction, while studies using low-dose hyperforin extracts (<4 mg/day) demonstrated no significant effect on CYP3A (thereby lessening the chance of increased metabolisation of many common drugs) (Whitten et al., 2006).

Two RCTs using 60–90 mg of concentrated *C. sativus* extract demonstrated significant improvement of depression over placebo on the HAMD (Akhondzadeh et al., 2005; Moshiri et al., 2006). The Akhondzadeh et al. (2005) RCT using the stamen had a large effect size of $d=1.51$, while the Moshiri et al. (2006) study which used the cheaper petals revealed a similar large effect size of $d=1.78$. Equivalent effects on HAMD occurred in three RCTs comparing *C. sativus* to imipramine and fluoxetine (Akhondzadeh et al., 2007; Akhondzadeh et al., 2004; Noorbala et al., 2005). Clinical trials have detailed anxiety, tachycardia, nausea, dyspepsia and changes in appetite as possible side effects (non-significant statistical trend against placebo) (Akhondzadeh et al., 2005; Moshiri et al., 2006). This reflects traditional knowledge of adverse reactions (Schmidt et al., 2007). Although the results are encouraging, limitations exist in confirming efficacy. Trial lengths are commonly short (4–6 weeks), sample sizes are small (n=30–40). Potential bias also exists, due to the same fraternity of researchers conducting the only human clinical trials. Other institutions are encouraged to validate this research, as *C. sativus* appears to be a promising antidepressant.

Only one human clinical trial was located evaluating *Echium amoenum* in the treatment of depression (Sayyah et al., 2006). Results revealed that the herb was superior to placebo in reducing depression on the HAMD at week four of a study with an effect size d of 0.92, however this result was not maintained at week 6 ($p=0.07$). *E. amoenum* also revealed no significant anxiolytic activity on the HAMA over placebo. This plant is currently scheduled in Australia due to the pyrrolizidine alkaloids. In this study the only notable difference between side effects of the herb and placebo groups were increased dry mouth in the active group (seven participants: 41%), although this was non-significant. One clinical trial compared *Lavandula* spp. against imipramine and the combination in patients with MDD (Akhondzadeh et al., 2003). Results revealed that although *Lavandula* spp. was not as effective as its synthetic counterpart, the combination of both was more effective than imipramine alone, indicating a synergistic effect.

Currently there is only one readily accessible study on *R. rosea* for depression, as previous research on its putative antidepressant activity are Russian in origin, and the original papers could not be obtained for this review. A three-arm study using *R. rosea* SHR-5 standardised extract (340 mg and 680 mg/day) against placebo in the treatment of mild-moderate depressive disorder revealed a significant dose-dependent improvement occurred in the active groups compared with placebo (Darbinyan et al., 2007). Effect sizes were large for both treatment groups, however conclusion from these strong results should be tempered as there was an unusually low response to placebo and a rather small standard deviation, which is not typical for trials using antidepressant compounds (Fournier et al., 2010). Although promising, confidence in the use of *R. rosea* to treat MDD cannot be established until more rigorous RCTs are undertaken.

3.2.3. Clinical evidence in anxiety

Several promising anxiolytics with traditional evidence as relaxants have been studied in clinical trials (see Table 4). A Cochrane review and meta-analysis of seven RCTs using *P. methysticum* in various anxiety disorders (Pittler and Ernst, 2003) revealed a statistically significant mean reduction of 3.9 points on the Hamilton Anxiety Scale (HAMA) over placebo (95% CI: 0.1, 7.7). A recent pooled analysis of *P. methysticum* studies in English (Sarris et al., 2010b), including a newly published positive study (Kava Anxiety Depression Spectrum Study) (Sarris et al., 2009a), revealed a similar conclusion, with a positive result occurring in four out of six studies reviewed (mean pooled Cohen's $d=1.10$). Not all studies however are positive, with a methodologically rigorous 4 week GAD study (n=37) by Connor and Davidson (2002) finding no significant difference between a standardised kava extract and placebo.

P. methysticum was withdrawn from European and UK markets in 2002 due to concerns over reported hepatotoxicity. Research has been conducted over recent years to determine the pathogenesis, and present understanding of factors potentially responsible for hepatotoxicity include incorrect cultivar (medicinal, tudie or wichmanni varieties) being used, individuals' hepatic insufficiency to metabolise kavalactones (cytochrome P450 (CYP) 3A4 and 2D6), preparations made using acetonic or ethanolic media low in glutathione, potentially contaminated or poorly stored material, and use of aerial parts or root peelings which are higher in alkaloids (Sarris et al., 2010c). Due to this, use of only the peeled roots from noble cultivars (cultivated species that are traditionally considered safe and therapeutic) using a water solute extraction method is advised (Teschke et al., in press).

S. lateriflora has been studied in one clinical trial to examine its anxiolytic activity. A clinical trial revealed that acute administration of the herb dose-dependently attenuated anxiety and tension on a numerical rating scale (Wolfson and Hoffmann, 2003). However, the methodology was poor and quantitative results on the outcome measures were not clearly elucidated (thereby precluding the calculation of an effect size). A pilot RCT using *P. incanata* extract revealed equivocal efficacy to oxazepam (30 mg/day) in reducing anxiety, with fewer side effects (Akhondzadeh et al., 2001). A non-statistical trend towards decreased sedation and impaired job performance occurred in the herbal medicine group. While the results are positive, no definitive conclusion can be reached, as anxiety conditions are notorious for high placebo response, and no placebo arm was used. An acute study using *P. incanata* against placebo control for pre-surgical anxiety revealed a significant reduction of anxiety in favour of the herb on a numerical rating scale ($d=1.30$) (Movafegh et al., 2008). Importantly, no difference in the anaesthetic sedation levels occurred between groups. Analysis of side effects of *P. incanata* studies in a Cochrane Review revealed no current evidence of any safety concerns with the plant (Miyasaka et al., 2007).

A recent RCT was conducted using a flexible dose of *M. recutita* in patients with diagnosed GAD and a moderate level of anxiety. Results revealed a significant effect in favour

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of the intervention with a large effect size $d=0.90$ (Amsterdam et al., 2009). No significant adverse reactions were found in the *M. recutita* group, even with higher doses. An RCT using *Ginkgo biloba* (ginkgo) EGb 761 extract (480 mg or 240 mg/day) or placebo in patients with GAD and adjustment disorder with anxious mood, revealed a significant dose-dependent reduction on the HAMA over placebo in both groups (Woelk et al., 2006). Effects sizes for GAD were large in both the 480 mg/day group ($d=1.14$), and the 240 mg/day group ($d=0.76$). While increased idiosyncratic bleeding time has been documented in rare case studies, the herb is regarded as having a good safety profile (Koch, 2005).

Aside from application in depression, *H. perforatum* has been studied for use in social phobia and OCD. In one controlled study, participants with a primary diagnosis of OCD were randomised to 12 weeks of treatment of *H. perforatum* (flexible dosing 600 mg–1800 mg depending on response) or matching placebo (Kobak et al., 2005a). Results revealed that the mean reduction on the Yale–Brown Obsessive Compulsive Scale (Y-BOCS) in the active group (−3.43) did not significantly differ from the placebo group (−3.60). Significant differences were also not found on any of the Y-BOCS subscales. A recent 6-week controlled study by Sayyah et al. (2009b) used the dried flower of *E. amoenum* versus placebo in patients with diagnosed OCD. Results revealed that while no significant effect occurred in the first weeks, a significant difference between the active and placebo on Y-BOCS and HAMA scores occurred at endpoint. However it should be noted that participants in both groups experienced only a slight reduction of OCD symptoms (five to six points on Y-BOCS). There was no significant difference between the two groups in terms of side effects, excepting an increase in constipation in the placebo group (potentially due to the use of talcum powder as an excipient). In social phobia one controlled study using an herbal medicine was found. A placebo-controlled pilot study testing *H. perforatum* (flexible-dose 600–1800 mg daily) in participants with social phobia (assessed via the Liebowitz Social Anxiety Scale), found no significant differential benefit over placebo, although a trend towards improvement was demonstrated (Kobak et al., 2005b).

Many of the anxiolytic plant medicines reviewed have potential additional applications. These include improving mood (*M. officinalis* or *P. methysticum*), providing a sedative or hypnotic action for insomnia (*P. incanata* or *S. lateriflora*), reducing muscle tension or pain (*E. californica*), or enhancing cognition via nootropic activities (*Bacopa monniera*: brahmi or *G. biloba*) (Mills and Bone, 2000; Spinella, 2001). Herbal medicines (such as *Withania somnifera*: withania, and *Centella asiatica*: gotu kola) may also provide an adaptogenic effect applicable in cases of comorbid fatigue (Panossian and Wikman, 2009).

3.2.4. Clinical evidence in insomnia

V. officinalis is the only botanical with sufficient research of adequate rigour in the area of insomnia (aside from a recently conducted isolated study using *P. incanata*). Meta-analyses and reviews by Bent et al. (2006) and Fernandez-San-Martin et al. (2010) reveal that the evidence concerning the soporific plant medicine is quite varied, and currently does not support its use in treating insomnia. The Bent et al. (2006) meta-analysis, which included 16 eligible RCTs on *Valeriana* spp. monotherapy or in combination with other herbal medicines, found that 9 out of 16 studies did not have positive outcomes in regard to improvement of sleep quality. The Fernandez-San-Martin et al. (2010) meta-analysis of 18 RCTs found that *Valeriana* spp. interventions reduced sleep latency over placebo by only 0.70 min (95% CI: −3.44, 4.83), with the standardised mean differences between the groups measured being statistically equivocal −0.02 (95% CI: −0.35, 0.31).The safety profile of *Valeriana* spp. appears good, however traditional pharmacopoeias caution it as a "cerebral stimulant" (Felter and Lloyd, 2008 (b) (1898)), thus it may not consistently provide somnolence. A recent 2 week crossover RCT (two 1-week phases with a 1-week washout in between) was conducted using *P. incanata* tea (2 g) versus a parsley placebo tea in healthy volunteers (Ngan and Conduit, 2011). Results revealed that differences at the conclusion of the active and placebo week of treatment were only significant (in favour of *P. incanata*) on the outcome of subjective sleep quality, with an effect size *d* of 0.44 (rated via sleep diary). No significant effects were found between treatments for total sleep time, sleep latency, sleep efficiency, or feeling of refreshment. Major flaws of this study included the lack of baseline measurement, non-standardisation of *P. incanata*, and short duration of treatment with a low once per day dose. Thus these results do not clearly inform on efficacy.

4. Discussion

As this review details, there is a growing abundance of preclinical and clinical studies which reveal a range of complex psychotropic activity from herbal medicines potentially beneficial for treating depression, anxiety and sleep disorders. However several caveats exist in being over-enthused by the current field of herbal psychopharmacology. Concerns exist over poor reporting of data in some studies, and the many unreplicated studies with small samples. Regarding study replication, only three herbal medicines reviewed have multiple replicated RCTs that have been analysed via meta-analysis (*H. perforatum*, *P. methysticum*, and *V. officinalis*). Another potential issue is that many herbal medicines with in vitro evidence have not yet been rigorously tested in robust human studies. As detailed in the mechanisms of action and clinical evidence tables, several herbal medicines (10 out of 21) that have in vitro or in vivo evidence of pharmacodynamic effects, have not been studied as monotherapies in human clinical trials. Regardless, an important consideration is that in vivo, plant constituents undergo significant metabolism via enzymatic and hepatic processes, being biotransformed into new chemical structures. Thus in vitro evidence cannot always be extrapolated to clinical efficacy in humans. A further consideration is that while studies conducted in Europe using *P. methysticum* or *H. perforatum* have often been positive (Sarris and Kavanagh, 2009), these results are not always replicated in countries such as the United States cf. (Connor and Davidson, 2002; Hypericum Depression Trial Study Group, 2002). In the case of *H. perforatum*, recent trials have revealed smaller effect sizes, thereby newer meta-analytic studies have provided weaker results than previous ones (Linde et al., 2008; Werneke et al., 2004). This also mirrors the "modest" result of a recent meta-analysis of antidepressants in MDD of mild to moderate severity, which revealed a Cohen's *d* effect size of 0.20 (Fournier et al., 2010).

Herbal medicines such as *Albizia julibrissin* (Mimosa), *M. officinalis*, *Z. jujuba*, and *E. californica* have been researched over the past three decades in preclinical models with positive results, however surprisingly these have not been studied as monotherapies in the treatment of psychiatric disorders. Preclinical evidence in these phytomedicines reveals an array

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of monoamine and neuropeptide modulatory activity that have potential to benefit sufferers of depression, anxiety and insomnia. Although, as stated above, positive in vitro or animal models do not always translate into clinical efficacy in humans, this information does provide a guidepost to potential future research. Promising anxiolytics that to date have not been tested as monotherapies by RCTs for anxiety disorders include *B. monniera*, *E. calfornica*, *M. officinalis*, and *W. somnifera*. Promising antidepressants include *Panax ginseng* (Korean ginseng), and *A. julibrissin*; while *H. lupulus* and *Z. jujuba* should be studied in the treatment of insomnia. It is interesting to note that while the plant medicines reviewed in this paper are used in modern phytotherapeutic practice to treat anxiety, depression, and insomnia, some have specific applications that may be utilised for complex conditions. For example *B. monniera* is considered beneficial in treating cognitive insufficiency; (Stough et al., 2001) *E. californica* has been used for insomnia and pain; (Rolland et al., 1991) *M. officinalis* is used for gastrointestinal complaints e.g. nervous dyspepsia; (Muller and Klement, 2006) while *W. somnifera* (Bhattacharya and Muruganandam, 2003) and *P. ginseng* (Rege et al., 1999) are regarded as "tonics" that via neuroendocrine modulation may allay fatigue.

In addition to exploring promising individual psychotropics for range of psychiatric disorders, future research could centre on combinations of various botanicals with preclinical and clinical evidence of activity. While gold standard methodology will usually be in the form of an RCT using a monotherapy, combination formulations may also be of merit. Such an example is found in a large, open label practice-orientated study, using a combination of *H. perforatum* and *V. officinalis* to treat depression co-occurring with anxiety (Muller et al., 2003). The results demonstrated marked success for the herbal combination which ameliorated anxiety more effectively than *H. perforatum* monotherapy. It should be noted however that not all combination studies are positive. A 4 week 2009 RCT using a combination of *H. perforatum* and *P. methysticum* for the treatment of MDD with comorbid anxiety had mixed results (Sarris et al., 2009b). Although there was significant relief of self-reported depression on the Beck Depression Inventory (BDI-II) over placebo in the first controlled phase, no effects were found in the pooled analysis or on anxiety outcomes. Regardless, other potential combinations exist that may be beneficial in the treatment of depression. Formulations involving combinations of *R. rosea*, *C. sativus*, *A. julibrissin*, and *H. perforatum* may provide increased synergistic antidepressant effects for treatment of depression. In the treatment of anxiety, novel formulations including *P. incanata*, *S. lateriflora*, in combination with *P. methysticum* may prove beneficial. While further research using *Z. jujuba* and *Vitex agnus castus* (chaste tree) in combination with other hypnotics may also provide benefit in insomnia. These combinations do exist commonly in over-the-counter herbal medicine products, however at present a paucity of research has been conducted to validate claims of efficacy. This remains a research area of great potential.

Currently, a lack of "bioequivalence" between extracts studied hampers the advancement of botanicals as viable mainstream medicines. While medicinal plants, or their combinations, have a multi-target polyvalent and synergistic mechanism of action (due to a complex mixture of active constituents), this potential strength also brings with it associated potential drawbacks. It is challenging to evaluate evidence of efficacy and safety due to differing bioequivalence between preparations used in the clinical trials. When results of different clinical studies are not consistent this limitation must be taken in consideration. Results derived from different herbal preparations produced by different manufactures (with differing bioequivalence) have not currently been evaluated. Evaluation and clinical assessment of efficacy of medicinal plants in general is a complicated task, with the chemical composition of herbal preparation dependant on many factors, such as: genetic differences (phytochemical variability); environmental differences (climate, temperature, light, and rain); soil quality (pH, fertilisation, and heavy metals); exposure to airborne vectors (insects, pests, and microbiological infection raw material production); differences in plant parts used (root, bark, leaf, fruit, etc.); harvest time (before, during, and after flowering time); and preparation methods (from storage to extraction and manufacture). Consequently, it is very difficult to produce standardised extracts with reproducible chemical composition, and consequently with reproducible pharmacological activity, particularly when extracts are produced by different manufacturers. While preclinical studies of main active constituents are helpful, the evidence cannot guarantee the same efficacy of total extract in replicated batches. This remains an area of concern, with future genetic "herbomic" studies potentially assisting in providing greater assurance of bioequivalence (Ulrich-Merzenich et al., 2007).

Future "herbomic" trials have the potential to greatly advance the field of herbal psychopharmacology, and should explore various different domains such as 1) Specific neurochemical pathways implicated in the pathogenesis of psychiatric disorders, and the phytomedicines which are known to affect these pathways, 2) Cytochrome P450 and P-glycoprotein polymorphisms which effect the metabolisation of the herbal medicine's active constituent and 3) Epigenetic differences affected between single active constituents versus whole extracts and complex prescriptive formulas. The nascent field of "herbomics" has the potential to provide over the coming years increased validation of the psychotropic effects of herbal medicines. As our knowledge advances in this area, herbal formulas may be personalised to take into account an individual's neurological and hepatic polymorphisms, and can monitor the epigenetic effects that occur in the person. Epigenetic studies can be used as a "proof of concept" in psychiatry, to show that whole extracts have specific affects on gene transcription that may be aligned with conventional pharmacotherapies. Furthermore, investigations of individualised prescriptions may demonstrate unique epigenetic effects.

In conclusion, while the literature reviewed in this paper provides encouraging evidence for the use of herbal medicines in the treatment of depression, anxiety and insomnia, further research utilising robust methodology, pharmaceutical good manufacturing practice and the use of biotechnologies to ensure bioequivalence of product, and greater application of genetic technologies, is still required to promote confidence in this area. This will provide the next significant step in the field of herbal psychopharmacology.

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Conflicts of Interest

No conflicts of interest noted.

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