15

# Herbal Remedies to Treat Anxiety Disorders

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## 1. Introduction

Anxiety, fear and worry are all completely natural human feelings. If these feelings occur and endure for an extended period, it affects both physical and mental health. This leads to clinical anxiety disorders. There are many types of treatment available to treat anxiety disorders. This article outlines more common herbal remedies to treat anxiety disorders.

Anxiety is an aversive emotional state, in which the feeling of fear is disproportionate to the threat (Weinberger, 2001). Anxiety is implicated in a number of psychiatric disorders, such as depression, panic attacks, phobias, generalized anxiety disorder, obsessive-compulsive disorder and post-traumatic stress disorder (Gross and Hen, 2004). Anxiety disorders are the most common class of neuropsychiatric disorders in USA (Kessler et al., 2005) and many other countries (Alonso and Lepine, 2007). The life time prevalence of panic attacks (a form of anxiety disorder) is around 7-9% in most countries and 1% alone in India with the prevalence of generalized anxiety disorder is very high i.e. 8.5% in the general population (WHO, 2001). Anxiety disorders affect 16.6% of population worldwide (Somers et al., 2006) and numerous efforts have been made to understand the pathophysiology of the disease and treatments.

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), anxiety is characterized by a feeling of persistent worry that hinders an individual's ability to relax [Diagnostic and Statistical Manual of Mental Disorders Washington D.C.: American Psychiatric Association, 4 2000]. Anxiety disorders are described and classified in DSM and several anxiety disorders share common clinical symptoms such as widespread anxiety, physiological anxiety symptoms, and behavioral disturbances.

## 2. Common anxiety disorders

### 2.1 Generalized anxiety disorders (GAD)

Generalized anxiety disorder is a syndrome of ongoing anxiety and worry about many events or feelings that the patient generally recognizes as extreme and inappropriate (DSM-IV-TR). Individuals manifest both physical and psychological symptoms leading to significant distress or impairment.

### 2.2 Obsessive-compulsive disorder (OCD)

People suffering from OCD tend to have bothersome and intrusive thoughts that generate anxiety (obsession) and perform repetitive actions (compulsion). Obsessions include unwanted thoughts, impulses, or images that cause great anxiety. Compulsions include repetitive behaviors or mental acts that those affected feel driven to perform.

### 2.3 Panic disorder

People suffering from panic disorders often have panic attacks, defined as discrete periods of sudden symptom onset usually peaking in 10 minutes and can occur with most anxiety disorders.

### 2.4 Post-traumatic stress disorder (PTSD)

Individuals with PTSD avoid stimuli associated with the trauma and feel an extreme amount of fear and anxiety after presenting stimuli. Stress is a condition which affects physiological and psychological homeostasis. Evidence indicates that chronic repeated stress precipitates neuropsychiatric disorders like anxiety and depression (Holsboer, 1988; McEwen and Stellar, 1993; McEwen, 2000; Vyas et al., 2002; Veena et al., 2009b; 2011). Previous work in an animal model of stress revealed that chronic stress impairs learning in the T-maze (Sunanda et al., 2000a) and radial arm maze (Srikumar et al., 2006; 2007; Veena et al., 2009a) tasks in addition to inducing anxiety-like behavior (Adamec et al., 1999; Vyas et al., 2002; Govindarajan et al., 2006). Stress-induced behavioral impairments are associated with structural (Ramkumar et al., 2008; Shankaranarayana Rao et al., 2001; Shankaranarayana Rao & Raju, 2004; 2005; 2007), biochemical (Sunanda et al., 2000b), molecular (Bennur et al., 2007; Pawlak et al., 2005; Veena et al., 2011) and electrophysiological (Hegde et al., 2008) alterations in the hippocampus and amygdala regions. Recent studies have clearly demonstrated the abnormal synaptic plasticity is responsible for cognitive deficits including enhanced anxiety in fragile X mental retardation and autism (Dolen et al., 2007; Hayashi et al., 2007). Induction of progressive plasticity is known to be responsible for amelioration of stress-induced cognitive deficits and depression-like behavior by enriched environment and brain stimulation rewarding experience (Asha Devi et al., 2011; Ramkumar et al., 2008; Shankaranarayana Rao, 2009; 2010; Veena et al., 2009a).

Anxiety and other psychiatric conditions are one of the most frequent conditions seen by clinicians and often require long-term treatment with medications. Selective serotonin reuptake inhibitor (SSRI) and benzodiazepines are important class of drugs used to treat generalized anxiety disorders (Davidson, 2001; Davidson, 2009) and depression (Bhagya et al., 2008; Bhagya et al., 2011). With the increasing cost of anti-anxiety medications and their increased side effects like suicidal ideation, decreased alertness, sexual dysfunction and dependency (Hu et al., 2004; Gunnell et al., 2005; O'brien, 2005; Lader et al., 2009), drugs of natural origin are promising alternatives to treat neuropsychiatric disorders (Kienzle-Horn, 2002; Carlini, 2003).

## 3. Common herbal remedies for anxiety

Ayurveda, the Indian traditional system of medicine uses herbs and their preparations to treat various neuropsychiatric disorders. Numerous herbs have been used for centuries in folk and other traditional medicine to calm the mind and positively enhance mood. Herbal medicine which plays an important role in developing countries, are once again becoming

popular throughout developing and developed countries. Study by Sparreboom et al. (2004) revealed that use of herbal medicine is increasing enormously in the Western world. In spite of the large number of animal studies evaluating the potential anxiolytic effects of plant extracts, very few controlled studies have been conducted in a clinical setup. The efficacy and safety of utilizing these natural drugs to treat anxiety, has only just begun to be exactly tested in clinical trials within the last 10 to 15 years (Saeed et al., 2007; Garcia-Garcia et al., 2008; Kinrys et al., 2009). For instance, both Kava-kava (*Piper methysticum*) and St. John's wort (*Hypericum perforatum*) showed beneficial effectiveness in double blind, randomized placebo controlled trials to treat anxiety and depression (Ernst, 2002). Also, extracts of valerian, hops, lemon balm and passion flower preparations have been employed for the prevention and treatment of psychiatric disorders such as anxiety, sleep disorders, convulsions, cognitive impairment and depression (Beaubrun and Gray, 2000). The commonly used herbal remedies for treating anxiety disorders are described below.

### 3.1 Passion flower

*Passiflora incarnata* is a folk remedy for anxiety. The anxiolytic effects of passionflower are well documented in rodents (Dhawan et al., 2001; Dhawan et al., 2002). In randomized double-blind study, passion flower extract was effective in 18 generalised anxiety disorder (GAD) out-patients as compared to oxazepam. Also, impairment in the job performance was increased in oxazepam group as compared to Passiflora extract treated group (Akhondzadeh et al., 2001). In another double-blind placebo-controlled study, preoperative oral *Passiflora incarnata* reduces anxiety in ambulatory surgery patients (Movafegh et al., 2008).

### 3.2 Kava kava (*Piper methysticum*)

There is substantial evidence that kava has a positive effect on the symptoms of anxiety disorders. Animal studies have demonstrated anti-anxiety activity of kava (Garrett et al., 2003; Bruner and Anderson, 2009). Several randomized double-blind clinical studies in GAD patients showed beneficial effect of kava-kava in reducing anxiety (Watkins et al., 2001; Connor and Davidson, 2002; Boerner et al., 2003; Sarris et al., 2009). Kava-kava was used in numerous controlled clinical studies to treat anxiety disorders, but the subjects included in these studies were heterogeneous i.e., they were diagnosed with agoraphobia, specific phobia, social phobia, adjustment disorder with anxiety (Volz and Kieser, 1997; Malsch and Kieser, 2001; Gastpar and Klimm, 2003; Lehrl, 2004). In the study by Connor & Davidson, kava extract was compared with placebo in GAD patients (2002). In another 8-week randomized, double-blind multi-center clinical trial, the efficacy of *Piper methysticum* was compared with two anxiolytic drugs opipramol and buspirone in GAD patients (Boerner et al., 2003). Meta-analysis study by Pittler and Ernst reinforced the anxiolytic effect of kava in generalized anxiety patients and indicated a significant reduction in anxiety parameters evaluated by the Hamilton Anxiety (HAMA) scale (Pittler and Ernst, 2000; 2002).

### 3.3 St. John's wort (*Hypericum perforatum*)

St. John's wort is a popular supplement for treating depression but is much less popular for treating anxiety disorders. Studies conducted by Flausino et al. and Singewald et al. have shown that chronic administration of *Hypericum perforatum* induced an antidepressant-like effect in Magnesium-depleted mice in the forced swim test and anxiolytic effect in the

elevated T-maze and the light/dark transition test (Flausino, Jr. et al., 2002; Singewald et al., 2004). St. John's wort administration resulted in anti-anxiety effect in animal models of restraint stress and sleep deprivation (Flausino, Jr. et al., 2002; Singewald et al., 2004; Kumar and Singh, 2007; Kumar et al., 2010). *Hypericum perforatum* inhibits the reuptake of serotonin, noradrenaline, dopamine (Wonnemann et al., 2000) and modulates neuronal excitability via glutamatergic and GABAergic mechanisms (Langosch et al., 2002).

Studies specifically testing the effects of St. John's wort on patients with anxiety are extremely limited. The evidence of positive effects of St. John's wort on anxiety disorders is weak. No placebo-controlled, randomized, double-blind trials have shown St. John's wort to be effective in treating generalized anxiety disorder, post-traumatic stress disorder, obsessive-compulsive disorder (OCD), or phobias. Volz et al. (2002) showed that Hypericum extract to 149 out patients diagnosed with somatization disorder, undifferentiated somatoform disorder, or somatoform autonomic dysfunctions, significantly reduced anxiety scores in HAMA scale. Another open-label uncontrolled observation with 500 subjects showed beneficial effect of St. John's wort extract in reducing anxiety disorder symptoms in patients diagnosed with depression comorbid with anxiety (Muller et al., 2003). However, stronger evidence is needed before St. John's wort should be considered as a treatment option for patients with diagnosable anxiety disorders.

### 3.4 *Valeriana officinalis*

Valerian is one of the most popularly used herbal medicines for insomnia (Donath et al., 2000) and is also used to treat anxiety. Hydroalcoholic and aqueous extracts of valerian roots have shown affinity for the GABA-A receptor in the brains of rats (Benke et al., 2009). In humans, valerian has been successful in the treatment of insomnia and tension (Schmidt-Voigt, 1986; Vorbach, 1996; Leathwood, 1985; Donath et al., 2000; Stevinson and Ernst, 2000; Ziegler, 2002). Andreatini et al. (2002) compared the extract of *Valeriana officinalis* L. (81mg of valepotriates as active ingredients) with placebo and diazepam (6.5 mg) in patients with GAD (DSM-III-R, 12 patients per group). Only the diazepam and valepotriates groups showed a significant reduction in the psychic factor of HAMA scale and the preliminary data obtained in the present study suggest that the valepotriates may have a potential anxiolytic effect on the psychic symptoms of anxiety. The limitations of this study are small sample size and a low dose of diazepam, such studies should be replicated with improved methodological design.

### 3.5 *Ginkgo biloba*

Extract of *Ginkgo biloba* (EGb 761) significantly reduced the detrimental effect of learned helplessness in a subsequent conditioned avoidance task. In the elevated plus maze, senescent mice treated with EGb 761 spent more time in open arms than those treated with vehicle control (Ward et al., 2002). Woelke et al. (2007) compared a standardized extract of *Ginkgo biloba* L. (EGb 761) in doses of 480mg and 240mg with placebo for four weeks, involving patients with GAD and adjustment disorder with anxious mood (DSM-III-R). The two doses of EGb 761 showed a greater reduction in HAMA scores compared to placebo, as well as a statistically significant reduction in somatic symptoms compared to baseline (which was not observed in the placebo group).

### 3.6 *Galphimia glauca*

*Galphimia glauca* Cav. is a plant used in Mexican traditional medicine as a "nerve tranquilizer". Previous studies have demonstrated anxiolytic effect of methanolic extract

from this plant species. Herrera-Arellano et al. (2007) conducted a controlled study comparing the extract *Galphimia glauca* Cav. with lorazepam in patients with GAD with 72 and 80 patients per group, respectively. Both groups of patients showed a significant reduction in scores of HAMA, without any difference between treatments.

### 3.7 *Matricaria recutita* (chamomile)

Chamomile is one of the most popular single ingredient of herbal teas, or tisanes. Chamomile tea, brewed from dried flower heads is used traditionally for several medicinal purposes like gastrointestinal tract ailments. Other uses include allergic rhinitis, attention deficit-hyperactivity disorder (ADHD), restlessness, insomnia, dysmenorrhea, mastitis and varicose ulcers. Chamomile contains flavonoids, which exert benzodiazepine-like activity (Avallone et al., 2000) and also has a phosphodiesterase inhibitory action, which leads to increased cAMP levels (Kuppusamy and Das, 1992). A recent study evaluated the efficacy of a standardized extract of *Matricaria recutita* (L), compared with placebo for eight weeks in patients with mild to moderate GAD (DSM-IV). There was a statistically significant reduction in the scores of HAMA in the group treated with extract compared to placebo-treated group (Amsterdam et al., 2009).

### 3.8 *Astragalus membranaceus*

*Astragalus membranaceus* (AM) is a useful Korean herb that has been clinically prescribed for stress-related illness. AM significantly restores learning and memory deficits in chronically stressed rats. In the elevated plus maze, AM treatment significantly increases the time spent in the open arms compared to control group. It also enhanced choline acetyltransferase (ChAT) expression in stressed rats (Park et al., 2009). No clinical data is available for its anxiolytic effect. But one clinical study demonstrated the protective effect of astragalous on oxidative stress status in maintenance of hemodialysis patients (Qu et al., 2008).

## 4. Indian traditional herbs

### 4.1 *Centella asiatica (Mandookaparni* or Gotu Kola)

*Centella asiatica* is reputed for its beneficial effects in various neurological disorders. Gotu Kola has been used for centuries in Ayurvedic and traditional Chinese medicine to alleviate symptoms of depression and anxiety. Recent studies in the rat have shown that long-term pretreatment with Gotu Kola decreases locomotor activity, enhance elevated-plus maze performance and attenuate acoustic startle response (Chen et al., 2006; Wijeweera et al., 2006). In a double-blind, placebo-controlled study, the anxiolytic activity of *Centella asiatica* in healthy subjects was undertaken and compared to placebo, Gotu Kola significantly reduced peak acoustic startle response amplitude 30 and 60 minutes after treatment (Bradwejn et al., 2000). In another clinical study, 70% hydro-ethanolic extract of *Centella asiatica* was given to 33 participants for two months and Hamilton's Brief Psychiatric Rating Scale (BPRS) was used to screen the subjects. The results show that, *Mandookaparni* significantly attenuated anxiety related disorders (Jana et al., 2010). These preliminary findings suggest that *Centella asiatica* has anxiolytic activity in humans and it remains to be seen whether this herb has therapeutic efficacy in the treatment of anxiety syndromes in large population.

### 4.2 *Bacopa monnieri (Brahmi)*

In Indian traditional medicine, several herbs have been used as nerve tonics. The most popular of these herbs is *brahmi*, a well known memory booster. This herb is used by Ayurvedic medical practitioners for almost 3000 years. The traditional use of *brahmi* as an anti-anxiety remedy in Ayurvedic medicine is supported by both animal and clinical studies. *Brahm*i is used in Indian tradition medicine in treatment of number of brain disorders namely anxiety and poor memory (Singh and Dhawan, 1997). Pharmacologically, *Bacopa monnieri* comprises of five major saponins: bacoside A3, bacopaside II, bacopasaponin C isomer, bacopasaponin C and bacopaside I (Phrompittayarat et al., 2007). *Bacopa monniera* extract or its constituent bacosides showed anxiolytic activity in animals (Bhattacharya and Ghosal, 1998: Shankar and Singh, 2000; Singh et al., 1979: Singh and Singh, 1980) and Singh et al. (1996) suggest an involvement of the GABA-ergic activity in *brahmi*'s action on central nervous system . *Brahmi* not only enhances memory, it also shows an anti-stress effect. Pretreatment with Bacosides resulted in decrease Hsp expression in the hippocampus; it restored P450 enzyme activity and increased superoxide dismutase activity in the stressed rats. *Brahmi* modulates the activities of Hsp70, P450 and SOD and thereby protects the brain from deleterious effect of stress (Kar Chowdhury et al., 2002). In another study, pretreatment with *brahmi* restored both acute and chronic immobilization stress-induced changes in ulcer index, adrenal gland weight, creatine kinase, and aspartate aminotransferase (Rai et al., 2003). Treatment with *Bacopa monnieri* extract 40 mg/kg/day effectively reversed behavioral deficits of PCAPP mice in open field tests compared with non-transgenic controls (Holcomb et al., 2006).

Previous clinical study demonstrated that administration of *brahmi* syrup to 35 patients diagnosed with anxiety neurosis resulted in significant decrease in anxiety symptoms and level of anxiety (Asthana et al., 1996). In a recent randomized, double-blind, placebo controlled clinical trial, effect of standardized *Bacopa monniera* extract in healthy elderly patients on anxiety, depression and recall memory was evaluated. *Bacopa* participants had enhanced delayed word recall memory scores in Rey Auditory Verbal Learning Test (AVLT) compared to placebo. Affective measures like depression scores, anxiety scores, and heart rate decreased in due course for the *Bacopa* group but increased for the placebo group (Calabrese et al., 2008). In a study by Stough et al., the chronic effects of *brahmi* extract were examined on memory function in forty six healthy human subjects aged between 18 to 60 years. The study was a double-blind placebo-controlled independent group design in which subjects were randomly allocated to one of the two treatment conditions, i.e., *brahmi* extract (300 mg) or placebo. Neuropsychological tests were conducted pre-baseline and at 5 and 12 weeks post-drug administration. *Brahmi* extract significantly improved speed of visual information processing measured by the Inspection Time, learning rate and memory consolidation measured by Auditory Verbal Learning Test, and state anxiety examined using Strait-Trait Anxiety Inventory. The results of the clinical trial suggested that *brahmi* extract improved higher order cognitive processes that are critically dependent on the input of information from our environment such as learning and memory (Stough et al., 2001). Another study to measure the effect of *brahmi* extract on human memory was conducted by Roodenrys et al. (2002). Seventy six adults aged between 40 and 65 years volunteered for the double-blind randomized, placebo control study in which various memory functions were tested and levels of anxiety measured in three testing sessions: one prior to the trial, one after three months on the trial, and one six weeks after the completion of the trial. The

results showed a significant effect of *brahmi* on the test for the retention of new information. In the follow-up tests it was found that the rate of learning was unaffected, suggesting that *brahmi* decreases the rate of forgetting of newly acquired information.

### 4.3 *Withania somnifera (ashwagandha)*

This has been an important herb in use within Ayurvedic and indigenous medical systems for over 3000 years. Both preclinical and clinical studies demonstrate the use of *ashwagandha* for anxiety, inflammation, Parkinson's disease, cognitive and neurological disorders. It is also used therapeutically as an adaptogen in nervous exhaustion, insomnia, debility due to stress (Mishra et al., 2000; Withania, Monograph 2004). Preclinically, the extract of *Withania somnifera* (WS) root exhibited anxiolytic activity in the elevated plus-maze, social interaction and feeding latency in an unfamiliar environment (Bhattacharya et al., 2000). Chronic stress-induced hyperglycemia, cognitive deficits, immunosupression and depression was attenuated by *ashwagandha*. The results indicate that *ashwagandha* has significant antistress adaptogenic activity, confirming the clinical use of the plant in Ayurveda (Bhattacharya and Muruganandam, 2003). A recent study has demonstrated the anxiolytic potential of a compound natural health product which had *Withania* as the main herb in an open label human trial (Seely and Singh, 2007). Also, studies have demonstrated that WS possesses GABA-mimetic properties (Kulkarni and Verma, 1993a; Mehta et al., 1991). Since GABA agonism has been linked to anxiolysis (Stahl, 1998), the extracts of WS may have beneficial effect in anxiety and related disorders. A double blind placebo control study in patients with ICD-10 anxiety disorders, 6 weeks treatment with ethanolic extract of *W. somnifera* showed anxiolytic activity over placebo. The extract was well tolerated and did not cause more adverse effects than placebo. So, it was concluded that the ethanolic extract of WS has useful anxiolytic potential (Andrade et al., 2000).

## 5. Polyherbal formulations

In Ayurveda, compound formulations are generally used in the therapy as the combination of many drugs provides a synergistic therapeutic effect and also includes ingredients which help to minimize the adverse effects of few other major drugs. A recent study demonstrated adaptogenic potential of a compound natural health product which had *Withania* as the main herb in an open label human trial. An open-label and uncontrolled clinical trial evaluated the impact of OCTA© on known parameters of stress (OCTA©, an aqueous-based liquid herbal preparation consisting of eight herbs as follows: *W. somnifera*, *Lagerstroemia speciosa*, *Bacopa monniera*, *Zizyphus jujuba*, *Morinda citrifolia*, *Punica granatum*, *Shisandrae chinensis* and *Lycium barbarum*) (Seely and Singh, 2007). Another herbal formulation, Sumind is (Ayurvedic nomenclature and the quantity of each ingredient are given in parentheses), *Nardostachys atamans* (*Jatamansi*), *Acorus calamus* (*Vacha*), *Celastrus paniculata* (*Jyotishmati*), *Convolvulus microphyllus* (*Shankapushpi*), *Bacopa monnieri* (*Brahmi*), *Withania somnifera* (*Ashwagadha*), *Valerian wallichii* (*Tagara*), *Eclipta alba* (*Bhringaraja*). Sumind showed antidepressant activity as indicated by reduced immobility time in rats subjected to swim stress. It also restored biogenic amine levels to normal levels and reduced corticosterone levels in stressed rats (Nanjappa et al., 2007).

Mentat (BR-16A) is an herbal medication contains 20 different ingredients. The main herbs present in the mentat are *Brahmi* (*Bacopa monnieri*), *Mandookparni* (*Centella asiatica*).

*Ashwagandha* (*Withania somnifera*), *Jatamansi* (*Nardostachys jatamansi*), *Shankhapuspi* (*Evolvulus alsinoides*), *Tagar* (*Valeriana wallichi*). *Vach* (*Acorus calamus*), *Guduchi* (*Tinospora cordifolia*), *Malkangni* (*Celastrus paniculatus*), Kuth (*Saussurea lappa*) Amla (*Embelica officinalis*), *Terminalia chebula* and *Terminalia belerica*. Some of these plants namely, *B. monnieri*, *C. asiatica*, *W. somnifera*, *N. jatamansi, E. alsinoides*, *V. wallichi*, *A. calamus*, *T. cordifolia* and *C. paniculatus*, have been classified in Ayurveda as Medharasayanas and claimed to improve memory and intellect (Sharma, 1978). Polyherbal formulations are generally used in Ayurveda, based on the concept that such combinations provide synergistic therapeutic effect. Mice show a natural aversion to open and high spaces and therefore, spend more time in enclosed arms. Mice receiving chronic treatment with BR-16A-Mentat (100 mg/kg) followed by ethanol failed to show any withdrawal-induced anxiety. There was a significant decrease in the time spent in closed arms. The duration and the number of entries in open arms increased significantly as compared with the ethanol withdrawn group (Kulkarni and Verma, 1993b). Also, the anti-stress effect of mentat was evident against social isolation-induced stress in mice (Kumar and Kulkarni, 2006).

Agrawal et al. (1990a,b) reported that BR-16A improves memory parameters and decreases anxiety parameters in normal volunteers. Also, mentat (BR-16) brought about marked improvement in memory in all age groups and caused decrease in anxiety level and neuroticism index (Agrawal et al., 1991). Mentat in the form of syrup was given to patients of anxiety neurosis and depression in a placebo controlled study. Both anxiety and depressive patients showed memory impairment and also increased fatiguability. 3 month treatment with Mentat improved memory and decreased fatiguability in these patients (Sharma et al., 1990). Psychological problems like stress, anxiety and depression play an important role in the prognosis, quality of life as well as the survival rate of cancer patients. Treatment with mentat in cancer patients reduced stress, anxiety and depressive symptoms (Durgesh Kumar, 2000).

Another polyherbal formulation Geriforte showed significant anxiolytic effect in clinical studies. Geriforte contains Chyavanprash concentrate and the extracts of *Asparagus adscendens*, *Withania somnifera*, *Glycyrrhiza glabra*, *Centella asiatica*, *Mucuna pruriens*, Shilajeet, *Asparagus racemosus*, *Terminalia arjuna*, Makardhwaj and *Piper longum*, besides some others. An earlier open study demonstrated the beneficial effects of Geriforte in anxiety patients as per DSM III R criteria. There was significant reduction in the total Hamilton Anxiety Rating Scale (HARS) score at the end of four weeks (Boral et al., 1989; Shah et al., 1990). Another double-blind, placebo-controlled study authors have observed improvement in HARS scores in patients of mixed anxiety-depression following 4 weeks of Geriforte treatment in comparison with placebo (Shah et al., 1993; Upadhyaya et al., 1990). Preclinical studies show that Geriforte stimulates antioxidant defense system in both mice and rats (Vandana et al., 1998). Various studies have demonstrated the efficacy of Geriforte as an anti-stress adaptogen. The prolongation of survival time and prevention of stress-induced changes in adrenals, prevention of stress-induced ulcers and milk-induced leucocytosis, indicate the anti-stress properties of Geriforte (Singh et al., 1978).

Another common polyherbal formulation Euphytose, which is a combination of six extracts: Crataegus, Ballota, Passiflora and Valeriana, which have mild sedative effects, and Cola and Paullinia, which mainly act as mild stimulants. Euphytose reduced HAMA scores in outpatients with adjustment disorder with anxious mood in multicenter, double-blind, placebo-controlled study (Bourin et al., 1997).

Recent preclinical studies have shown anxiolytic activity of several herbal drugs. *Securidaca longepedunculata* is a savannah shrub commonly used by traditional medicine practitioners in Nigeria. The aqueous root extract of *Securidaca longepedunculata* showed anxiolytic activity in the elevated plus maze (EPM) by significantly increasing time spent in the open arms as compared to control (Adeyemi et al., 2010). Another herbal medicine yokukansan improved age related anxiety in the open filed and EPM (Mizoguchi et al., 2010). *Petiveria alliacea* L has been traditionally used in South America and Brazil for anxiety and whole plant extract of *Petiveria alliacea* caused anxiolytic-like effects in mice subjected to the EPM (Blainski et al., 2010). *Cirsium rivulare* (Jacq.) All. (Asteraceae) is an herbaceous perennial plant traditionally used in Polish folk medicine to treat anxiety. In a recent study, methanolic extracts from flowers and leaves of *Cirsium rivulare* produced anxiolytic activity in the EPM. Extract from flowers in addition to its anxiolytic effects, improves memory of the appetitively and aversively motivated tasks (Walesiuk et al., 2010). In Brazil, *Erythrina mulungu* and *Erythrina velutina* (Fabaceae) are widely used as a tranquilizer and/or sedative, and their extract exerts an anxiolytic-like effect profile in animal models. In herbal medicine, a leaf or bark decoction or tincture from mulungu is considered to calm agitation and other disorders of the nervous system, including insomnia and depression. Chronic *Erythrina mulungu* exerted anxiolytic effect in the elevated T maze inhibitory avoidance and in the light/dark transition model (Onusic et al., 2003). *Erythrina velutina* administration increased the percentage of open arm entries in the elevated plus maze (Raupp et al., 2008). No clinical data is available to substantiate anxiolytic effect of these herbs.

Our own studies have demonstrated the role of different herbs and herbal formulations namely *Euphorbia hirta*, *Celastrus paniculatus* Willd and Sumind in amelioration of anxiety, depression, cognitive deficits and associated neurodegeneration in these disorders (Anuradha et al., 2008; 2010; Nanjappa et al., 2007). Recent studies have shown that treatments with the crude extract of *Astragalus membranaceus* reduced repeated stress induced anxiety and memory loss (Park et al., 2009). In similar lines, our previous work demonstrated that *Euphorbia hirta* (Eh) reverses chronic immobilization stress-induced anxiety behavior in elevated plus maze and open field test. Extracts of Eh Linn have been found to possess central analgesic, antipyretic, anti-inflammatory properties in addition to its central antidepressant, sedative and anxiolytic effects (Lanhers et al., 1990; Lanhers et al., 1991; Johnson et al., 1999). The anxiolytic activity of this drug has been established in mice subjected to two-compartment, staircase and light/dark choice situation tests (Lanhers et al., 1990). *Euphorbia hirta* produces its anxiolytic effect in an animal model of chronic stress through $GABA_A$ receptor-benzodiazepine receptor-$Cl^-$ channel complex. Eh also appears to mediate its anxiolytic action through this complex since all of the three antagonists, flumazenil, bicuculline and picrotoxin inhibited Eh-induced increase in open arm exploration and also recovered the acetylcholinesterase (AChE) activity in discrete regions of the brain (Anuradha et al., 2008; 2010).

*Celastrus paniculatus* Willd has been known for centuries as "the elixir of life". Ayurveda describes drug the *Jyotishmati* (*Celastrus paniculata*) as early as 1500BC in Charaka samhita (the most ancient and authoritative text book of ayurveda) for diseases of the brain and as *buddhiprada* (enhancing intellect), *smritiprada* (enhancing memory). *Jyotishmati* translates as *Jyoti* and *mati* (enlightens intellect). *Celastrus paniculatus* (CP), a plant belonging to Celastraceae was in use from time immemorial to treat brain related disorders and to enhance learning and memory. CP treated rats exhibited a significantly increased learning

curve compared with vehicle treated animals in the avoidance paradigm (Karanth et al., 1980). In another study, rats treated daily with 850 mg/kg of CP oil for 15 days exhibited a significant improvement in their retention time in a two-way passive avoidance task. CP also produced a significant decrease in the content of norepinephrine, dopamine and serotonin and certain of their respective metabolites in the brain (Nalini et al., 1995). Previous findings indicate that the aqueous extract of CP seed has cognitive-enhancing properties and an antioxidant effect might be involved (Kumar and Gupta, 2002). CP enhanced learning and memory in naïve rats when tested in a partially baited radial arm maze task by altering acetyl cholinesterase activity in the hippocampus and frontal cortex (Lekha et al., 2010a). Acute and chronic immobilisation-induced oxidative stress was restored back to normal after CP oil treatment (Lekha et al., 2010b). Recently we have demonstrated that chronic stress-induced learning impairment in radial arm maze task was restored by chronic CP oil treatment. The behavioural recovery was associated with restoration of both hippocampal long-term potentiation and cholinergic activity. This opens up the possibility of developing novel agents from nature to enhance synaptic plasticity as a means of treating a variety of psychiatric diseases, including depression (Unpublished data). An *in vitro* study has demonstrated neuroprotective effect of CP water extract in forebrain primary neuronal cell cultures. Pre-treatment of neuronal cells with CP-water extract significantly attenuated glutamate-induced neuronal death. Also, CP significantly and reversibly inhibited whole-cell NMDA currents (Godkar et al., 2004).

## 6. Conclusion

Despite a large number of animal studies evaluating the potential anxiolytic effects of herbal drugs, very few controlled clinical studies have been conducted. These studies have methodological problems like small number of subjects, lack of placebo and control groups, and inclusion of heterogeneous subjects and short treatment duration, which hinders consistent conclusion about these herbal preparations. Some herbs like kava-kava, gingko showed promising results with substantial clinical significance when compared with benzodiazepines, buspirone and antidepressants. Although evidence of effectiveness of herbs and their preparations in treating neuropsychiatric disorders is increasing, translating these results to treat patients effectively is slowed down by the limited knowledge regarding chemical composition of the products, lack of standardization of these preparations and the paucity of well controlled studies. Preliminary evidence suggests that herbal medicines may have a role in the treatment of anxiety disorders and warrants further research. However, we would like to clearly warn that most of the remedies are not approved for clinical use and herbal remedies are not solely alternatives of clinical treatment regimens. Also some of the herbal remedies may interact with other medicines leading to drug-drug interactions, which may cause severe side effects and in some cases it may be fatal. Accordingly, it is advised to use herbal drugs under strict supervision of qualified ayurvedic physicians with periodic follow-ups.

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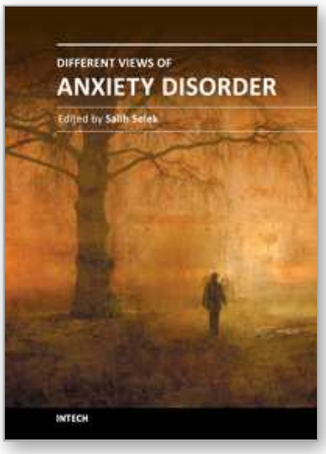


**Different Views of Anxiety Disorders**

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Anxiety, whether an illness or emotion, is a term with historical roots even in the Bible, but it was not popular until the modern age. Today, we can group, diagnose and treat several anxiety disorders to an extent, but the assessment of symptoms and severity, dealing with resistant conditions, new treatment modalities and specific patient population, such as children, are still the challenging aspects of anxiety disorders. This book intends to present anxiety disorders from a different view and discuss a wide variety of topics in anxiety from a multidimensional approach. This Open Access book addresses not only psychiatrists but also a broad range of specialists, including psychologists, neuroscientists and other mental health professionals.

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