Living in a complex and dangerous environment as humans have for most of our evolutionary history requires one to possess effective mechanisms of arousal, both consciousness and emotional, in order to meet the demands of the environment. An organism needs to be able to arouse behaviorally in order to deal with predators and other environmental threats. While many of the physical threats of survival have arguably minimized for most individuals with the advent of civilization, some physical threats (e.g., violent crime) do remain. Moreover, a host of psychological threats to our well-being exist, including unemployment, taxes, and divorce, which can be equally distressing. In many circumstances, mechanisms of arousal serve an adaptive purpose, but when acutely or chronically over-activated, they become maladaptive, manifesting as stress, anxiety, and insomnia.

To treat these conditions of over-activation, we have developed several effective pharmacological treatments. However, there are also in existence several plant-derived medications which have also long been used. This chapter will review the known herbal medications used to promote sleep, focusing especially on those for whom pharmacological and empirical evidence exists. As can be discerned from the evidence presented here, this field is far from complete. Further research is needed in all known sleep-promoting herbal medicines, and perhaps to identify other species that have potential as sleep-aids. This chapter focuses on the psychopharmacology of herbal medications relevant to sleep.

Valerian

**History & Botany**

Valerian (Valeriana officinalis) is native to Europe and Asia, but now grows in most parts of the world. It grows 50 to 100 cm in height, with an erect stem with pinnate leaves and numerous small pink-white flowers, and has a distinct, unpleasant odor. Valerian has been used for at least 1000 years, and in 16th century Europe it was used as a treatment for epilepsy. It’s most commonly reported uses are to treat insomnia and anxiety.

**Chemical Constituents**

Valerian's primary chemical constituents are monoterpenes, sesquiterpenes, and alkaloids. The monoterpenes include bornyl acetate, l-borneol, valenol, valeranone, and valmane. A subgroup of the monoterpenes are the valepotriates, which include valtrate and its derivatives, baldrinal, and homobaldrinal. However, valepotriates rapidly decompose in the stored herb, so their content in valerian preparations is very low. The sesquiterpenes present in valerian include isovaleric acid, valerenic acid, valerenal, valeranone, and valerenol. The alkaloids found in valerian include valeranine and actinidine. The content of valepotriates and sesquiterpenes varies across species of the Valeriana genus. For example, Valeriana officinalis has relatively high content of sesquiterpenes and low content of valepotriates, while Valeriana edulis has a high proportion of valepotriates and low content of sesquiterpenes.

**Pharmacodynamic Mechanisms**

The mechanisms of action of valerian are not entirely certain, but they likely involve a facilitation of GABA transmission. Low microgram concentrations of an aqueous valerian extract inhibits uptake and stimulates release of GABA from synaptosomes. GABA release by the valerian extract is independent of Ca2+ and membrane depolarization, and thus not from vesicular stores. Further, the GABA release is dependent on Na+ concentrations, suggesting that valerian inhibits and reverses the GABA reuptake transporter. Thus, valerian extract appears to reverse GABA uptake and release it from the cytosolic pool. However, further investigation found that it is the actual GABA content of the extract that can partially account for the reversal of GABA uptake in vitro. Alternately, since GABA does not pass the blood-brain barrier well, it is possible that the glutamine content of valerian extract contributes to this effect since it both crosses the blood-brain barrier and serves as a precursor for GABA.

Some binding of valerian extract occurs at GABA_A receptors. Valerian extracts inhibit neuronal firing in a rat brainstem preparation in a concentration-dependent manner comparable to that of the GABA_A agonist muscimol and blocked by the GABA_A antagonist bicuculline. While Cavadas and colleagues attributed this effect to the amino acid content of the extract, Yuan and colleagues showed both total extract and valerenic acid to have this effect. Valerenic acid also inhibits breakdown of GABA. Low concentrations of valerian extracts enhance benzodiazepine binding ([3H]flunitrazepam). A flavonoid, 6-methylapigenin, has been isolated from Valeriana wallichii that may confer a benzodi-
Valerian used hydroalcoholic extract of Valeriana edulis to investigate the effects on sleep quality. The most recent polysomnographic study of Valerian showed an increase in slow-wave sleep stages 1, 2, and 3, and reduced stage 4 and REM. Dose-dependent effects were noted, where the 120 mg dose produced greater sedative effects. Peak effects occurred 2-3 hours after administration. Another study showed no effects on sleep stages or EEG spectra. A variety of GABAergic mechanisms have been identified as potential mechanisms for the sedative effects of valerian, but this was later discredited due to their unstable nature.

**Effects**

**Muscle Relaxant**

Valerian extracts have been shown to induce muscle relaxation, probably by a direct action on the muscle. However, GABAergic drugs have muscle relaxant effects in the spinal cord. This is a likely mechanism for valerian but has yet to be explicitly investigated.

**Behavioral Effects**

Several behavioral effects have been reported in animals. These include suppression of the orienting response in an open-field paradigm, decreasing spontaneous and caffeine-induced motor activity, and potentiation of the behavioral actions of barbiturates. Oral and intravenous doses of valerine and acetoxylvaltrate reduce locomotor activity. Valerian extracts show sedative effects in animals that are dose-dependent manner. These effects are moderate compared to diazepam and the chlorpromazine. However, valeropatriates reverse the anxiogenic effects of diazepam withdrawal in rats in the elevated plus maze.

**Sleep Electrophysiology**

A few studies have been published which examine the effects of valerian on human sleep electrophysiology, which have produced variable results. An early study showed that a combined preparation of valerian and hops in sleep-disturbed subjects increased the amount of slow wave and REM sleep. Another study using an aqueous extract (400 mg) of valerian did not show significant EEG effects, but suggested a relation between the EEG effects and subjective effects, i.e., shortened sleep latency and increased latency to first waking. Another study using aqueous extracts showed no effects on sleep stages or EEG spectra.

A controlled study of valerian in sleep was published which utilized double-blind placebo controls, and randomization with two doses of valerian (60 and 120 mg). Valerian increased sleep stages 1, 2, and 3, and reduced stage 4 and REM. Dose-dependent effects were noted, where the 120 mg dose produced greater sedative effects. Peak effects occurred 2-3 hours after administration. Mood ratings did not differ, positively or negatively, between the experimental and control conditions.

Sleep quality

Valerian improves subjective ratings of sleep particularly when taken nightly over one- to two-week periods. Valerian was studied with a randomized, placebo-controlled, and double-blind crossover study using a commercially available valerian preparation. The preparation used contained primarily sesquiterpenes, and very low amounts of valepotriates. The subjects were 27 adults who were seen in a medical clinic for sleep difficulties. Those receiving valerian experienced improvements in sleep quality (89%), with a proportion (44%) rating highest quality sleep.

**Cognitive Effects**

There are few formal studies of the cognitive effects of valerian. Whereas the benzodiazepine flunitrazepam produces significant impairment of memory, improvements were seen in sleep quality and decreases in sleep latency. Further, sleep quality was most improved in poor sleepers and tobacco smokers.

Six weeks of valerian extract (600 mg daily) reduced ratings of stress severity, producing vivid dreams in 16% of subjects in a methodologically controlled study. Valerian also improved sleep in insomniacs withdrawn from benzodiazepine medication. It created a decrease in wake time after sleep onset in when compared to placebo, improving this variable to the level seen in normal controls. Valerian improved sleep in a small sample of children with intellectual deficits in a randomized, placebo controlled study. The greatest effectiveness was observed in children who had the most hyperactivity.

**Toxicity**

No health hazards have yet been reported with normal use of valerian, and it has been approved by the German Commission E as a treatment for anxiety and sleep. Concern has been raised over valepotriates potentially affecting the liver, based on their...
chemical structure. However, Valeriana officinalis has a low valepotriate content, they decompose rapidly in the stored herb, and they are not well-absorbed. Liver toxicity in animals or humans has never been demonstrated.5 Thus, valepotriates, in practice, are not likely to cause toxicity.

High doses of valerian produce headache, vomiting, stupor, dizziness, and cardiac dysfunction.7 A case was reported of a single overdose (approximately 20 times the recommended therapeutic dose), reportedly producing mild symptoms that resolved in 24 hours. Given its central depressant effects and putative GABAergic mechanisms, concurrent use with other central depressants, including ethanol, should be avoided.

Kava

History and Botany

Kava (Piper methysticum) is a plant native to the South Pacific islands.8 It is also known by the names kava, awa, waka, lawena, or yaquona. It was used in those cultures for ceremonial and recreational purposes. Kava may also be given reciprocally as a gift in the resolution of a social conflict, or partaken as an after-work drink for relaxation. It is known traditionally for producing a relaxed but alert mental state.9 The large rhizome is the part of the plant used medicinally, which is pounded, chewed, or grated and then drunk in a cold-water infusion. In the West, it is typically sold in dried, ground encapsulated form, extract, or prepared as a tea.

Chemical Constituents

The pharmacologically active chemicals most studied from the kava plant are collectively called kavalactones. The principal kavalactones are: kavain, dihydrokavain, yangonin, dimethoxyyangonin, methysticin, and dihydromethysticin.10 Kavalactones, given in combination, produce create pharmacokinetic and pharmacodynamic synergy.11

Pharmacodynamic Mechanisms

Kava facilitates GABA transmission. Low micromolar concentrations enhance the binding of ligands to the GABA_A receptor, potentiating binding of GABA and enhancing Cl^- influx.12,13 Kavalactones do not alter the binding of flunitrazepam, so their effect on GABA_A is not through the benzodiazepine receptor.14 Kavalactone displacement of the GABA_A agonist muscimol is not through the benzodiazepine receptor.10 Therefore, their GABAergic effects, it is likely to cause muscle relaxant effects in the spinal cord.

Neuromuscular

Kava has direct neuromuscular relaxing effects through a mechanism similar to that of local anesthetics: by a direct blocking effect on ion channels of the muscle. Given kava's central GABAergic effects, it is likely to cause muscle relaxant effects in the spinal cord.

Electrophysiology

The effects of kavain on human electrophysiology were examined in a double-blind, placebo-controlled study.15 Dose-dependent increases were seen in delta, theta, and alpha 1 power, and decreases occurred in alpha 2 and beta power. These changes were suggestive of a sedative effect of kavain, and were maximal in frontal areas. An initial activating effect was seen at the lowest dose (200 mg) but not at the largest dose (600 mg). Event-related potentials (ERPs) were used to study the cognitive effects of kava, as compared to oxazepam during verbal memory and attention tasks.16,17 While oxazepam impaired performance, kava actually improved performance and was associated with an enhanced task-associated potentials in frontal, parietal, and occipital areas.

Cognitive

A study of the cognitive effects of kava on psychometric tests was undertaken by Foo and Lemon.18 Kava only produced minor effects on the digit symbol task, but no other tests of attention, reaction time, visuomotor tracking, and short-term memory. Kava and ethanol combined produced potentiated effects on subjective and objective cognitive measures. Very large doses of kavalactones (205 g, or 150 times the clinical dose) produce more pronounced cognitive and saccade impairments.19

Anxiolytic

Several controlled studies have been performed to assess the anti-anxiety effects of kava. The studies employed standardized doses of kavalactones ranging from 60 to 240 mg per day, and
were 4 to 24 weeks in duration. A meta-analysis found kava to be superior to placebo across all controlled studies. Kavain was found to be equivalent in efficacy to the benzodiazepine oxazepam.

Sleep
Despite its potential for improving sleep, only two studies to date have formally investigated this. One study found six-week, daily treatment with kava reduced stress-induced insomnia. The other study similarly found kava extract to improve anxiety-related sleep problems, ameliorating quality and restorative aspects of sleep.

Toxicity
Kava has been approved by the German Commission E for treatment of anxiety and insomnia. In clinical studies of kava for anxiety, adverse effects were uncommon and did not differ across placebo and kava groups. Given its kava's central depressant effects, it should not be taken with other similar drugs, including benzodiazepines, barbiturates, ethanol, or anti-seizure medications. There is one clinical report of combined administration of kava and the benzodiazepine alprazolam, causing lethargy and disorientation for several hours. Concern has been raised recently over liver toxicity with kava. Several cases have been reported of liver toxicity associated with kava use, some leading to liver failure or death. There are many variables to be considered in this matter, including concurrent use of other medications which could increase hepatotoxicity, amount and duration of use, the type of kava preparation used, and prior liver illness. Some short-term studies report a lack of effect on liver enzymes. Long-term aboriginal Australian users of kava showed mild elevation of certain liver enzymes which were reversible. There is evidence that the extraction process using acetone is partly responsible for the hepatotoxic effect. While this matter remains unresolved at present, prudent use of kava would be short-term, not in combination with other drugs affecting the liver, and in low to moderate doses. More traditional preparations might afford greater safety than many currently-used chemical extraction processes. Avoidance of using combinations of herbs may also best be avoided until the hepatic effects are known.

A scaly skin eruption called kava dermopathy has been reported to occur from kava use. It is reversible, and appears to only occur with heavy chronic use, but it has not been reported in the west.

A few cases were reported of dyskinesias presenting with kava use in individuals with Parkinson's disease. These consisted of dystonia, tonic head rotation, twisting of the trunk, oculogyric crises, and increased duration of "off" periods in a Parkinsonian patient. These symptoms subsided with discontinuation of kava and treatment with a cholinergic muscarinic antagonist. The authors suggest that this represents a dopamine antagonist action of kava, and raise caution about their use in the elderly.

Passionflower
History & Botany
A few members of the Passionflower family (passifloraceae) which have sedative and anxiolytic effects. The most studied is Passiflora incarnata, although some work has been done on P. coerulea and P. edulis. The whole plant or aerial parts are used for medicinal effects. It is native to the mid- to southeastern United States. Native Americans used passionflower prepared as a tea for sedative and anxiolytic effects.

Chemical Constituents
There are 3 categories of constituents in passionflower: flavonoids, maltol, and indole alkaloids. The greatest accumulation of flavonoids occurs in the leaves. The indole alkaloids are small amounts (up to 0.01 percent), including harman, harmine, harmaline, and harmalol.

Pharmacodynamic Mechanisms
The most studied constituent of passionflower is the flavonoid, chrysin. Chrysin was isolated from P. coerulea, a species closely related to P. incarnata. It binds to benzodiazepine receptors with micromolar affinity and competes for binding with the benzodiazepine flunitrazepam. Behavioral assays suggest that chrysin acts as a partial agonist at central benzodiazepine receptors. Anxiolytic effects of chrysin are blocked by flumazenil, arguing for a benzodiazepine mechanism. However, chrysin antagonized the electrophysiological effects of GABA at GABA_A receptors. These conflicting effects need to be reconciled with further, more careful research. A benzodiazepine partial agonist mechanism of chrysin is still possible, although other mechanisms may exist. The remaining constituents have not been well characterized for their neuropharmacological action or are present in small quantities and not presumed to contribute to the psychotropic effects.

Effects
Anxiolytic
Peripherally-injected chrysin exhibits anxiolytic effects in mice. Chrysin (1 mg/kg i.p.) in the elevated plus maze similar to diazepam, reversed by pretreatment with a benzodiazepine antagonist. The anxiolytic effect was not likely due to sedation since there is no concurrent reduction in motor activity at the doses used. Unlike diazepam, chrysin does not produce muscle relaxation at higher doses. The sedative and anxiolytic effects of passionflower were examined in two other animal behavioral assays (staircase test, light/dark box choice test). Both anxiolytic and sedative effects occur, as well as potentiation of pentobarbital sedation, at 400 mg/kg of hydroalcoholic extract in mice. The anxiolytic and sedative activity occur in a dose-dependent continuum. Passiflora edulis has sedative effects as well. Chronic administration of passionflower flavonoids produced anxiolytic effects and prevented the incurrence of diazepam-dependence. A small, controlled trial showed passionflower extract improved anxiety in Generalized Anxiety Disorder better than placebo. Passionflower performed equivalently to oxazepam, but appeared to cause less cognitive impairment. Despite the potential of passionflower as a treatment for insomnia, particularly anxiety-related insomnia, no clinical trials have been published to date.

Cognitive
In rats, chrysin does not have any amnestic effects on either acquisition or retention in three tests of memory (inhibitory avoidance, shuttle avoidance, and habituation to an open field tests), even at higher doses than required to produce anxiolytic effects.
The cognitive effects of passionflower have not been examined in humans.

**Anti-seizure**

Central, but not peripheral, injections of chrysirificantly reduced chemically-induced (pentyleneterazol) seizures in mice. This effect was abolished by prior injection of a benzodiazepine antagonist. This has not been tested in humans and should not be substituted for conventional treatments for seizures.

**Toxicity**

There have been no formal studies of the toxicity of passionflower, but adverse effects have not been reported. There is one report of a case of inflammatory vasculitis associated with a preparation of passionflower. Like other herbs in this category, its putative benzodiazepine action contra indicates its combined use with other central depressants.

**Chamomile**

**History and Botany**

Chamomile refers to two similar species of plants: German chamomile (Matricaria recutita) and Roman Chamomile (Chamaemelum nobilis), both of which are members of the Asteraceae family. Chamomile has been used throughout history, including ancient Egyptian, Roman, and Greek cultures. The two species look very much like daisies, with white petals and a yellow central disc. They are both native to Europe, Africa and Asia, and have been naturalized in North America. The flowering tops are used for their fragrance. It has not been well studied, but catnip has in it several terpenes, including nepetalactone. Humans have reported sedative effects of catnip, and one reported accidental ingestion by a young child reportedly produced sedative effects. Controlled trials of its effects have not been reported.

**Chemical Constituents**

Chamomile contains the terpenoids, (-)-alpha-bisabolol, (+)-alpha-bisabololoxides A and B, and a gauianolide lactone called matricin. Also contained are the flavonoids apigenin and apigenin-7-glucoside.

**Pharmacodynamic Mechanisms & Effects**

Apigenin binds with micromolar affinity at benzodiazepine receptors (4 µM), but has no effect at muscarinic, α1 adrenergic receptors, or the GABA binding site of the GABA channel. However, others report an antagonistic effect at GABA channels, which are insensitive to flumazenil. While another study confirmed a sedative effect of apigenin in mice, it also failed to reverse the effect with flumazenil.

Apigenin showed anxiolytic effects in mice, but no anti-seizure effects. At doses ten times greater than required for anxiolytic effects, apigenin showed mild sedative effects. The neuropharmacological mechanisms of chamomile have yet to be elucidated. Since doubt has been cast on a benzodiazepine mechanism of apigenin, other mechanisms by apigenin and other constituents, including flavonoids, must be evaluated.

Regardless of its mechanisms, controlled trials of chamomile preparations have not yet been reported in humans.

**Toxicity**

Chamomile appears very low in toxicity. It has been listed as Generally Regarded as Safe (GRAS) by the Food and Drug Administration. Adverse reactions may include allergic reactions to the pollen in the flowers, which are uncommon.

**Other Sedative Herbs**

The herbal medicines in this section have far less empirical research to support their use in improving aspects of sleep. However, they is some research for each suggesting that further research is warranted.

**Catnip**

Catnip (Nepeta cataria) has a long recorded history of use and is noted for sedative properties in humans. The active agent for this effect is uncertain, but catnip has in it several terpenes, including nepetalactone. Humans have reported sedative effects of catnip, and one reported accidental ingestion by a young child reportedly produced sedative effects. Controlled trials of its effects have not been reported.

**Hops**

Hops (Humulus lupulus) is a flowering vine that grows in Europe, Western Asia, and North America. It has reputed anxiolytic and sedative effects, often obtained by placing the female flowers in a pillow for their fragrance. It has not been well studied, but the responsible agent is believed to be 2-methyl-3-butene-2-ol, since it produces sedation when injected intraperitoneally in mice. In humans, one study found no CNS depressant effects when administered orally. However, effects via inhalation have not been studied.

**Skullcap**

Skullcap (Scutellaria laterifolia) is an herb which has been used in Chinese and Western medicine for sedative and anti-seizure effects. Its pharmacological and behavioral effects have not been established in animals or humans. It does contain the flavonoids baiacil and baicalin, and the amino acid glutamine, so GABAergic mechanisms are possible. One methodologically-controlled study in humans showed anxiolytic effects.

**Lemon Balm**

Lemon balm (Melissa officinalis) is flowering perennial plant, and a member of the mint family. In mice, lemon balm has sedative effects and analgesic activity. It also increased the sedative activity of a barbiturate (pentobarbital). A controlled study in humans showed improvement of memory performance in humans and increased ratings of calmness. This study also demonstrated binding of lemon balm constituents to muscarinic and nicotinic receptors in human cerebral cortex tissue.

**St. John's Wort**

St. John's wort (Hypericum perforatum) has been studied extensively for the treatment of depression. Evidence supports it's use in cases of mild to moderate depression. However, it also has potential for the treatment of sleep disorders. Several active constituents have been identified in St. John's wort. These have a variety of mechanisms including monoamine mechanisms (blocking reuptake, weak inhibition of MAO and COMT), as well as effects on adenosine, GABA, and glutamate receptors. Chronic use leads to adaptation of monoamine receptors. Controlled studies of St. John's wort show that it increases slow wave sleep and increases REM latency. Studies on the qualitative effects on sleep would be needed to demonstrate an...
improvement in sleep as well. Serious side effects from St. John’s wort monotherapy have not been reported, but it’s potential for interaction with antidepressants and drugs metabolized by the cytochrome P450 3A4 enzyme have been reported.  

### Conclusions

There are several herbs that have central depressant effects and have been used for anxiolytic and sedative effects historically. This has been supported by neuropharmacological, animal, and human studies. Kava, valerian, and passionflower have been the best supported by research in this regard, although others show potential. Much work remains to be done in further testing the safety and efficacy of these drugs. However, with further study some of these medicines may prove favorable in the treatment of sleep-related conditions.

### References

Herbal Medicines and Sleep


