HERBAL MEDICINES FOR DEPRESSION AND ANXIETY: A COMPREHENSIVE STATE OF THE ART REVIEW

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ABSTRACT

This review looks at all the herbal medicines and formulas in treating depression and anxiety disorders. Pubmed and the Cochrane Library were searched for pharmacological and clinical evidence of herbal medicines with antidepressant and anti-anxiety action. Good evidence exists for the use of kava and St John’s wort in the treatment of anxiety and depression respectively, while there is insufficient clinical evidence for the use of many other herbal medicines in psychiatric disorders. Newer herbal preparations that potentially have significant use in depression and anxiety and urgently require more research are Rhodiola rosea (roses root), Crocus sativus (saffron), Passiflora incarnata (passion flower) and Piper methysticum (kava). They need further evidence base via clinical studies. Depression and anxiety are commonly researched but the efficacy of herbal medicines in these disorders requires attention. The review addresses all the current issues in herbal therapy, safety issues and future areas of application in the field.

KEY WORDS: Herbal medications, depression, anxiety, kava, St John’s wort, passion flower.
INTRODUCTION

Mood disorders, anxiety and sleep disorders are largely prevalent and highly comorbid psychiatric conditions (Kessler et al., 2005). It is estimated that by 2020 depression will result in 2nd greatest increase in morbidity after cardiovascular diseases, presenting a significant socioeconomic burden (WHO, 2006). Since the past decade, many herbal medicines have been used in people with mood and anxiety disorders (Schulz et al., 2001). Due to the increasing popularity of herbal medications majority of the patients are consulting herbalists, naturopaths, and other healers, in addition to physicians. A data from a nationally representative sample of 2055 people interviewed during 1977–1988 revealed that 57% of those suffering anxiety attacks, and 54% of those with severe depression reported using herbal medicine during the previous 12 months to treat their disorder (Kessler et al., 2001). Similarly interviews of 82 psychiatric North American inpatients revealed that 44% had used herbal medicine (mainly for psychiatric purposes) during the previous 12 months (Elkins et al., 2005).

There is however, a limited data regarding the benefits and liability of herbal remedies and other natural remedies. There have been few reports of serious adverse effects from these medications and by and large these medications have been considered safe and effective (Schulz et al., 2001; Mischoulon, 2004). This article reviews the literature on various herbal medications in the treatment of depression and anxiety.

MECHANISM OF ACTION OF HERBAL MEDICATIONS

The primary mechanism of action involves modulation of neuronal communication, via specific plant metabolites binding to neurotransmitter/neuromodulator receptors (Spinella, 2011) and via alteration of neurotransmitter synthesis and general function (Sarris, 2007). Other mechanisms involve stimulating or sedating CNS activity, and regulating or supporting the healthy function of endocrine system (Kumar, 2006; Sarris, 2007; Spinella, 2011). The psycho-pharmacological effects of herbal medicines and their clinical validation can be explored by the use of “omic” genetic technologies (Ulrich-Meriezenich et al., 2007).

HERBAL MEDICATIONS USED IN THE MANAGEMENT OF DEPRESSION

Hypericum perforatum L. (St.John’s wort)

For centuries, hypericum an extract of the flower of St. John’s Wort (Hypericum perforatum L.) is used for the treatment of depression (Schulz et al., 2001). Its use in the United States has been dramatically increased in the past decade. Polycyclic phenols, hypericin and pseudohypericin are the active compounds in extract of St. John’s Wort. Other compounds include flavonoids (hyperoside, quercetin, isoquercitrin, rutin), kaempferol, luteolin, biapigenin and hyperforin (Muller-Kuhrt and Boesel, 1993; Staffeldt et al., 1993; Wagner et al., 1993). Out of all the active compounds hypericin is the main active compound.

Hypericin decreases serotonin receptor density (Muller-Kuhrt and Boesel, 1993). It also inhibits monocyte production of interleukin 6 and 1β resulting in a decrease in corticotropin releasing hormone and thus dampening cortisol production (Thiele et al., 1993). It decreases expression of β adrenoreceptors and increases density of serotonin by nonselective inhibition of neuronal reuptake of serotonin, dopamine, norepinephrine, GABA and l-glutamate, decreased degradation of neurochemicals, and a sensitization of and increased binding to various receptors (e.g. GABA, glutamate and adenosine) (Butterweck, 2003; Mennini and Gobbi, 2004; Zanolou, 2004; Muller et al., 1993; Teufel-Mayer et al., 1997). SJW modulates salivary and serum cortisol levels, and has a slight effect on growth hormone (Franklin et al., 2006). Hyperforin, hypericin and various flavonoids appear to be responsible for the neurochemical modulation (Butterweck, 2003; Laakmann et al., 1998; Zanolou, 2004).
In a large number of clinical European clinical trials, hypericum has been compared with low dose imipramine and maprotiline (75 mg/day) (Varbach et al., 1994; Harrer et al., 1993). Despite these low doses of active controls, the response rates in these trials seemed comparable to those in studies that use higher doses of tricyclic antidepressant agents (TCAs) (e.g., Imipramine ≥ 150 mg/day). The response rates for hypericum ranged from 35.3% to 81.8%, and the response to TCAs ranged from 41.2% to 77.8%. In a meta-analysis (Nirenberg et al., 2002), hypericum, 300 mg three times a day was judged to be effective in 79 of 120 subjects (65.8%), whereas placebo was considered effective in only 36 of 125 subjects (28.8%). The placebo response rate seemed comparable to that observed in many outpatient studies of antidepressants conducted in United States. A recent meta-analysis conducted by Rahimi et al., (2009) yielded a significant relative risk (RR) for response in favour of the active of 1.22 (95% CI: 1.03, 1.45) and weighed a mean difference between treatments of 1.33 points (95% CI: 1.15, 1.51) on the Hamilton Depressing Rating Scale (HAM-D). Where as comparison with SSRIs yielded a non significant difference between treatments of 0.32 (95% CI: -1.28, 0.64) for mean reduction in HAM-D score from baseline.

A meta-analysis (Linde et al., 1996) examined 15 trials comparing Hypericum with placebo and eight trials comparing Hypericum with TCAs in 1757 patients who had mild to moderate depression. In six trials that used single preparation of Hypericum, (containing only St. John’s Wort), hypericum yielded greater response rates than placebo (55.1% for Hypericum versus 22.3% for placebo) and comparable response rates to tricyclic antidepressants (69.3% for Hypericum versus 58.5 & for tri-cyclic antidepressants). In two trials that used combination preparations of Hypericum (containing St. John’s wort and other herbal medications such as Kava), Hypericum was found to be more effective than TCAs (67.7% versus 50%).

In a 6-week trial with 375 patients, Lecrubier and colleagues (Lecrubier et al., 2002) found that St. John’s Wort, 900 mg/day, was significantly more effective than placebo, especially who had higher base line HAM-D scores. Shelton and colleagues (2001) found that St. John’s Wort (900–1200 mg/day) was no more effective than placebo in the full intent to treat analysis, although among completers the remission rates were significantly higher with St. John’s Wort than the placebo. A 2004 meta-analysis of SJW (dosage 300–1200 mg/day) in the treatment of mild to moderate depression (Roder et al., 2004) reviewed 30 trials and concluded a significant advantage of SJW over placebo (n=2129, relative risk , RR = 0.66, 95% CI 3.0 to 6.6, mean response 53.2 SJW vs 51.3 % synthetic antidepressants). A meta-analysis of 16 trials , inspection of individual studies showed that SJW was found to demonstrate greater efficacy than synthetic antidepressants. Six RCTs tested SJW against placebo and fluoxetine in treating MDD, as commonly assessed via the Hamilton rating scale for depression (HAM-D) and clinical global impression (CGI). Four studies demonstrated that SJW had similar (Behnke et al., 2002; Bjerkenstedt et al., 2005) or superior (Fava et al., 2005; Schradar, 2000) effects to fluoxetine. An analysis of the sub-sample of a 12-week 3-arm study discovered that SJW (160- 900mg/day) ameliorated depression – based vegetative presentations, while fluoxetine (20mg/day) was statistically equivalent to placebo (Murck et al., 2005).

In comparison to paroxetine, SJW was statistically more effective in treating moderate-severe depression (Szegedi et al., 2005). Other comparative trials demonstrated SJW’s statistical equivalence to imipramine (Woelk, 2000), citalopram (Gasperi et al., 2006), Maprotiline (Harrer et al., 1994) and amitriptyline (Wheatley, 1997) in treating major depressive disorder. The Hypericum Depression Study, the medicine is currently used for the treatment of mild to moderate depression (Clement et al., 2006; Lawvere and Mahoney, 2005; Linde et al., 2005).
A comparative analysis between paroxetine and Hypericum extract WS 5570 revealed that paroxetine had 10 to 38 times higher adverse event rate. An increasing number of adverse drug reaction have been noted between St John’s Wort and other medications. Majority of the interactions are due to the liver enzyme CYP-450-3A4 which results in the decreased activity of several drugs, including warfarin, phenprocoumon, digoxin, indinavir, and irinotecan (Baede-van Dijk et al., 2000; Miller et al., 1998; Moore et al., 2000; Miller et al., 2000; Piscitelli et al., 2000). The interactions are mainly due to high dose hyperforin extracts (Izzo, 2004). Hyperforin increases the expression of pregnane-X-receptor, which increases P-glycoprotein expression (Dresser et al., 2003; Izzo, 2004; Moore et al., 2000). Low hyperforin preparations may not affect this response and hence may be safer (Izzo 2004, Muller et al., 2006). A systematic review of 19 studies showed that high dose hyperforin extracts (>10mg/day) had outcomes consistent with CYP3A induction while studies using low dose hyperforin extracts (<4mg/day) demonstrated no significant effects on CYP3A (Whiten et al., 2004). Because of the monoaminase inhibiting activity of St John’s Wort, its combination with SSRI’s may result in serotonin syndrome, hence it should not be combined with SSRI’s (Hu et al., 2005). As monotherapy adverse effects are mild (Schulz, 2005). Adverse events include dry mouth, dizziness, constipation, other gastrointestinal symptoms and allergic reactions (Schulz, 2001; Schulz, 2005).

Phototoxicity has been found in animals with hypericum but rarely in humans. Hypericum at a dose of 1800mg caused minor increase in sensitivity to uv light in humans but no phototoxicity. It is recommended that patients taking high dose of hypericum should be isolated from UV radiation for 7 days (Seigerse et al., 1993). At least 17 cases of psychosis have been resulted from St, John’s Wort, of which 12 comprised mania or hypomania. Researchers compared St, John’s Wort, 900 to 1800mg/d with sertraline 50 to 100mg/d, in 12 community based primary care offices. It was found that St John’s Wort resulted in significantly fewer adverse events (Van Gurp et al., 2002). In a 2006 review of 16 post marketing surveillance studies (n=34834) (Schulz, 2006), SJW was deemed to be 10 fold safer than synthetic antidepressants (adverse effects 0.1% to 2.4%). Overall SJW has demonstrated equal efficacy to pharmaceutical antidepressants with a more favourable side effect profile and fewer dropouts than its synthetic counterparts. SJW has been recommended as a first line treatment in milder forms of depression (Roder et al., 2004).

*Crocus sativus L. (Saffron)*

It increases the re-uptake inhibition of monoamines (dopamine, norepinephrine and serotonin). It is also a NMDA receptor antagonist and a GABA-α receptor agonist (Hosseinzadeh and Noraei, 2009; Lechtenberg et al., 2008; Schmidt et al., 2007). There have been two trials (Akhondzadeh et al., 2004; Noorbala et al., 2005) comparing saffron with imipramine and fluoxetine, it was found that saffron demonstrated improvement of depression. A similar response was demonstrated in a study in which 30 mg saffron was effective over placebo (Akhondzadeh et al., 2004; Mosher et al., 2006). Clinical trials have detailed anxiety, tachycardia, nausea, dyspepsia and changes in appetite as possible side effects (Mosher et al., 2006).

*Lavandula spp. (Lavender)*

It causes GABA modulation. In animal studies it is effective in anxiety symptoms (Atsumi and Tonosaki, 2007; Bradley et al., 2007; Perry and Parry, 2006; Shaw et al., 2007; Toda and Morimoto, 2008). In a 4 week RCT comparing comparing lavender tincture (1:5 50% alcohol, 60 drops) against imipramine in patients (n=45) with a HAM-D rating of at least 18 it was found that although lavender was less effective than the synthetic counterpart, the combination of both was more effective than Imipramine alone, indicating a synergistic effect (Akhondzadeh et al., 2003).
Rhodiola rosea L. (Rose root)

It causes inhibition of cortisol, stress induced protein kinases, nitric oxides and Monoamine oxidase A. In animal models it has shown to cause normalization of 5-HT and anti stress effects (Chen et al., 2009; Panossian et al., 2007; Panossian et al., 2008; Mattioli et al., 2009; Perfumi and Matticki, 2007; Van Dierman et al., 2009). Authors (Schvtsov et al., 2003) assessed the influence of roseroot on various mental and biological parameters of 161 adults, it was found to have an ant fatigue effect. This property along with the monoamine modulation can be used in the treatment of monopolar depression (Stancheva and Mosharrof, 1987). A three-arm study using R. rosea 5HR-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).

S-Adenosyl Methionine (SAMe)

It is a methyl donor in the brain and is involved in the pathways for synthesis of hormones, neurotransmitters, nucleic acids, proteins and phospholipids. Its potential role in mood regulation was determines by its activity as an intermediate in the synthesis of norepinephrine, dopamine, and serotonin. It is used in the treatment of major depression as well as in other medical conditions (Spillmann et al., 1996). Depression has been associated with Folate and vitamin B12 deficiency and about 10% to 30% of depressed patients have a low folate and these patients respond less to antidepressants (Alpert et al., 2000). Vitamin B12 is converted to methylcobalamin which is involved in the synthesis of various neurotransmitters. Hence its deficiency may result in earlier age of onset of depression (Fava et al., 1997). SAMe is synthesized from the amino acid l-methionine through the one carbon cycle, a metabolic pathway involving the vitamins folate and B12 (Spillmann et al., 1996). Low SAMe levels have been found in cerebrospinal fluid of depressed individuals (Bottiglieri et al., 1990) and higher plasma SAMe levels have been associated with improvement in depressive symptoms (Bell et al., 1994). It has been found that folate augmentation in partial responders has achieved good results (Coppen et al., 2000; Alpert et al., 2002). In 8 placebo controlled studies SAMe demonstrated superiority to placebo in 6 studies and equivalency to placebo in the other 2 studies (Spillmann et al., 1996; Alpert et al., 2000; Coppen et al., 2000). In 6 of the 8 comparison studies with TCAs, SAMe was equivalent in efficacy to TCAs and was more effect than imipramine in one study and SAMe may have a relatively faster onset of action than conventional depressants (Spillmann et al., 1996; Alpert et al., 2000; Coppen et al., 2000). In one study, some patients improved within a few days, and most did so within 2 weeks (Fava et al., 1995). Two studies have shown that combination of SAMe and a low dose TCA resulted in earlier onset of onset than a TCA alone (Alvarez et al., 1987; Berlanga et al., 1992).

Researchers have examined the efficacy of SAMe as an adjunctive treatment for partial and nonresponders to SSRIs (Alpert et al., 2004). Thirty subjects who had residual depression despite SSRI or venlafaxine treatment received a 6-week course of 800–1600mg. Response and remission rates with SAMe augmentation were 50% and 43% respectively, and the treatment was well tolerated. Besides depression, SAMe is effective for dementia-related cognitive defects, depression in patients who have Parkinson’s disease or other medical illness, psychological distress during the puerperium and opioid and alcohol detoxification (Miscoulon et al., 2002). SAMe is well tolerated and relatively free of side effects. Side effects include mild insomnia, lack of appetite, constipation, nausea, dry mouth, sweating, dizziness and nervousness (Spillmann et al., 1996). Cases of increased anxiety, mania or hypomania in bipolar depression have been reported (Spillmann et al., 1996; Carney et al., 1987; Carney et al., 1983) and therefore it should be used carefully in patients with bipolar disorders.
Omega-3 fatty acids

The intake of more and more processed foods rich in omega-6 containing vegetable oils has decreased the intake of omega-3 fatty acids in the Western diet. This has resulted in higher physiologic ratio of omega-6:omega-3 fatty acids in Western countries (Adams 1996; Hibbeln, 1995; Cross-National Collaborative Group, 1992; Hibbeln, 1998; Hibbeln, 1999). It has been postulated that the modern western diet and the additional stresses of twenty-first century create a proinflammatory state in humans that may contribute to cardiovascular and also may play a role in the development of mood disorders (Stoll and Lacke, 2002). So administration of omega-3 supplements may potentially reverse this proinflammatory state by correcting the omega-6:omega-3 ratio. It has an effect on membrane-bound receptors and enzymes involves in the regulation of neurotransmitter signaling, as well as regulation of calcium ion influx through calcium channels (Stoll and Lacke, 2002). Omega-3 fatty acids cause decrease corticosteroid release and dampen mood-altering effects associated with cortisol by inhibiting secretion of inflammatory cytokines. Eicosapentanoic acid resembles amitriptyline in antidepressant action, it inhibits the synthesis of prostaglandin E2, thus dampening the synthesis of p-glycoprotein (Murck et al., 2004). Peet and Horrobin (2002) conducted a randomized, placebo-controlled, dose finding study of ethyl-eicosapentaenoate (EPA) as adjunctive therapy for 70 adults who had persistent depression despite treatment with a standard antidepressant. Subjects who received 1 g/d EPA for 12 weeks showed significantly higher response rates (53%) than subjects receiving placebo (29%), with notable improvement of depressed mood, anxiety, sleep disturbance, libido, and suicidality. The 2 g/d group showed little evidence for a drug-placebo difference, and the 4 g/d group showed a nonsignificant trend toward improvement. These results suggest that there may be an optimal dose of omega-3 that humans require for maximum benefit, and it is possible that an overcorrection of the omega-6:omega-3 ratio with higher omega-3 doses may limit the antidepressant effect of EPA.

Researchers (Su et al., 2002) conducted an 8-week, double-blind, placebo-controlled trial comparing adjunctive omega-3 (6.6 g/d) against placebo in 28 depressed patients. Patients in the omega-3 group had a significant decrease in HAM-D scores compared with placebo. Nemets and colleagues found a statistically significant benefit of adjunctive EPA in 20 subjects who had major depressive disorder and who were on antidepressant therapy, 1 g/d, and a clinically important difference in the mean reduction of the 24-item HAM-D scale by the study endpoint at week 4 compared with placebo (12.4 versus 1.6). A single placebo-controlled study with 36 subjects showed lack of efficacy of DHA, 2 g/d, for depression (Marangell et al., 2003). Researchers (Osher et al., 2005) treated 12 bipolar I depressed subjects with open adjunctive EPA, 1.5 to 2 g/d, for up to 6 months. Ten patients completed at least 1 month of follow-up, and eight achieved a 50% or greater reduction in HAM-D scores. No cycling occurred with any patients. Further investigation is needed to determine whether bipolar disorder actually requires higher doses of omega-3 fatty acids than unipolar illness and to unravel the respective contributions of EPA and DHA. Omega-3 fatty acids are relatively very safe. Side effects include gastrointestinal upset and fishy aftertaste tends to occur with higher doses (> 5 g/d) with less pure prepararions. At doses of 1 g/d with highly purified omega-3 preparations, these adverse effects are less common. There is a documented risk of bleeding but it is minimal at doses less than 3 g/d. Hence individuals taking warfarin should be cautious and should use omega-3 fatty acids under a physician’s supervision. Also, there are few documented cases of cycling in bipolar patients (Freeman et al., 2006).

Hence it is recommended hat low doses of omega-3 fatty acids may be effective and well tolerated monotherapy or adjunctive therapy for depressed adults. Freeman and colleagues (2006) recommends that depressed individuals
may safely use approximately 1 g/d of an EPA-DHA mixture but should not substitute omega-3s for conventional antidepressants at this time. For, individuals who take more than 3 g/d of omega-3 should do so under a physician’s supervision (Freeman et al., 2006). They can also be used to treat specific populations (e.g. Pregnant or lactating women) for whom antidepressants may be used with a caution (Chiu et al., 2003), for elderly people and for those with cardiovascular diseases.

**Echium amoenum Fisch. & C.A.Mey** (Borage)

Its antidepressant action is currently unknown and anxiolytic activity is shown in animal studies (Rabbani et al., 2004). In a RCT single dose of *Echium amoenum* (375mg/day for 6 weeks) was compared against placebo in 35 patients with depression and anxiety, assessed via HAM-D and Hamilton anxiety scale (HAM-A). It was found that the herbal medication was superior than placebo in reducing depressive symptoms with a effect size d of 0.92 but this result was not maintained at week 6 (Sayyah et al., 2006). It also had no anxiolytic activity.

**Dan Zhi Xiao Yao**

It is a chinese preparation which contains *Dan Pi* (Cortex Moutan), *Zhi Zi* (Fructus Gardneiae), *Chai Hu* (Radix Bupleuri), *Dang Gui* (Radix Angelicae Sinensis), *Bai Shao* (Radix Alba Paeonieia), *Bai Zhu* (Rhizoma Atractylodis Macrocephalae), *Fu Ling* (Poria) *Gan Cao* (Radix Glycyrrhizae).It is modified from Xiao yao san (Rambling powder) herbal preparation which is used in the treatment of depression by moving stasis (Bensky and Gamble, 1991) and in addition it has Dan zhi (Cortex Moutan). In a RCT, 63 patients with depression assessed via the HAM-D, self rating depression scale (SDS), self rating anxiety scale (SAS) and the scale for TCM syndrome and symptom differentiation, the formulation was compared with maprotiline. It was found that maprotiline was effective in 84% patients in reduction of depression whereas Dan zhi xizo yao was effective in 87% (Lou et al., 2006).

**Banxia Houpu**

It consists of *Pinella ternata, Poria cocos, Magnolia officinalis, Perilla frutescens and Zingiber officinale*. There is no human clinical data to determine the efficacy of Banxia houpu but large number of animal studies have demonstrated its anti-depressant activity comparable to fluoxetine in trail suspension and forced swimming tests (Li et al., 2003; Luo et al., 2000). It was found that an increase in serotonin (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) levels was found to occur in mouse hippocampus and striatum. Researchers (Wang et al., 2005) found that Banxia houpe decoction decreased the level of triglycerides in serum enhanced the activity of the natural killer cellsin the spleen, decreased the activity of superoxide dismutase in red blood cells and the activity of the nitric oxide synthase in the serum and the tissue, and reduced the content of malondialdehyde in tissue via the effect on lipid peroxidation.

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**Piper methysticum L.f (Kava)**

It causes GABA channel modulation (lipid membrane structure and sodium channel function) and weak GABA binding which causes increased synergistic effect of [3H] muscimol binding of GABA-α-receptors. It also causes β-adrenergic downregulation and MAO-B inhibition. It inhibits reuptake of norepinephrine in prefrontal cortex (Bonon and Haberlein, 1998; Dacies et al., 1992; Jussofie et al., 1994; Magura et al., 1997; Uedelhack et al., 1998). A 2003 cochrane review of randomosid ,double blind ,controlled trials of rigorous methodology using Kava mono preparations (60-280 mg of kavalactones), Pittler and Ernst found that Kava had a stastically significant anxiolytic activity on Hamilton Anxiety Scale (HAMA) compared with placebo (95% CI:0.17.7) but one trial demonstrated that kava was effective in short term treatment of anxiety. A meta analysis (Sarris et al., 2010b) revealed a similar conclusion A meta-analysis of 7 homogenous
trials using HAM-A demonstrated that kava reduced anxiety significantly than placebo (weighted mean difference 3.9 over placebo on the HAM –A; 95% CI: 0.1 to 7.7 p=0.05; n=380). A 4 week study by Connor and Davidson (2002) found no significant difference between a standardised Kava extract and placebo.

A meta-analysis based on six placebo controlled randomized trials using Kava extract WS 1490 in anxiety demonstrated that kava significantly reduced anxiety, with a mean improvement of 5.94 better than placebo (Witte et al., 2005). A 3-month randomized prospective open study investigating kava in peri menopausal women revealed that the reduction in anxiety with kava was significantly greater than in controls (on calcium supplementation) as assessed via the State trait anxiety index (STATI). It was also observed that depression depression declined at 3 months (-5.03+/-1.4) as assessed via the Zung’s depression scale (Cagnacci et al., 2005). A randomized controlled double blind, multicenter clinical trial compared kava with synthetic agents like busiprone or opipramol (Boerner et al., 2003). The outcomes were measured using HAM-A, Boerner anxiety scale, SAS, CGI, a self rating scale for well being, a sleep questionnaire, a quality of life questionnaire (QOL) and global judgement by investigator and patients.It was found there was no significant difference between Kava and Busiprone or opipramol regarding all efficacy and safety measures.75% of the patient were classified as responders (50% reduction of HAM-A score) in each treatment group with 60% achieving full remission. A novel study involving 13 subjects evaluated kava’s potential in improving vagal control in suffers of GAD (Watkins et al., 2001). It was observed that significantly more patients treated with kava showed improved BRC compared with placebo group,reflecting a favourable effect on reflex vagal control of heart rate in patients with GAD. Due to potential hazard of hepatotoxicity, *P. methysticum* was withdrawn from the European and UK markets in 2002. It was found that the factors responsible for hepatotoxicity included individuals hepatic insufficiency to metabolise kavalactones (cytochrome P-450 (CYP) 3A4 and 2D6), incorrect cultivation (medicinal, tudie or wichmanni varieties) being used, preparations made using acetone or ethanolic media low in glutathione, potentially contaminated or poorly stored material, and use of ariel parts or root peelings which are higher in alkaloids (Sarris et al., 2010c). It is recommended that only peeled roots from noble cultivers (cultivated species that are traditionally considered safe and therapeutic) using water soluble extraction method is advised (Teschke et al., in press).

In a study of kava use( Av 118g/week,median duration of use=12 years) in an Arnhem Land community in northern territory of Australia it was found that liver functions in users of aqueous kava at these moderate levels of consumption appears to be reversible and began to return to baseline after 1–2 weeks abstinence from kava. No evidence of irreversible liver damage has been found (Clough et al., 2003). Kava has also been found to cause significant drug interaction and interactions with CYP 450 enzyme (Singh, 2005). One human pharmacokinetic trial determined that kava caused CYP2E1 inhibition in approximately 40% (Gurley et al., 2005). Whole kava extract (normalized to 100µm total kavalactones), caused concentration dependent decreases in P450 activities, with significant inhibition of the activities of CYP1A2 (56% inhibition), 2C9 (92%), 2C19 (86%), 2D6 (73%), 3A4 (78%) and 4 A9/11(65%) following preincubation (Mathews et al., 2002). Kava also interacts with benzodiazepines and causes sedation (Singh, 2005; Stevinson et al., 2002). However, the risk-benefit ratio is highly favourable towards kava due to respectable clinical efficacy and relative low risk of potential liver toxicity (1 case /million monthly doses (Bauer, 2003).

**Passiflora incarnata L. (Passion flower)**

It is a benzodiazepine receptor partial agonist and causes GABA-system mediated anxiolysis. Animal behavioural models have shown non-sedative anxiolytic effect.In an in
vivo study employing a methanol extract of passion flower (125 mg/kg, orally) measured anxiolytic activity in mice, using the elevated plus-maze model, an increase in number of entries in open arm was demonstrated (Dhawan et al., 2001a; 2001b; 2002; Grundmann et al., 2008; Sena et al., 2009). A 4 week RCT using passion flower extract on patients with GAD (n=36) showed that passion flower was as effective as oxazepan (30 mg/day) in reducing anxiety and it had less number of side effects (Akhoundzadek et al., 2001). In an acute study RCT (n=60) using 500 mg of passion flower vs placebo for presurgical anxiety (Movafegh et al., 2008), it was demonstrated that anxiety scores were significantly lower in the passionflower group than in the control group on a numerical rating scale.

Valeriana spp. (Valerian)

Felter and Lloyd demonstrated that species of valerian officinalis and edulis have been used in traditional American and European medicine as a soporific and to treat various nervous system disorders. It decreases the degradation and simultaneously increases the binding of GABA. Also, valeric acid from valerian has demonstrated GABA-A receptor (β3 subunit) agonism and also 5-HT\textsubscript{3a} partial agonism (Benke et al., 2009; Dietz et al., 2005; Murphy et al., 2009; Ortiz et al., 1999; Sichardt et al., 2007; Trauner et al., 2008). A large 8 week internet based RCT (n=391) using a valerian (6.4 valerenic acids/day) placebo, kava (300 mg kavalactones/day) + placebo or double placebo was conducted to determine the efficacy in treating co-morbid anxiety and insomnia (Jacobs et al., 2005). The primary outcome measure used in rating change in anxiety state was STATI-State. The results suggested that neither kava norvalerin relieved anxiety and insomnia more than placebo. But the design of this trial presents several potential problems, with internet recruitment for trials resulting in samples of questionable representativeness, and the STATI-state having the inadequate test-retest reliability to be a sensitive measure of therapeutic change in anxiety. In a systemic review and metaanalysis of 18 RCTs (Fernandez-San Martin et al., 2010) using 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 standardized mean difference between the groups measured being stastically equivocal-0.02 (95% CI-0.35, 0.31).

Scutellaria lateriflora L. (Skull cap)

It has a GABA-α binding affinity (Awad et al., 2003). A double blind placebo controlled cross over study of healthy individuals (n = 19) revealed that skullcap dose-dependently reduced symptoms of anxiety and tension after acute administration compared to that with control (Wolfson and Hoffmann, 2003). In animal maze model test skullcap demonstrated anxiolytic activity (Awad et al., 2003).

Melissa officinalis L. (Lemon balm)

It is shown to cause MAO-inhibition. Also it is found to be a potent invitro inhibitor of rat brain GABA transaminase (GABA-T) (Awad et al., 2009; Lopez et al., 2009). An RCT with 20 participants who were given single doses of 300,600 and 900 mg of lemon balm or a matching placebo at 7-day intervals revealed that self rating calmness as assessed by Bond Lader mood scales was elevated at the earliest time points by the lowest dose, while alertness was significantly reduced at all time points following the highest dose (Kennedy et al., 2002). A double blind placebo controlled, randomized, balanced cross over experiment utilizing a standardized product containing lemon balm and valerian extracts in healthy volunteers (n=24) assessed mood and anxiety via a DISS test (Kennedy et al., 2006). The results demonstrated that a 600 mg dose of the combination ameliorated the negative effects of the DISS the level of anxiety. In a 4 week open, multicenter study in children less than 12 years (n=918) suffering from restlessness and nervous dyskinesia a combination of valerian and lemon balm preparation (2x2 tablets /day of 160 mg valerian root dry extract (4-5:1) and 80 mg lemon balm leaf dry extract (4-6:1) was given. The primary symptoms of dyssomniasia and restlessness were reduced from ‘moderate/severe’ to ‘mild’ or ‘absent’ in most
of the children with 70.4% of the patients with restlessness improving. Both parents and investigators assessed efficacy as ‘very good’ or ‘good’ (65.5% and 67.7%, respectively) (Muller and Klement, 2006).

**Eschscholzia californica (DC.) Stapf. (Lemon grass)**

In 50 participants lemongrass infusion was evaluated for hypnotic and anxiolytic activity (Aleite et al., 1986), it was found that there was no difference between lemon grass and placebo.

**Centella asiatica (L.) URB (Gotu Kola)**

It is used in ayurvedic and traditional pacific medicine for the treatment of anxiety and depression (Bone, 2003). In a double blind placebo controlled study (Bradwejn et al., 2000), 40 healthy participants were randomly assigned to receive either a single 12 g orally administered dose of gotu kola or placebo, it was found that gotu kola significantly attenuated peak ASR amplitude 30 and 60 min after treatment indicating anxiolytic activity in humans.

**Withania somnifera (L.) Dona. (Ashwagandha)**

It is classified as rasayana in ayurvedic medicine and it is used to enhance mental and physical performance. It is widely used in the western countries in various nervous system disorders (Bone, 2003). In an animal study (Bhattacharya and Muruganandam, 2003) it was observed the adaptogenic behavior of ashwagandha in stress–inducing procedure, via the attenuation of stress related parameters (cortisol levels, mental depression, sexual dysfunction.

**Bacopa monnieri (L.) Wettst. (Brahmi)**

A 12 week RCT using 300 mg of brahmi revealed that there was marked reduction in anxiety by brahmi as compared to placebo (Stough et al., 2001).

**Ginkgo biloba L. (Maiden hair)**

In a RCT using EGb 761 extract (480 mg or 240 mg per day) or placebo for 4 weeks in adults with GAD or adjustment disorder with anxious mood as assessed by DSM-III R using HAM-A as the primary outcome measure and CGI/Erlangen anxiety tension and aggression scale (EAAS) as the secondary outcome measure it was demonstrated that the HAM-A total scores decreased by -14.3 (8.1), -12 (9.1), and -7.8 (9.2) in the 480 mg per day Ginkgo biloba group, the 240 mg per day Ginkgo biloba group and the placebo group respectively. It demonstrated specific dose dependent anxiolysis compared with placebo in both higher dose and lower dose group (Woelk et al., 2007).

**Crataegus spp. (Hawthorn berry/leaf)**

In a RCT (Walkar et al., 2002) administered 500 mg of hawthorn extract to mildly hypertensive patients, there was a non significant reduction in anxiety as compared to placebo. A double blind, randomized placebo controlled trial involving adults presenting with mild moderate GAD as assessed via DSM-III R (n=264) were prescribed two tablets containing fixed quantities of Crataegus oxycantha (300 mg), Eschscholtzia californica (80 mg) and magnesium (300 mg elemental) twice daily for 3 months (Hanus et al., 2004), it was observed that the formula was highly effective in decreasing anxiety as compared to placebo which was determined by HAM-A and subjectively assessed anxiety.

**CONCLUSIONS**

Herbal medications in psychiatry are still under researched. The present review looked at various herbal preparations used in depression and anxiety over the years. The preparations excluding St Johns wort and kava have been under used and need further clinical trials including randomized double blind clinical evidence and direct comparisons with antidepressant drugs to help us understand their efficacy. Most herbal medications may serve as alternatives to traditional antidepressants in
patients who do not tolerate them as they have a favorable safety profile and are free from major side effects. There is also a need for research of herbal medication in the management of various subtypes of depression, bipolar disorder and anxiety disorders like post traumatic stress disorder and obsessive compulsive disorder. The use of these medications in various age groups and diverse clinical populations is warranted.

REFERENCES


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