



Journal of Medicinal Plants Studies

Herbal Medicines and Anxiety Disorders : an overview

Dr. Avinash De Sousa

1. Consultant Psychiatrist – Private Practice, De Sousa Foundation, Mumbai

*[Email: avinashdes888@gmail.com, Tel: 91-22-26460002]

This review paper looks at all the herbal medicines and formulas in treating anxiety disorders. A thorough Pubmed and the Cochrane internet search was made for pharmacological and clinical evidence of herbal medicines with anti-anxiety action. Good evidence exists for the use of kava in the treatment of anxiety, 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 anxiety and urgently require more research are *Rhodiola rosea* (roseroot), *Crocus sativus* (saffron), *Passiflora incarnata* (passionflower) and *Piper methysticum* (kava). They need further evidence base via clinical studies. Anxiety disorders are commonly researched but the efficacy of herbal medicines in these disorders needs to be studied further. The review addresses herbal therapy, safety issues and future areas of application in the field.

Keyword: Herbal medications, anxiety, kava, passion flower.

1. Introduction

Anxiety disorders are one of the most prevalent and highly comorbid psychiatric conditions ^[1]. Since the past decade, many herbal medicines have been used in people with anxiety disorders ^[2]. Due to the increasing popularity of herbal medications majority of the patients are consulting herbalists, naturopaths, and other healers, in addition to physicians. A study reveals that 44% of psychiatric patients with anxiety disorders had used herbal medicine (mainly for psychiatric purposes) during the previous 12 months ^[3]. There is however, a limited data regarding the benefits and liability of herbal 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 ^[4]. This article reviews the literature on various herbal medications in the treatment of anxiety disorders as well as anxiety in general.

2. 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 ^[5] and via alteration of neurotransmitter synthesis and general function ^[6]. Other mechanisms involve stimulating or sedating CNS activity, and regulating or supporting the healthy function of endocrine system ^[5-7].

3. Herbal Medicines Used In The Management of Anxiety

3.1 *Piper Methysticum* (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 ^[8-11]. A 2003 cochrane review

of randomised, double blind, controlled trials of rigorous methodology using Kava mono preparations (60-280 mg of kavalactones), found that Kava had a statistically significant anxiolytic activity on Hamilton Anxiety Scale (HAMA) compared with placebo (95% CI; 0.1,7.7) but one trial demonstrated that kava was effective in short term treatment of anxiety [12]. A meta-analysis [13] revealed a similar conclusions. A 4 week study however found no significant difference between a standardised Kava extract and placebo [14].

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 [15]. 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 declined at 3 months (-5.03±1.4) as assessed via the Zung's depression scale [16]. A randomized controlled double blind, multicenter clinical trial compared kava with synthetic agents like busiprone or opipramol [17]. 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 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 [18]. 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 [19]. It is recommended that only peeled roots from noble cultivars (cultivated species that are traditionally considered safe and therapeutic) using a water soluble extraction method is advised [20].

In a study of kava use (Av 118 g/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 [21]. Kava has also been found to cause significant drug interaction and interactions with CYP 450 enzyme [22]. One human pharmacokinetic trial determined that kava caused CYP2E1 inhibition in approximately 40% [23]. 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 [24]. Kava also interacts with benzodiazepines and causes sedation [25]. 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) [26].

3.2 *Passiflora Incarnata* (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 [27-31]. A 4 week RCT using passion flower extract on patients with GAD (n=36) showed that passion flower was as effective as oxazepam (30 mg/day) in reducing anxiety and it had less number of side effects [32]. In an acute study RCT (n=60) using 500mg of passion flower vs placebo for presurgical anxiety [33], it was demonstrated that anxiety scores were significantly lower in the passionflower group than in the control group on a numerical rating scale.

3.3 *Valeriana Spp. (Valerian)*

Felter and Lioyd 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, valerianic acid from valerian has demonstrated GABA-A receptor ($\beta 3$ subunit) agonism and also 5-HT_{5a} partial agonism [34-39]. 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 [40]. The primary outcome measure used in rating change in anxiety state was STATI-State. The results suggested that neither kava nor valerian 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 meta-analysis of 18 RCTs [41] using Valerian vs placebo or active controls, valerian reduced sleep latency over placebo by only 0.70min (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)

3.4 *Scutellaria Lateriflora (Skullcap)*

It has a GABA- α binding affinity [42]. 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 [43].

3.5 *Mellissa Officinalis (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) [44-45]. 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 [46]. 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 [47]. The results demonstrated that a 600mg 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 dyskoimesis a combination of valerian and lemon balm preparation (2x2 tablets/day of 160 mg valerian root dry extract (4-5:1) and 80mg lemon balm leaf dry extract (4-6:1) was given. The primary symptoms of dyssomnia 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) [48].

3.6 *Escholtzia California (California Poppy)*

It is used by the Native Americans and Eclectic physicians as a sedative, analgesic and anxiolytic [49]. Authors [50] demonstrated that California poppy possess an affinity with benzodiazepine receptors with flumazenil (a benzodiazepine receptor antagonist) suppressing these sedative and anxiolytic effects.

3.7 *Cymbopogon citratus* (Lemon grass)

In 50 participants lemongrass infusion was evaluated for hypnotic and anxiolytic activity^[51] it was found that there was no difference between lemon grass and placebo.

3.8 *Centella asiatica* (Gotu Kola)

It is used in ayurvedic and traditional pacific medicine for the treatment of anxiety and depression^[52]. In a double blind placebo controlled study^[53], 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.

3.9 *Withania Somnifera* (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^[52]. In an animal study^[54] 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).

3.10 *Bacopa Monniera* (Brahmi)

A 12 week RCT using 300 mg of brahmi revealed that there was marked reduction in anxiety by brahmi as compared to placebo^[55].

3.11 *Ginkgo Biloba* (Maidenhair)

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 Ginko biloba group, the 240 mg per day Ginko biloba group and the placebo group respectively. It demonstrated specific dose dependent anxiolysis compared

with placebo in both higher dose and lower dose group^[56].

3.12 *Crataegus Spp.* (Hawthorn Berry/Leaf)

In a RCT^[57] patients were 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 prescribes two tablets containing fixed quantities of *Crataegus oxycantha* (300 mg), *Eschscholtzia californica* (80 mg) and magnesium (300 mg elemental) twice daily for 3 months^[58], 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.

4. Conclusions

Herbal medications in psychiatry are still under researched. The present review looked at various herbal preparations used in anxiety. The preparations excluding kava have been under used and need further clinical trials including randomized double blind clinical evidence and direct comparisons with anxiolytic drugs to help us understand their efficacy. Most herbal medications may serve as alternatives to traditional anxiolytics 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 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.

5. Acknowledgements – Nil

6. References

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