Herbal Medication and Nutraceuticals for the Management of Anxiety and Depression

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Anxiety and Depression

- 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.

- 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.

- Depression is one of the most common diseases, and according to WHO it may become a primary cause of disability in the future.

- Although there is a wide range of anxiety and depression treatment strategies, both pharmacological and psychotherapeutic, they are not effective with all patients.

- More than 20 herbal remedies have been identified that may potentially be applied in medicine as anti-depressive, anxiety-relieving or sleep-inducing agents.
Epidemiology

Depression
• Fourth highest cause of disability worldwide
• 6.7% of Adults in the US (30% severe)
• 11.2% of 13-18 yr. old in US (3.3% severe)
• Women are affected twice as often as men
• $83+ billion per year which exceeds the costs of the war in Afghanistan.

Anxiety
• 18.1% of US adults in the US (22% severe)
• 25.1% of 13-18 yrs. In the US (5.9% severe)
• Women are twice as likely to be affected as men.
• $42+ billion per year for anxiety conditions
Signs and Symptoms of Clinical Anxiety

- Feelings of panic, fear, and uneasiness
- Uncontrollable, obsessive thoughts
- Repeated thoughts or flashbacks of traumatic experiences
- Nightmares
- Ritualistic behaviors, such as repeated hand washing
- Problems sleeping
- Cold or sweaty hands and/or feet
- Shortness of breath

- Palpitations
- An inability to be still and calm
- Dry mouth
- Numbness or tingling in the hands or feet
- Nausea
- Muscle tension
- Dizziness

Anything where the reaction is inappropriate to the situation.
Signs and Symptoms of Clinical Depression

**Physical:**
- Sleep disturbances—insomnia, oversleeping, waking up early
- Changes in appetite or eating: much more or much less
- Decreased energy, fatigue
- Headaches, stomachaches, digestive problems unexplained

**Behavioral/Attitude:**
- **Loss of interest or pleasure** in activities that were once enjoyed, such as going out with friends, hobbies, sports, sex, etc.
- Difficulty concentrating, remembering, or making decisions
- Neglecting responsibilities or personal appearance

**Emotional:**
- Persistent sad or "empty" mood, lasting two or more weeks
- Crying "for no reason"
- Feeling hopeless, helpless, guilty or worthless
- Feeling irritable, agitated or anxious
- Thoughts of death or suicide
Complications

**Depression**
- Alcohol abuse
- Substance abuse
- Anxiety
- Work or school problems
- Family conflicts
- Relationship difficulties
- Social isolation
- Suicide
- Self-mutilation, such as cutting

**Anxiety**
- Depression
- Substance abuse
- Trouble sleeping (insomnia)
- Digestive or bowel problems
- Headaches
- Teeth grinding (bruxism)
- Substance use disorders
St. John’s Wort

- It is called St. John’s Wort because it flowers around **St. John’s day** and **wort** is an **Old English term** for **plant**.

- **Botanical Name:** *Hypericum perforatum*

- **Family:** *Hypericaceae*

- **Habitat:** is native to parts of Europe and Asia but has spread worldwide including to temperate regions of India, China, Canada, Africa, and the United States.

- **Composition:** Contains at least 10 substances including **hypericin** & **hyperforin**, which are shown to have biological activity.

- **Leaves are used for antidepressant** and other purposes

- **Flowers are used to promote wound healing**
Chemical Constituents

• Substances found and described using various chromatographic methods (esp. HPLC).

• Flavonol derivatives

• Biflavones

• Proanthocyanidines

• Xanthones

• Phloroglucinols*

• Naphthodianthrones*

• *Most notable: hypericin and hyperforin
Uses:

• Treatment of mild to moderate depression.
  • #1 Anti-depressant in Germany
• Relieves anxiety, insomnia, and headaches.
• Dosage: Daily dose of 900 mg of SJW extract (standardized to 0.3% hypericin) found to be equivalent to 20 mg fluoxetine
• Doses up to 1800 mg tolerated in severe depression

Traditional Uses:

• Anti-inflammatory, Sedative, Diuretic, Anti-malarial
• Used on first degree burns and healing of other wounds.

Adverse Effects:

• Sun-exposure: Photosensitivity/Phototoxicity
• Insomnia, vivid dreams, headache, dizziness, nervousness, sexual dysfunction, GI upset and fatigue.
Mechanism of Controlling Depression

• Depression is caused by a deficiency of serotonin (5HT, 5-Hydroxytryptamine) or norepinephrine.

• **Mechanism of action of SJW:**
  
  • **Reuptake inhibition of monoamines** (specifically, serotonin, norepinephrine, and dopamine).
  
  • **Monoamine oxidase inhibitors (MAOIs):** There are two isoforms of monoamine oxidase, MAO-A and MAO-B. MAO-A preferentially deaminates serotonin, melatonin, epinephrine, and norepinephrine. MAO inhibition occurs with high concentrations of SJW.
  
  • Causes up-regulation of 5-HT2 receptors
  
  • These effects exerted by a combination of mainly hypericin, and hyperforin.
Herb-drug Interactions: Committee on Safety of Medicine

- **HIV Medications**
  - Reduced blood levels with possible loss of HIV suppression
- **Warfarin**
  - Reduced anticoagulant effects and need for increased dose
- **Cyclosporin**
  - Reduced blood levels with risk of transplant rejection
- **Oral Contraceptives**
  - Reduced blood levels with risk of unintended pregnancy
- **Anticonvulsants**
  - Reduced blood levels with risk of seizures
- **Digoxin**
  - Reduced blood levels and loss of control of heart rhythm or heart failure
- **Theophylline**
  - Reduced blood levels and loss of control of asthma
- **Triptans & SSRIs**
  - Increased serotonergic effects with increased incidence of adverse reaction
Kava Kava

• Botanical Name: *Piper methysticum*

• Family: *Piperaceae*

• Habitat: It is a crop of the western Pacific.

• The **roots** of the plant are used to produce a **drink** with **sedative, anesthetic, euphoriant, and entheogenic properties**.

• The mature **roots** of the kava plant are harvested after a minimum of four years for peak kavalactone content.

• **Uses**: Nervous tension (anxiety), stress and agitation, insomnia.

• Kava pyrones have central muscle-relaxing, anticonvulsive, hypnotic/sedative effects by interaction with ion channels and GABA sites.
Kava Kava

Composition:
• Its active ingredients are called **kavalactones** (15% Dried root). A total of 18 different kavalactones (or kavapyrones) have been identified to date.
• However, six of them, including **kavain**, **dihydrokavain**, **methysticin**, **dihydromethysticin**, **yangonin**, and **desmethoxyxyangonin**, have been determined to be responsible for about 96% of the plant's pharmacological activity.

![Chemical structures](image-url)
**Mechanism of Action:** The following pharmacological actions have been reported for kava and/or its major active constituents:

- However, **kavain** and **dihydrokavain** appears to contribute significantly to the **anxiolytic effects** of kava.

- **Potentiation of GABA\textsubscript{A} receptor** activity (by kavain, dihydrokavain, methysticin, dihydromethysticin, and yangonin).

- **Inhibition of the reuptake of norepinephrine** (by kavain and methysticin) and possibly also of **dopamine** (by kavain and desmethoxyyangonin).

- **Monoamine oxidase B reversible inhibition** (by all six of the major kavalactones).
Valerian

- It is a **perennial flowering plant**, with heads of sweetly scented pink or white flowers that bloom in the summer.

- **Botanical Name**: *Valeriana officinalis*

- **Family**: *Caprifoliaceae*

- **Habitat**:
  - Native to **Europe** and parts of **Asia**, valerian has been introduced into **North America**.

- **Uses**:
  - The **roots** of the plant are used to treat **insomnia** (sedative) and **anxiety**.
  - Valerian **flower extracts** were used as a **perfume** in the 16th century.

- **MOA**: **Valerenic acid** demonstrated
  - agonism at GABA-A receptor and
  - partial agonism at 5HT5a
Withania (Ashwagandha)

- **Withania** is a genus of flowering plants in the nightshade family, *Solanaceae*, with 23 species that are native to parts of North Africa, western Asia, south Asia, southern Europe, the Mediterranean, and the Canary Islands.

- The name **Ashwagandha** is from the Sanskrit language and is a combination of the word *ashva*, meaning horse, and *gandha*, meaning smell.

- The **ROOT** and berry are used to make medicine.

- The species **Withania somnifera** (Ashwagandha) is economically significant, and are cultivated in several regions for their medicinal uses.

- Main constituents are withanolide and withaferin.

- **Uses**: It is used for fatigue, anxiety, insomnia, improving thinking ability, tumors, tuberculosis, asthma, bronchitis, hiccups, leukoderma, arthritis, backache, menstrual problems, and chronic liver disease.

- It is also used as an “adaptogen” to help the body cope with daily stress, and as a general tonic.

- It is also used for fertility problems in men and women and also to increase sexual desire.

- **MOA**: GABA mimetic activity.
Rose root

• Botanical Name: *Rhodiola rosea*
• Family: *Crassulaceae*
• Habitat: It is a perennial flowering plant. It grows in cold regions of the world, including much of the Arctic, the mountains of Central Asia, scattered in eastern North America.

• Rhodiola roots contain **rosavin, p-tyrosol**, and **salidroside** that is responsible for the **antidepressant** and **anxiolytic** actions of this plant.

• **Uses:** It is helpful for **enhancing physical performance** and **alleviating mental fatigue**; as **anxiolytic** and **antidepressant**; improvement of cognitive impairment; to prevent altitude sickness.

• **MOA:** Inhibitor of MAO-A; inhibition of stress-induced protein kinases, nitric oxide; normalisation of 5-HT.
Borage

- **Botanical Name:** *Echium amoenum*
- **Family:** *Boraginaceae*
- **Habitat:** It is a biennial or perennial herb indigenous to the narrow zone of northern part of Iran and Caucasus, where it grows at an altitude ranging from 60 to 2200 m.

- **Uses:** The extracts are used for variety of effects such as anxiolytic, sedative, anti-depressent and Demulcent, anti-inflammatory and analgesic, especially for common cold.

- **MOA:** Inhibitor of serotonin reuptake (due to rosmarinic acid)

- Borage oil is a source of gamma-linolenic acid and used in the treatment of atopic dermatitis and rheumatic disease.

- It is one of the important medicinal herbs in traditional Iranian medicine.
Chamomile

- **German chamomile:** *Matricaria chamomilla* (most commonly used species)
- **Roman, English or garden chamomile:** *Chamaemelum nobile* (less frequently used species)
- **Family:** *Asteraceae*
- **Used part:** Dried flower head
- Major chemical compounds include **apigenin** and **α-bisabolol**.
- **Uses:** German chamomile possesses anti-anxiety properties and could be used to treat stress, insomnia and depression.
- **MOA:** Chamomile bind to GABA receptors and modulate monoamine neurotransmission.
- **Other uses:** treating hay fever, inflammation, muscle spasms, menstrual disorders, insomnia, ulcers, gastrointestinal
Passion Flower

- **Botanical Name:** *Passiflora incarnata*
- **Family:** *Passifloraceae*
- *Passiflora* is a genus of about 500 species of flowering plants.
- **Habitat:** Most species are found in South America, eastern Asia, southern Asia and New Guinea. A number of species of *Passiflora* are **cultivated** outside their natural range for of their beautiful flowers and delicious fruit.
- Mainly contain **Harman** and **chrysin**
- **Uses:** *Passiflora incarnata* is a folk remedy for **anxiety** and **insomnia**. Passionflower is also used for seizures, asthma, **attention deficit-hyperactivity disorder** (ADHD), nervousness and excitability, palpitations, irregular heartbeat, and high blood pressure.

**MOA:**
- Inhibitor of MAO-A;
- GABA-system mediated anxiolysis
Centella (Gotu Cola)

• The aerial parts of *Centella asiatica*

• **Family:** Umbelliferae or Apiaceae

• **Habitat:** Grows in tropical swampy areas and wetlands in Asia. It is found in Pakistan, India and Africa.

• **Uses:** The main constituents are triterpene saponins asicoside (centilloside or asciaticoside) which is mainly responsible for alleviating symptoms of anxiety and stress.

• **MOA:** GABA transaminase inhibition.

• Also, it contains small amounts of volatile oil (chiefly α-humulene) which have antibacterial activity. In addition, it contains flavonoids like quercetin, and phytosterols.

• **Other uses:** Anti-rheumatic, dermatological agent for wound-healing and cosmetic preparations, and peripheral vasodilator.
Lemonbalm

- **The leaves of** *Melissa officinalis*
- **Family:** Lamiaceae
- **Habitat:** *M. officinalis* is native to Europe, central Asia and Iran, but now naturalized around the world.
- The leaves have a gentle lemon scent, related to mint. Its flavour comes from citronellal (24%), geranial (16%), linalyl acetate(12%) and caryophyllene (12%).
- **Uses:** Lemon balm is used medicinally as an herbal tea, or in extract form.
- Leaves have been prescribed for internal (as tea) or external (essential oil) application for the treatment of disorders of the gastrointestinal tract, nervous system, liver, and bile. Lemon balm essential oil is very popular in aromatherapy.
- A standardized medicinal extract of *M. officinalis* Leaves is used for the treatment of insomnia, anxiety and depression. It also reduce oxidative stress.
- **MOA:** Inhibit GABA transaminase, and MAO-A.
Ginkgo

• **The aerial parts** of *Ginkgo biloba*

• **Family:** Ginkgoaceae

• **Habitat:** It is the only living species in the division Ginkgophyta, all others being extinct. It is **found in fossils dating back 270 million years.** Native to China, the tree is widely cultivated and was introduced early to human history.

• The active constituents are **ginkgolide** and **bilobalide.**

• **Uses:** It has various uses in traditional medicine and as a source of food. A standardized medicinal extract of Ginkgo biloba **LEAF** is used for the treatment of cognitive impairment (**dementia**) in Alzheimer’s disease, **anxiety** and **depression.**

• **MOA:** Modulation of cholinergic and monoamine pathways; Antioxidant, GABAergic effects; anti-inflammatory effect.
Brahmi

• Botanical Name: *Bacopa monnieri*
• Family: Scrophulariaceae
• Habitat: It is a perennial, *creeping herb* native to the wetlands of southern and Eastern India, Australia, Europe, Africa, Asia, and North and South America. Bacopa is a medicinal herb used in Ayurveda, where it is also known as "Brahmi", after *Brahmā*, the creator God of the Hindu pantheon.

• Uses:
  - Bacopa monnieri contains two *flavonoids* - *apigenin* and *luteolin* that make good *antioxidants*. It also contains two *saponins* called *bacopaside I* and *II*.
  - It is extensively used in traditional Indian medicine as a *neurotonic*.
  - *Bacopaside* helps to improve memory, enhance focus and concentration, and aids with learning new tasks. It also helps with the *repair of damaged neurons in the brain*, helping *enhance brain function* and boosting memory and also of benefit to those with *Alzheimer's, Anxiety* and *depression*.

• MAO:
  - Metal chelation/β-amyloid protection; Cholinesterase inhibition
  - 5HT-2c modulation; Antioxidant effects
Brahmi

Bacopaside I
Lavender

• Lavandula (lavender) is a genus of 39 known species of flowering plants in the mint family, Lamiaceae.

• The most widely cultivated species, *Lavandula angustifolia*, is often referred to as lavender.

• **Lavender oil**: Commercially, the plant is grown mainly for the production of essential oil of lavender. This has antiseptic and anti-inflammatory properties. It is also used in balms, perfumes, cosmetics, and topical applications.

• It showed meaningful efficacy in alleviating anxiety and related sleep disturbances and depression. Lavender oil with a high percentage of linalool and linalyl acetate available in the form of capsules.

• Lavender oil is approved for use as an Anxiolytic in Germany under the name *Lasea* (GABA modulation).

• **Lavender honey** (created from bees feeding on lavender plants), instead of lavender essential oil has the best effects of uninfected wounds.
Saffron

- **Botanical Name:** *Crocus sativus*
- **Family:** Lamiaceae
- The *styles* and *stigmas*, called threads, are collected and dried to be used mainly as a *seasoning* and *colouring agent in food*.
- **Habitat:** Saffron is native to Greece or Southwest Asia. It was slowly propagated throughout much of Eurasia and was later brought to parts of North Africa, North America, and Oceania. It is widely used in Persian, Indian, European, Arab, and Turkish cuisines.
- **Uses:** The chemical constituents *crocin* (responsible for the color of saffron), *crocetin* and *safranal* are responsible for alleviation of *anxiety* and *depression*.
- **MOA:**
  - *Reuptake inhibition* of *monoamines* (serotonin, dopamine, norepinephrine);
  - GABA-α agonism,
  - NMDA (N-Methyl-D-aspartate) receptor antagonism.
Thank You