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ANXIETY DISORDERS AND HERBAL MEDICINES

Riehana Gani* and Z. A. Bhat

Department of Pharmaceutical Sciences, Pharmacognosy Division, University of Kashmir, Hazratbal, Srinagar, 190006, Jammu and Kashmir, India.

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Correspondence to Author:

Zulfikar Ali Bhat

Professor and Head
Department of Pharmaceutical
Sciences, University of Kashmir,
Hazratbal, Srinagar - 190006,
Jammu and Kashmir, India.


Email: rehanagani35@rediffmail.com

ABSTRACT: Anxiety is a common and normal phenomenon, involving multiple brain regions, including amygdala, locus ceruleus and frontal cortex. Moreover, multiple brain transmitters regulate the presence and severity of anxiety; these include classical transmitters such as gamma amino butyric acid, serotonin, and dopamine, as well as neuropeptides that include corticotrophin releasing hormone, substance P, neuropeptide Y, cholecystokinin and vasopressin. Anxiety is highly adaptive and involves both acute fear, related to an immediate threat and anticipatory anxiety that is associated with possible future threat. Certain individuals are predisposed to develop anxiety disorders. Predisposing variables include both genetic factors (that may dispose toward anxious temperament), emotional traumas and other psychologically mediated factors. Anxiety disorders represent a family of conditions with important distinguishing elements. Panic disorder and phobias involve reactions that are reminiscent of acute fear (albeit often worse). Specific and social phobias involve excessive fearful responses to identifiable things or circumstances in the environment. Generalized anxiety disorder is a condition that, essentially, involves anticipatory fear (*i.e.*, worry). Worries of everyday life are enhanced beyond any normal or adaptive functioning. Although complex, anxiety disorders are treatable conditions that respond to certain medications and specialized forms of psychotherapy.

INTRODUCTION: Anxiety Disorders: Anxiety disorders are characterized by an excessive fear response; these disorders are extremely prevalent among the general population and have a 2:1 female predilection¹. Functional impairment is common with these disorders and along with depression, is among the leading causes of disability and work related absences. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), defines fear as “the emotional response to real or perceived imminent threat” and anxiety as anticipation of future threat.”

Fear typically induces surges of autonomic arousal and thoughts of immediate danger and escape, where as anxiety typically manifests as muscular tension and avoidant behaviors. Epidemiological studies suggest that approximately 25% of the population will suffer from clinically significant anxiety at some point in their lives with a 12 month prevalence rate of approximately 18%². Anxiety disorders generally maintain a chronic course when untreated and result in substantial impairment across the lifespan. In addition to the immense personal suffering created by clinically significant anxiety syndromes, these disorders create a considerable public expense that includes treatment costs, lost work time, and mortality.

Causes of Anxiety Disorders: Most research indicates that anxiety disorders are complex and arise from intricate neurochemical, neuroanatomic, neuroinflammatory, genetic, neuroendocrinologic and psychoimmunologic factors^{3,4}.

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Cognitive-behavioral and environmental and stress factors also play a role in anxiety disorders. Neurochemical theories indicate dysregulation of a host of neurotransmitters, including excitatory neurotransmitters, such as noradrenalin and glutamate and inhibitory neurotransmitters, such as gamma-aminobutyric acid and serotonin. Additional data indicate neurochemistry alterations in dopamine metabolites in cerebral spinal fluid, reduced sensitivity in postsynaptic dopamine and dysregulation in endogenous opioid systems. Support of the neurochemistry theory is seen in the efficacy of pharmacologic agents, such as benzodiazepines for acute anxiety and various antidepressants, including serotonin reuptake inhibitors (eg, sertraline, fluoxetine), and serotonin-norepinephrine reuptake inhibitors (e.g, venlafaxine)⁵.

There is further evidence that supports the use cognitive enhancers, such as Dcycloserine and yohimbine in the regulation and treatment of contextual information in fear extinction, specifically the acquisition, consolidation, and retrieval of fear-based memories⁶. Neuroanatomic alterations include imprinting or memory consolidation of emotionally traumatic memories and conditioned fear that are mediated through dopamine 1 and dopamine 2 receptor signaling in the amygdala through the posterior hippocampus and avoidance conditioning mediated through the ventromedial prefrontal cortex^{6,7}.

Psychoimmunologic or immune-mediated theories suggest that various anxiety disorders, particularly PTSD and OCD, may compromise the immune system. These theories arise from the studies that indicate that alterations in the hypothalamic pituitary-adrenal axis and increased levels of the glucocorticoid hormone cortisol and pro inflammatory and antiinflammatory cytokines contribute to the neurogenesis of various anxiety disorders. The precise basis of these assumptions is unclear, but prevailing findings show that individuals with PTSD and other anxiety disorders are more likely to have medical conditions associated with prolonged immunosuppression, such as rheumatoid arthritis, irritable bowel syndrome, and cardiovascular disease^{8,9}. Genetic predisposition contributes to anxiety disorders. Family aggregated and twin studies support the role

of genetic influence and heritability of various anxiety disorders, such as OCD.

Cognitive-behavioral theorists assert that anxious individuals often hold irrational or distorted beliefs about themselves, others and the future. They tend to overgeneralize or exaggerate a potential for catastrophic situations and negative consequences¹⁰. Environmental factors and stress issues also contribute to anxiety disorders, particularly acute stress or PTSD which are associated with an overwhelming traumatic or life-threatening situation or exposure.

Specific Anxiety Disorders:

Separation Anxiety Disorder: Separation anxiety disorder is categorized by excessive and developmentally inappropriate fear or anxiety triggered by separation from home or attachment figures. There is persistent fear or anxiety of potential harm toward the attachment figure and/or worry about events that could lead to loss for separation from attachment figures. Persistent reluctance to separate from home may lead to poor academic performance or inability to perform tasks of daily living. Repeated nightmares about separation and physical complaints of headache, nausea or abdominal pain are common when impending separation is anticipated. The onset of separation anxiety disorder can start as early as preschool, but is more commonly diagnosed during childhood and less commonly in adolescence. The disturbance must last for at least 4 weeks in children and 6 months in late adolescence. Individuals may exhibit sadness, social withdrawal and a constant demand for attention.

Independent activities also may be affected (*i.e.*, school avoidance, fear of sleeping alone, leaving for college) and should be explored. Other social stressors to consider include school bullying, bereavement or exposure to a recent traumatic event. This disorder is often comorbid with generalized anxiety disorder, specific phobia, PTSD, social anxiety disorder, agoraphobia, OCD and personality disorders¹¹.

Panic Disorder: Panic disorder is a common anxiety disorder characterized by discrete or unexpected, unprovoked periods of intense fear or dread (cognitive); physical distress (biological),

avoidance (behavioral), or all three. It affects 2% to 3% of the general population^{2, 11}. Chief complaints of panic disorder¹² include the following:

- Increased heart rate, blood pressure and respiration rate
- Palpitations
- Diaphoresis
- Shortness of breath
- Dizziness
- Derealization or Depersonalization
- GIT distress
- Tremulousness or Shakiness
- Numbness or Tingling sensations
- Hot flashes or Chills

Agoraphobia: Panic disorder may exist with or without agoraphobia and agoraphobia may exist without panic disorder. The prevalence of agoraphobia among adults is 1.7%². Agoraphobia is defined as individuals who are fearful and/or anxious about being in open spaces (*e.g.*, public venues), standing in line or in a crowd, using public transportation or being alone outside the home. The onset of agoraphobia is typically early adulthood. The situational fear encompasses thoughts of inability to escape or of becoming embarrassed. The course is typically persistent and chronic, with only 10% remission reported. Approximately a third of affected adults are home bound and unable to work. Common comorbidities include other anxiety disorders, depressive disorders, post-traumatic stress disorder (PTSD) and alcohol use disorder¹¹.

Generalized Anxiety Disorder: GAD is a prevalent psychiatric disorder that affects about 2.9% of adults and 0.9% of adolescents². Similar to other anxiety disorders, GAD carries a substantial risk of disability and poor quality of life. GAD tends to have an early onset with duration of more than 5 years. The chronicity and longitudinal course of anxiety disorders, including GAD, is influenced by partner status; age of onset; history of childhood trauma; coexisting psychiatric disorders, including depression and bipolar disorder; and substance use disorders^{13, 14}.

Research indicates that a high co-occurrence of these disorders is characteristic of the course and nature of GAD and is associated with significant disability, interference with function and reduced

quality of life. The co-existence of these disorders has important clinical implications for its course and treatment outcomes¹⁴. GAD is costly and prevalent in primary care settings. It is one of the most common diagnoses in patients with unexplained physical symptoms¹⁵.

Implications for nurses include identification of symptoms; health education; assessment of coexisting conditions, such as mood and substance use disorders; and risk of danger to self and others. An essential feature of GAD is excessive worrying occurring more days than not for at least 6 months. Patients also experience an array of physical symptoms, such as feeling keyed up and sleep disturbances. In addition, the diagnosis of GAD involves at least 3 of the following¹¹:

- Fatigue
- Restlessness
- Impaired concentration
- Irritability
- Muscle tension
- Sleep disturbances
- Gastrointestinal distress
- Feeling keyed up or edgy

Specific Phobias: Specific phobias involve the manifestation of marked fear, anxiety, or avoidance in the context of specific objects or situations. Individuals with specific phobias commonly have fears of more than one situation or object. Specific phobias may develop after a traumatic event; however, the trigger is not always identifiable. There are various types of specific phobias: objects, animals, natural events and situational. Symptoms usually develop in early childhood, predominantly before age of 10 years and usually fluctuate in occurrence. Symptoms which persist into adulthood tend to be persistent and are unlikely to remit. Specific phobia, though low in prevalence, remains a commonly experienced disorder in late life¹¹.

Social Anxiety Disorder (Social Phobia): Similar to other anxiety disorders, SAD is chronic psychiatric disorder, with a lifetime prevalence of 7%². SAD produces significant interference with function, personally and professionally. Likewise, SAD often coexists with other psychiatric disorders, such as depression and substance use disorder^{16, 17, 18, 19}.

The onset of social phobia occurs during adolescence, with a median age of 13 years, when interpersonal relationships are significant and plays a role in adult relationships. Clinical features of SAD arise from exposure to feared social situations and production of marked and persistent fear and intense anxiety caused by 1 or more social performance situations, scrutiny by others, and avoidant behaviors¹¹.

Posttraumatic Stress Disorder: The lifetime prevalence of PTSD in the United States is high at about 8%, with a higher incidence among Veterans and inner city populations^{2, 19}. There is a higher prevalence of PTSD among women, previously married individuals, military service personnel, combat veterans^{20, 21} and individuals who experience various traumas (*e.g.*, child abuse, intimate partner violence *etc.*). PTSD is characterized by responses to an overwhelming and traumatic event that emerge 1 month after exposure to trauma, with following sets of symptoms, which are listed in below.

PTSD Symptoms:

1. Intrusive symptoms:

- a) Intrusive and distressful images or thoughts of event
- b) Flashbacks
- c) Nightmares and sleep disturbances

2. Avoidance behaviours:

- a) Avoidance of the situation or reminders of the event
- b) Numbness
- c) Psychological amnesias

3. Negative cognitions and mood associated with the trauma:

- a) Startle response
- b) Hypervigilance
- c) Concentration disturbances
- d) Negative emotional states (*e.g.*, fear, guilt, sadness, shame)
- e) Loss of awareness of present surroundings (derealization)
- f) Numbness
- g) Psychological amnesias

4. Intense alterations in arousal and reactivity:

- a) Irritable behavior and angry outbursts with little provocation

(*e.g.*, aggressive behaviors); hypervigilance

b) Exaggerated startle or stress response

Sleep disturbances

Other Anxiety Disorders: This group of disorders includes the following: substance-/medication-induced anxiety disorder, anxiety disorder due to another medical cause, other specified anxiety disorders and unspecified anxiety disorder. Substance-/medication-induced anxiety disorder presents with symptoms of panic and anxiety that have developed during or immediately following intoxication and/or withdrawal of a substance or medication. Anxiety disorder due to another medical condition is explained by the physiological effect of an underlying medical condition (*e.g.*, hyperthyroidism, arrhythmia, asthma, seizure disorders). Other specified anxiety disorders and unspecified anxiety disorders do not fit criteria for one of the aforementioned anxiety disorders¹¹.

Obsessive-Compulsive and Related Disorders:

This group of disorders includes obsessive-compulsive disorder (OCD), body dysmorphic disorder, hoarding disorder, trichotillomania (hair-pulling disorder), excoriation (skin-picking) disorder, substance-/medication-induced OCD, OCD due to another medical condition and unspecified OCD. Age of onset is typically late adolescence or early adulthood, but can present in late childhood as well. The presence of recurring intrusive and persistent thoughts (obsessions) and repetitive behaviors or mental acts that result (compulsions) are a hallmark of this collection of disorders.

The specifics of OCD vary by individual, but there are common themes which include contamination obsessions and cleaning compulsions; symmetry obsessions with repeating, ordering, and counting compulsions; religious, aggressive or sexual obsessions and related compulsions; and harm obsessions and related compulsions.

Body dysmorphic disorder is characterized by a perceived flaw in physical appearance that is minor or absent. Repetitive acts of checking the mirror, excessive grooming and reassurance-seeking behaviors are common. Hoarding disorder is described as significant difficulty with discarding possessions, irrespective of value, resulting in an

intense need to save items. Symptoms include accumulation of items that congest and clutter living spaces to the point that their intended use is compromised^{11, 22}. Trichotillomania (hair-pulling) disorder involves recurrent hair pulling with resultant hair loss, despite repeated attempts to stop the behavior.

Excoriation (skin-picking) disorder involves recurrent picking of the skin despite repeated attempts to cease. These two disorders are usually preceded by feelings of anxiety or boredom^{11, 22, 23}. Substance-/medication-induced OCD involves symptoms related to intoxication or withdrawal of a substance or medication. Symptoms resulting from OCD due to another medical condition are specifically associated with that medical condition.

Pathophysiology: Stress is an important factor causing anxiety disorder. The stress related anxiety disorder is produced by persistent changes in the stress responsive CNS -CRF system. Cell bodies containing CRF are highly found in medial parvocellular region of hypothalamic paraventricular nucleus (PVN). The parvocellular region of hypothalamic PVN is considered as the neuroendocrine stress response system. The stress response in humans involves a series of hormonal events by the activation of hypothalamus pituitary adrenal axis which leads to the increased release of cortisol and adrenaline (stress hormones).

These stress hormones reacts with body and brain in various complicated mechanism producing anxiety disorders (a maladaptive emotional state causing fear, worry and excessive stress characterized by physiological arousal, unpleasant tension and feeling of apprehension).

Pathophysiology of anxiety is associated with multiple regions of the brain such as (a) Amygdala, a temporal lobe structure which assess the fearful stimuli and produces responses to fear.(b) Locus ceruleus a noradrenaline (NA) containing site located in the brain stem with widespread projections to areas responsible for producing fear responses (vagus, lateral and paraventricular hypothalamus). (c) Hippocampus region. (d) The hypothalamus is the principle area for generating neuroendocrine and autonomic responses to fear. The neurochemical theory of anxiety includes the

abnormal functioning of several neurotransmitters such as NA, gamma aminobutyric acid (GABA) and serotonin (5-HT). The autonomic nervous system of anxious patient is hypersensitive and over reacts to various stimuli such as threat or fear, in such condition the locus ceruleus acts as an alarm center causing NA release and stimulate the sympathetic and parasympathetic nervous system producing anxiety symptoms. 5-HT is primarily an inhibitory neurotransmitter and the abnormalities in its function through release and uptake at the presynaptic autoreceptors (5-HT_{1A} / 1D), the serotonin reuptake transporter site or effect of 5-HT at the postsynaptic receptors plays a major role in the development of anxiety.

The greater 5-HT activity reduces the release of NA from locus ceruleus, inhibits the defense response and reduces hypothalamic release of corticotropin-releasing factor (CRF).The lesser 5-HT activity may lead to dysregulation of other neurotransmitters. GABA the major inhibitory neurotransmitter in the central nervous system (CNS) has a strong regulatory or inhibitory role on the 5-HT, NA or dopamine²⁴.

Management of Anxiety: Anxiety disorders are the most prevalent of psychiatric disorders, yet less than 30% of individuals who suffer from anxiety disorders seek treatment²⁵. People with anxiety disorders can benefit from a variety of treatments and services. Following an accurate diagnosis, possible treatments include²⁶ psychological treatments and mediation.

Psychological treatments: Psychotherapy is almost always the treatment of choice except in cases where anxiety is so severe that immediate relief is necessary to restore functioning and to prevent immediate and severe consequences. This includes the following:

- **Behavioral therapies:** These focus on using techniques such as guided imagery, relaxation training, biofeedback (to control stress and muscle tension); progressive desensitization, flooding as means to reduce anxiety responses or eliminate specific phobias. The person is gradually exposed to the object or situation that is feared. At first, the exposure may be only through pictures or audiotapes. Later, if

possible, the person actually confronts the feared object or situation. Often the therapist will accompany him or her to provide support and guidance.

- **Cognitive-behavioral therapy (CBT):** In this therapy, people learn to deal with fears by modifying the ways they think and behave. A major aim of CBT and behavioral therapy is to reduce anxiety by eliminating beliefs or behaviors that help to maintain the anxiety disorder. Research has shown that CBT is effective for several anxiety disorders, particularly panic disorder and social phobia. It has two components. The cognitive component helps people change thinking patterns that keep them from overcoming their fears. The behavioral component of CBT seeks to change people's reactions to anxiety-provoking situations. A key element of this component is exposure, in which people confront the things they fear, *i.e.*, CBT addresses underlying "automatic" thoughts and feelings that result from fear, as well as specific techniques to reduce or replace maladaptive behavior patterns.

- **Psychotherapy:** Psychotherapy centers on resolution of conflicts and stresses, as well as the developmental aspects of anxiety disorders solely through talk therapy. Psychotherapy involves talking with a trained mental health professional, such as a psychiatrist, psychologist, social worker, or counselor to learn how to deal with problems like anxiety disorders²⁷.
- **Psychodynamic therapy:** This therapy, first suggested by Freud, is based on the premise that primary sources of abnormal behavior are unresolved past conflicts and the possibility that unacceptable unconscious impulses will enter consciousness.

Family therapy and parent training: Here the focus is on the family and its dynamics. This is based on the assumption that the individuals of a family cannot improve without understanding the conflicts that are to be found in the interactions of the family members. Thus, each member is expected to contribute to the resolution of the problem being addressed^{28,29}.

TABLE 1: MAJOR CLASSES OF MEDICATIONS USED FOR VARIOUS ANXIETY DISORDERS

Class	Generic name	Used for
Anticonvulsants	Gabapentin	SAD
Benzodiazepines	Lorazepam, Clonazepam Oxazepam, Diazepam Alprazolam	GAD, SAD, Panic disorder
Azaspirones	Buspirone	GAD
Atypical Antipsychotics	Quetiapine Risperidone	GAD, PTSD
Monoamine oxidase inhibitors (MAOIs)	Selegiline, Isocarboxid, Phenelzine, Tranylcypromine	Panic disorder, SAD, PTSD
Beta blockers	Propranolol, Atenolol	SAD
Calcium Channel Modulators	Pregabalin	GAD
Noradrenergic and specific serotonergic antidepressant (NasSA)	Mirtazapin, Antihistamine Hydroxyzine	GAD, PTSD
Tricyclic antidepressants (TCAs)	Nortriptyline, Amitriptyline Imipramine, Clomipramine	Panic disorder, PTSD, OCD
Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)	Venlafaxine, Duloxetine	Panic disorder, PTSD, GAD
Selective serotonin reuptake inhibitors (SSRIs)	Citalopram, Fluvoxamine Paroxetine, Fluoxetine Sertraline, Escitalopram	Panic disorder, OCD, SAD, GAD

Note: GAD = Generalized anxiety disorder, OCD = Obsessive compulsive disorder, PTSD = Post Traumatic stress disorder, SAD=Social anxiety disorder.

Herbal Remedies to Treat Anxiety Disorders:

Anxiety disorders are prevalent and disabling conditions that are often chronic and highly comorbid³⁰. While conventional pharmacotherapies and psychological interventions are front-line

approaches, plant-based medicines may offer an additional safe and effective option. Phytotherapeutic interventions that may benefit anxiety disorders are classed as 'anxiolytics' and usually have effects on the GABA system³¹,

either *via* inducing ionic channel transmission by voltage-gated blockage or through alteration of membrane structures³² or less commonly *via* binding with benzodiazepine receptor sites (*e.g.* GABA-a)³³, GABA transaminase or glutamic acid

decarboxylase inhibition³⁴ or interactions with a range of monoamines. A number of drugs from natural source either in the form of extracts or as active principles is isolated or evaluated for anxiolytic properties³⁵.

TABLE 2: MEDICINAL PLANTS EXHIBITING ANXIOLYTIC ACTIVITY

Plant name and family	Chemical constituent
<i>Aethusa cynapium</i> (Apiaceae)	Unsaturated fatty acid ³⁶
<i>Alangium ssalvifolium</i> (Alangiaceae)	Flavonoids and tannins ³⁷
<i>Allium ascalonium</i> (Liliaceae)	Alkaloids, flavonoids and tannins ³⁸
<i>Apocynum venetum</i> (Apocynaceae)	Flavonoids ³⁹
<i>Alternanthera brasiliana</i> (Amaranthaceae)	Alkaloids, steroids ⁴⁰
<i>Albies pindrow</i> (Pinaceae)	Terpenoids, flavonoids, glycosides ⁴¹
<i>Bacopa monniera</i> (Scrophulariaceae)	Bacosides A and B, triterpinoid, saponins ⁴²
<i>Bellis perennis</i> (Asteraceae)	Alkaloids, phenolic compounds and flavonoids ⁴³
<i>Benincasa hispida</i> (Cucurbitaceae)	Triterpinoids, flavonoids, carotenes, uronic acid ⁴⁴
<i>Boerhaavia diffusa</i> (Nyctaginaceae)	Alkaloids(punarnavine), Boeravinones A-F, Flavonoids ⁴⁵
<i>Byrsocarpus coccineus</i> (Connaraceae)	Flavonoids, alkaloids and terpenoids ⁴⁶
<i>Crocus sativus</i> (Iridaceae)	Safranal, crocins, picrocrocin ⁴⁷
<i>Cedrus deodara</i> (Pinaceae)	Alkaloids and tannins ⁴⁸
<i>Centella asiatica</i> (Apiaceae)	Asiaticoside (triterpinoid) ⁴⁹
<i>Clinopodium mexicanum</i> (Lamiaceae)	Neoponicin ⁵⁰
<i>Crataegus oxycantha</i> (Rosaceae)	Flavonoids, triterpenes ⁵¹
<i>Dolichandrone falcata</i> (Bignoniaceae)	Flavonoids, phenolic compounds ⁵²
<i>Davilla rugosa</i> (Dilleniaceae)	Flavonoids ⁵³
<i>Echium amoenum</i> (Boraginaceae)	Flavonoids ⁵⁴
<i>Erythrina suberosa</i> (Fabaceae)	Erysodine, Erysothrine ⁵⁵
<i>Euphorbia hirta</i> (Euphorbiaceae)	Alkaloids, phenolics ⁵⁶
<i>Foeniculum vulgare</i> (Umbelliferae)	Essential oil ⁵⁷
<i>Fumaria indica</i> (Fumariaceae)	Protopine ⁵⁸
<i>Gastrodia elata</i> (Orchidaceae)	Phenolics(4-hydroxy benzaldehyde) ⁵⁹
<i>Gynostemma pentaphyllum</i> (Cucurbitaceae)	Gypenoside, flavonoids ⁶⁰
<i>Hydrocotyle umbellata</i> (Araliaceae)	Triterpenes, essential oils, flavonoids, Saponins ⁶¹
<i>Justicia gendarussa</i> (Acanthaceae)	Flavonoids, alkaloids, steroids, saponins ⁶²
<i>Lea indica</i> (Vitaceae)	Triterpenoid glycosides, hydrocarbons, ursolic acid ⁶³
<i>Mangifera indica</i> (Anacardiaceae)	Polyphenols, flavonoids, triterpinoids ⁶⁴
<i>Nauclea latifolia</i> (Rubiaceae)	Isoquinoline alkaloids ⁶⁵
<i>Morinda citrifolia</i> (Rubiaceae)	Scopoletin, rutin ⁶⁶
<i>Ocimum sanctum</i> (Lamiaceae)	Ursolic acid ⁶⁷
<i>Oxalis corniculata</i> (Oxalidaceae)	Flavonoids, tannins ⁶⁸
<i>Passiflora actinia</i> (Passifloraceae)	Beta, carboline flavonoid (Isovetixen) ⁶⁹
<i>Panax ginseng</i> (Araliaceae)	Triterpenoid saponins (ginsenosides) ⁷⁰
<i>Punica granatum</i> (Puniaceae)	Flavonoids ⁷¹
<i>Rubia cordifolia</i> (Rubiaceae)	Alkaloids, flavonoids, terpinoids ⁷²
<i>Rubus fruticosus</i> (Rosaceae)	Gallotannins, ellagitannins, flavonoids ⁷³
<i>Siparuna guianensis</i> (Siparunaceae)	<i>Siparuna guianensis</i> (Siparunaceae) ⁷⁴
<i>Stachys lavandulifolia</i> (Lamiaceae)	Flavonoids, terpenoids, essential oils ⁷⁵
<i>Tagetes erecta</i> (Asteraceae)	Flavonoids ⁷⁶
<i>Turnera diffusa</i> (Turneraceae)	Flavonoids (apigenin), essential oils ⁷⁷
<i>Terminalia chebula</i> (Combretaceae)	Tannic acid, polyphenols ⁷⁹
<i>Tylophora indica</i> (Asclepiadaceae)	Tylophorine ⁷⁸
<i>Uraria picta</i> (Fabaceae)	Flavonoids, triterpinoids ⁷⁹
<i>Valeriana jatamansi</i> (Valerianaceae)	Borneol ⁸⁰
<i>Vitex negundo</i> (Verbanaceae)	Volatile oil, flavonoids, terpenes ⁸¹
<i>Withania somnifera</i> (Solanaceae)	Sitoindosides vii-x, withaferin-A ⁸²
<i>Nymphaea stellata</i> (Nymphaeaceae)	Alkaloids, saponins, flavonoids ⁸³

CONCLUSION: Anxiety disorders, obsessive-compulsive and related disorders and trauma-and stressor-related disorders account for significant morbidity and mortality among mental health patients. Specifically, the anxiety disorders account for the majority of cost burden due to their high prevalence and the increasing cost of appropriate therapies. Timely and accurate diagnoses followed by appropriate treatment are of the utmost importance due to the pervasive nature of these disorders and their effects. Conventional pharmacotherapy is limited by side effects such as psychomotor impairment, potentiation of other central depressant drugs and dependence liability. Hence, complementary and alternative medicine and plant-derived medications are being investigated as potential anxiolytic agents.

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REFERENCES:

- American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Association; 2013. p. 607–913.
- Kessler RC, Petulhova M, Sampson NA, *et al.* Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. *Int J Methods Psychiatr Res* 2012; 21:169–84.
- Furtad M, Katzman MA. Neuroinflammatory pathways in anxiety, posttraumatic stress, and obsessive compulsive disorders. *Psychiatry Res* 2015; 229:37–48.
- Meir DS, Merz CJ, Hamacher-Dang TC, *et al.* Effects of cortisol on reconsolidation of reactivated fear memories. *Neuropsychopharmacology* 2015; 40:3036–43.
- Mayo-Wilson E, Dias S, Mavranzouli I, *et al.* Psychological and pharmacological interventions for social anxiety disorder in adults: a systematic review and network meta-analysis. *Lancet Psychiatry* 2014; 1: 368-76.
- Singewaldk N, Schmuckermair C, Whittle N, *et al.* Pharmacology of cognitive enhancers for exposure-based therapy of fear, anxiety and trauma-related disorders. *Pharmacol Ther* 2015; 149:150–90.
- Haaker J, Lonsdorf TB, Kalisch R: Effects of post-extinction L-DOPA administration on the spontaneous recovery and reinstatement of fear in a human fMRI study. *Eur Neuropsychopharmacol* 2015; 25:1544–55.
- Griffin GD, Charron D, Al-Daccak R. Post-traumatic stress disorder: revisiting adrenergics, glucocorticoids, immune system effects and homeostasis. *Clin Transl Immunology* 2014; 3:e27.
- Jergovic M, Bendelja K, Savic Mlakar A, *et al.* Circulating levels of hormones, lipids, and immune mediators in post-traumatic stress disorder - a 3-month follow-up study. *Front Psychiatry* 2015; 14(6):49.
- Bergin J, Verhulst B, Aggen SH, *et al.* Obsessive compulsive symptom dimensions and neuroticism: an examination of shared genetic and environmental risk. *Am J Med Genet B Neuropsychiatr Genet* 2014; 165 B: 647–53.
- American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th edition. Washington, DC: Author; 2013.
- Ho AK, Thorpe CT, Pandhi N *et al.* Association of anxiety and depression with hypertension control: a US multidisciplinary group practice observational study. *J Hypertens* 2015; 33: 2215–22.
- Backhaus A, Agha Z, Maglione ML, *et al.* Video conferencing psychotherapy: a systematic review. *Psychol Serv* 2012; 2012(9):111-31.
- Batelaan NM, Rhebergen D, Spinhoven P, *et al.* Two-year course trajectories of anxiety disorders: do DSM classifications matter? *J Clin Psychiatry* 2014; 75: 985-93.
- Schaffer A, McIntosh D, Goldstein BI, *et al.* The CANMAT task force recommendations for the management of patients with mood disorders and comorbid anxiety disorders. *Ann Clin Psychiatry* 2012; 24: 6-22.
- Kessler RC, Aguilar-Gaxiola S, Alonso J, *et al.* The global burden of mental disorders: an update from the WHO World Mental Health (WMH) surveys. *Epidemiol Psychiatr Soc* 2009; 18 (1):23–33.
- Bener A, Abou-Saleh MT, Dafeeah EE, *et al.* The prevalence and burden of psychiatric disorders in primary health care visits in Qatar: too little time? *J Family Med Prim Care* 2015; 4:89–95.
- Whiteford HA, Degenhardt L, Rehm J, *et al.* Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet* 2013; 382:1575–86.
- Breslau N, Peterson EL, Schultz LR. A second look at prior trauma and the posttraumatic stress disorder effects of subsequent trauma: a prospective epidemiological study. *Arch Gen Psychiatry* 2008; 65:431–7.
- Bernardy NC, Friedman MJ. Psychopharmacological strategies in the management of posttraumatic stress disorder (PTSD): what have we learned? *Curr Psychiatry Rep* 2015; 17:564.
- Steenkamp MM, Litz BT, Hoge CW, *et al.* Psychotherapy for military-related PTSD: A review of randomized clinical trials. *JAMA* 2015; 314:489–500.
- Sneider F, Milrod B. Gabbard's treatments of psychiatric disorders. 5th ed. American Psychiatric Publishing, Arlington; 2014; 7–913.
- Grant JE, Odlaug BA, Won KS. N-Acetylcysteine, a glutamate modulator, in the treatment of Trichotillomania. *Arch Gen Psychiatry*. 2009; 66(7):756–63.
- Dipiro JT, Talbert RL, Yees GC, Matzke GR, Wells BG, Poseyn LM. Pharmacotherapy A Pathophysiologic Approach. 6th edition. Mc graw hill publishing division. 2002; 128687.
- Lépine, JP: The epidemiology of anxiety disorders: prevalence and societal costs. *Journal of Clinical Psychiatry*, 2002; 63 Supp.14, 14-18.
- Barlow, D. H. (2001). *Clinical handbook of psychological disorders* (3rd ed.). New York, NY: Guilford.
- Knekt P, Lindfors O, Laaksonen MA, Raitasalo R, Haaramo P, Järvikoski A: The Helsinki Psychotherapy Study Group.: Effectiveness of short-term and long-term psychotherapy on work ability and functional capacity -A randomized clinical trial on depressive and anxiety

- disorders. Journal of Affective Disorders 2008; 107(1-3): 95-106.
28. American Psychological Association (2004). Anxiety Disorders: The Role of Psychotherapy in Effective Treatment. Retrieved from <http://www.apahelpcenter.org/articles/article.php>.
 29. Feldman, R. S. (2004). Understanding Psychology (6th ed.). New Delhi: Tata McGraw-Hill.
 30. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, text revision. 4th ed. Arlington: American Psychiatric Association; 2000.
 31. Sarris J. Herbal medicines in the treatment of psychiatric disorders: a systematic review. *Phytother Res.* 2007; 21(8): 703–16.
 32. Sarris J, Kavanagh DJ. Kava and St John's wort: current evidence for use in mood and anxiety disorders. *J Altern Complement Med.* 2009; 15(8): 827–36.
 33. Spinella M. The psychopharmacology of herbal medicine: plant drugs that alter mind. In: Brain and behavior. Cambridge: MIT Press; 2001.
 34. Awad R, Levac D, Cybulska P, *et al.* Effects of traditionally used anxiolytic botanicals on enzymes of the gamma-aminobutyric acid (GABA) system. *Can J Physiol Pharmacol.* 2007; 85(9): 933–42.
 35. Sparrboom A, Cox MC, Acharya MR, Figg WD. Herbal remedies in the United States: Potential adverse interaction with anticancer agents. *J Clin Oncol.* 2004; 22(12): 2489-503.
 36. Shri R, Singh M, sharma A. Bioactivity directed separation of an anxiolytic fraction of *Aethusa cynapium*. *J Pharmacognosy phytother.* 2010; 2(2): 017-023.
 37. Ronok Z, Anamul HH, Laizuman N, Ashik MM, Ekramul HM. Evaluation of anxiolytic and CNS depressant activity of *Alangium salvifolium* ang flowers. *IRJP.* 2013; 3(4): 144-47.
 38. Abidemi JA, Sanni HA, Edeh PC. Anxiolytic activity of aerial part of hydroethanolic extract of *Allium ascalonium* linn (liliaceae) in mice. *Functional Foods in Health and Disease.* 2012; 2(11): 448-59
 39. Grundmann O, Nakajima J, Seo S, *et al.* Anti-anxiety effects of *Apocynum venetum* L. in the elevated plus maze test. *J Ethnopharmacol.* 2007; 110 (3):406–11.
 40. Barua CC, Begum SA, Barua AG, Borah RS, Lahkar M. Anxiolytic and anticonvulsant activity of methanolic extract of leaves of *A. brasiliense* (Amaranthaceae) in laboratory animals. *Indian J Exp Biol.* 2013; 51: 450-57.
 41. Kumar S, Madaan R, Sharma A. Pharmacological evaluation of bioactive principle of *Turnera aphrodisiaca*. *Indian J Pharm Sci.* 2008; 70(6): 740-44.
 42. Chatterjee M, Verma P, Palit G. Comparative evaluation of *Bacopa monniera* and *Panax quinquefolium* in experimental anxiety and depressive models in mice. *Indian J Exp Biol.* 2010; 48: 306-313.
 43. Marques THC, Melo CHSD, Freitas RMD. In vitro evaluation of antioxidant, anxiolytic and antidepressant like effects of *Bellis perennis* extract. *Braz J Pharmacogn.* 2012; 22(5): 1044-52.
 44. Nimbalkar SK, Venkatrao N, Ladde S, Pujar B. Anxiolytic behavioural model for *Benincasa hispida*. *Int J Pharm Biopharmacol.* 2011; 1(3) 96-101.
 45. Venkateswarlu B, Rama Rao Y. Anxiolytic and hypnotic activity of whole plant extract of *Boerhaavia diffusa*. *Inter J of Phytotherapy.* 2013; 3(1): 33-36.
 46. Akindede AJ, Adeyemi OO: Anxiolytic and sedative effects of *Byrsocarpus coccineus* (Connaraceae) extract. *International Journal of Applied Research in Natural Products.* 2010; 3(1): 28-36.
 47. Schmidt M, Betti G, Hensel A. Saffron in phytotherapy: pharmacology and clinical uses. *Wien Med Wochenschr.* 2007; 157(13–14):315–9.
 48. Viswanatha GL, Nandakumar K, Shylaja H, Ramesh C, Rajesh S, Srinath R. Anxiolytic and Anticonvulsant activity of alcoholic extract of wood of *Cedrus deodara* in rodents. *JPRHC.* 2009; 1(2): 217-39.
 49. Wijeweera P, Arnason JT, Koszycki D, Merali Z. Evaluation of anxiolytic properties of Gotukola (*Centella asiatica*) extracts and asiaticoside in rat behavioural models. *Phytomedicine.* 2006; 13: 668-76.
 50. Cassani J, Araujo AGE, Vazques MM, Manjarrez N, Moreno J, Reyes RS. Anxiolytic and antinociceptive effects of 2(S) – Neoponricin in mice. *Molecules.* 2013; 18: 7584-599.
 51. Ankitkumar A, Ashok M, Jyothsna MV, Radhakrishna MV, Shivalinge Gowda KP. Evaluation of anxiolytic activity of aqueous and alcoholic extract of leaves *Crataegus oxyacantha* in mice. *Int J Pharm Biomed Sci.* 2011; 2(3): 86-91.
 52. Arome D, Enevide C, Ameh Sf. Pharmacological evaluation of anxiolytic property of aqueous root extract of *Cymbopogon citratus* in mice. *Chon Young Sci.* 2014; 5(1): 33-38. 21.
 53. Badgular VB, Surana SJ. Anxiolytic effects of *Dalichandrone falcata* (Bignoniaceae) stem bark in elevated plus maze and marble burying test on mice. *Braz J Pharmacogn.* 2010; 20(5): 773-80.
 54. Guaraldo L, Chagas DA, Konno AC, *et al.* Hydroalcoholic extract and fractions of *Davilla rugosa* Poirlet: effects on spontaneous motor activity and elevated plus-maze behavior. *J Ethnopharmacol.* 2000; 72(1–2):61–7.
 55. Shafaghi B, Naderi N, Tahmarb L, Kamalinejad M. Anxiolytic effect of *Echium amoenum* in mice. *Iranian Journal International Journal of Pharma Research & Review,* Jan 2015; 4(1):56-61
 56. Serrano MAR, Batista ANDL *et al.* Anxiolytic like effects of Erythranian alkaloids from *Erythrina suberosa*. *Quim nova.* 2011; 34(5): 808-11.
 57. Lanhers MC, Fleurentin J, Cabalion P, *et al.* Behavioral effects of *Euphorbia hirta* L.: sedative and anxiolytic properties. *J Ethnopharmacol.* 1990; 29(2):189–98.
 58. Mesfin M, Asres K, Shibeshi W. Evaluation of anxiolytic activity of the essential oil of the aerial part of *Foeniculum vulgare* in mice. *BMC Complement Altern Med.* 2014; 14: 1-7.
 59. Singh, Gireesh K, Chauhan, Sudhir K, Rai, Geeta *et al.* Potential antianxiety activity of *Fumaria indica*: A preclinical study. *Pharmacogn Mag.* 2013; 9(33): 14-22.
 60. Jung JW, Yoon BH, Oh HR, *et al.* Anxiolytic-like effects of *Gastrodia elata* and its phenolic constituents in mice. *Biol Pharm Bull.* 2006; 29(2):261–5.
 61. Choi HS, Zhao TT, Shin KS, Kim SH, Hwang BY, Lee CK *et al.* Anxiolytic effects of herbal ethanolic extract from *Gynostemma pentaphyllum* in mice after exposure to chronic stress. *Molecules.* 2013; 18: 4342-356.
 62. Rocha FF, Almeida CS, Santos RTD, Santana SA, Costa EA, Paula JRD. Anxiolytic like and sedative effects of *Hydrocotyle umbellata* extract in mice. *Braz J Pharmacogn.* 2011; 21(1): 115-20.
 63. Subramanian N, Jothimanivannan C, senthil kumar R, Kameshwaran S. Evaluation of antianxiety activity of *Justicia gendarussa*. *Pharmacologia.* 2013; 4(5): 404-07.
 64. Raihan MO, Habib MR, Brishti A, *et al.* Sedative and anxiolytic effects of the methanolic extract of *Leea indica* (Burm. f.) Merr. leaf. *Drug Discov Ther.* 2011; 5(4):185–9.

65. Patel NB, Kumar S, Prasad AK, Patel JA, Patel HA. Assessment of anxiolytic activity of aqueous extract of *Mangifera indica* Leaves rodents exposed to chronic unpredictable mild stress. IRJP. 2013; 4(1): 247-51.
66. Ngo Bum E, Taiwe GS, Moto FC, *et al.* Anticonvulsant, anxiolytic, and sedative properties of the roots of *Nauclea latifolia* Smith in mice. Epilepsy Behav. 2009; 15(4):434-40.
67. Kannan S, Manickam S, Rajamohammed MA. Anxiolytic, sedative and hypnotic activities of aqueous extract of *Morinda citrifolia* fruit. Ayurveda Integr Med. 2014; 5(2): 73-75.
68. Pemminati S, Gopalakrishna HN, Venkatesh V, Amritha R, Shetty S, Vinod A. Anxiolytic effect of chronic administration ursolic acid in rats. Journal of Applied Pharmaceutical Science. 2011; 1(3): 6871.
69. Gupta G, Kazmi I, Afzal M, Rahman M, Anwar F. Anxiolytic effect of *Oxalis corniculata* (Oxalidaceae) in mice. Asian Pacific Journal of Tropical Diseases. 2012; 837- 40.
70. Santos KCD, Kurtz SMTF, Muller SD, Biavatti MW, Oliveira RMMWD, Santos CADM. Sedative and Anxiolytic effects of methanolic extract from the leaves of *Passiflora actinia*. Brazilian Archives of Biology and Biotechnology. 2006; 49: 56573.
71. Dang H, Chen Y, Liu X, *et al.* Antidepressant effects of ginseng total saponins in the forced swimming test and chronic mild stress models of depression. Prog Neuropsychopharmacol Biol Psychiatry. 2009; 33(8): 1417-24.
72. Sarma P, Das S. A study on the Anticonvulsant and antianxiety activity of ethanolic extract of *Punica granatum*. Int J Pharm Pharm Sci. 2014; 6(2): 389-92.
73. Patil RA, Jagdale SC, Kasture SB. Antihyperglycemic, antistress and nootropic activity of roots of *Rubia cordifolia*. Indian J Exp Biol. 2006; 44: 987-92.
74. Riaz M, Zia ul haq M, Ur Rahman N, Ahmad M. Neuropharmacological effects of methanolic extracts of *Rubus fruticosus*. Tur j Med Sci. 2014; 44: 454-60.
75. Negri G, Santi DD, Tabach R. Chemical composition of hydroethanolic extracts from *Siparuna guianensis* medicinal plant used as anxiolytics in amazon region. Braz J Pharmacogn. 2012; 22(5): 1024-34.
76. Rabbani M, Sajjadi SE, Zarei HR. Anxiolytic effects of *Stachys lavandulifolia* Vahl on the elevated plus-maze model of anxiety in mice. J Ethnopharmacol. 2003; 89(2-3):271-6.
77. Manisha RL, Shaik R, Satyanaraya B, Nazma SK, Nadeem SK, Sadhik SK *et al.* Evaluation of anxiolytic activity of flower extracts of *Tagetes erecta* in rats. JAPS. 2013; 3(12): 75-82.
78. Kumar S, Madaan R, Sharma A. Pharmacological evaluation of bioactive principle of *Turnera aphrodisiaca*. Indian J Pharm Sci. 2008; 70(6): 740-44.
79. Chandrashekar R, Manohar VR, Rao SN. Acute anxiolytic activity of aqueous extract of *Terminalia chebula* fruit pulp in rats. IJRAP. 2013; 4(1): 112-15.
80. Manikkoth S, Chandrashekar R, Rao SN. Antianxiety effect of ethanolic extract of leaves of *Tylophora indica* in Wistar albino rats. IJRAP. 2013; 4(1): 127-29.
81. Garg N, Garg M, Maan AS, Sandhu BS, Mittal S, Goyal S. Phytochemical studies and antianxiety activity of *Uraria picta* leaves. JPRO. 2012; 5(2): 39-40.
82. Gupta GL, Rana AC. Effect of *Withania somnifera* dunal in ethanol induced anxiolysis and with drawal anxiety in rats. Indian J Exp Biol. 2008; 46: 470-75.
83. Saravanan N, Rather SA. Antistress activity of ethanolic extract of *Nymphaea stellata* flowers against immobilization induced stress in albino rats. Der Pharmacia Sinica. 2013; 4(2): 24-32.

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