CHAPTER #

Herbal Medicines and Sleep

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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.[1] 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.[2] It's most commonly reported uses are to treat insomnia and anxiety.[3]

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.[4] However, valepotriates rapidly decompose in the stored herb, so their content in valerian preparations is very low.[5] 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.[6]

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.[7,8] GABA release by the valerian extract is independent of Ca^{2+} 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 can partially account for the reversal of GABA uptake in vitro.[9] 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.[10] While Cavadas and colleagues[11] attributed this effect to the amino acid content of the extract, Yuan and colleagues[10] showed both total extract and valerenic acid to have this effect. Valerenic acid also inhibits breakdown of GABA.[12] Low concentrations of valerian extracts enhance benzodiazepine binding ([^{3H}]flunitrazepam).[13] A flavonoid, 6-methylapigenin, has been isolated from *Valeriana wallichii* that may confer a benzodi-

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azepine mechanism to this species.[14] The valpotriates may have central depressant effects through in vivo conversion to homobaldrinal.[15]

Collectively, valerian extracts show a variety of GABAergic mechanisms. The predominant mechanism has yet to be determined, but an additive or synergistic interaction among the several mechanisms is possible. Future research on valerian extracts needs to address any compositional differences between aqueous and nonaqueous extracts, and to determine the responsible active constituents. For some time it was thought to be the valepotriates, but this was later discredited due to their unstable nature.

Effects

Muscle Relaxant

Valepotriates (isovaltrate and valtrate) and valerenone were investigated show muscle relaxant effects in the guinea pig ileum, probably by a direct action on the muscle.[16] 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.[17] Oral and intravenous doses of valtrate and acetoxyvaltrate reduce locomotor activity.[18] Valerian extracts show sedative effects in animals that are dose-dependent manner.[19,20] These effects are moderate compared to diazepam and the chlorpromazine.[20] However, valepotriates 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.[21] 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.[22,23] Another study using aqueous extracts showed no effects on sleep stages or EEG spectra.[24]

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).[25] 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.

The effects of valerian in poor sleepers was studied comparing it to placebo controls.[26] Valerian showed an increase in slow-wave and a decrease in stage 1 sleep. K-complex density was increased, but REM was unaltered, and no effects were reported on subjective sleep quality. The most recent polysomnographic study of Valerian used hydroalcoholic extract of *Valeriana officinalis* and *Valeriana edulis*.[27] *V. edulis* reduced the number of awaking episodes, decreased stages 1 and 2, and increased delta sleep and REM.

The physiological effects of valerian across animals and humans are consistent with its sedative effects. The human electrophysiological findings are somewhat incongruent, but the methodology must be taken into account. Earlier studies used less rigorous controls, and one used aqueous extract instead of the entire herb, likely excluding much of the hydrophobic constituents. Another difference between the two latter studies which may account for differing results is the different populations used (normal versus sleep-disturbed).[25,26] Further work using larger samples and more careful methodological controls is warranted to evaluate these inconsistencies. However, the EEG effects of valerian are consistent with a sleep-promoting effect.

Sleep Quality

Valerian improves subjective ratings of sleep particularly when taken nightly over one- to two-week periods.[28] Valerian was studied with a randomized, placebo-controlled, and double-blind crossover study using a commercially available valerian preparation.[29] 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 were in sleep quality (89%), with a proportion (44%) rating highest quality sleep. No differences were seen between those who received either valerian or placebo first before the crossover. An absence of adverse side effects, including nightmares, was reported. This study unfortunately used a preparation which included two other herbs, which limit the conclusions that can be exclusively drawn with valerian. Another controlled study was performed that had a much larger (N = 128) sample.[30] 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.[31] Valerian also improved sleep in insomniacs withdrawn from benzodiazepine medication.[32] 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.[33] The greatest effectiveness was observed in children who had the most hyperactivity.

Cognitive Effects

There are few formal studies of the cognitive effects of valerian. Whereas the benzodiazepine flunitrazepam produces significant impairment the morning after administration, valerian (alone or in combination with hops) does not.[34] However, 1 to 2 hours after administration valerian produced a slight but statistically significant decrease in vigilance and processing of complex information. Although mild, this effect may contraindicate valerian use in situations where peak cognitive performance is required (e.g., driving).

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.[35] 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, valeportriates, in practice, are not likely to cause toxicity.

High doses of valerian produce headache, vomiting, stupor, dizziness, and cardiac dysfunction.[3] 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.[36] 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.[36] 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.[36] Kavalactones, given in combination, produce create pharmacokinetic and pharmacodynamic synergy.[37]

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.[38,39] Kavalactones do not alter the binding of flunitrazepam, so their effect on $GABA_A$ is not through the benzodiazepine receptor.[40] Kavalactone displacement of the $GABA_A$ agonist muscimol is highest in the hippocampus and amygdala.[39] Combination with pentobarbital caused a synergistic effect on binding.

A second mechanism by which kava produces CNS depression is by inhibition of voltage-gated ion channels. Kavain, dihydrokavain and dihydromethysticin act as noncompetitive inhibitors of the Na^+ channel.[41] Kavain blocks the $[^3H]$batrachotoxin binding, but not $[^3H]$saxitoxin binding.[42] This suggests an action at receptor site 2 of the Na^+ channel, a site common to local anesthetic drugs. Kavain inhibits L-type Ca^{2+} channels as well, and the subsequent release of glutamate.[42,43,44] These effects on voltage-gated ion channels are obtained in the micromolar range, and consistent with concentrations reached in the brain by peripheral administration.[45]

A third mechanism of kavalactones relevant to sleep involves monoamine effects. Kavalactones block the reuptake of norepinephrine.[46] This occurrs at concentrations of less than 10 μM, but this study only used a single kavalactone in vitro, ruling out additive and synergistic actions of combined administration. Kavalactones also inhibit MAO_B in the micromolar range.[47] Kavalactones reversibly inhibited platelet MAO_B in the low micromolar range. A dose of 120-240 mg of kavalactones for 3-4 weeks caused a 26-34% reduction of MAO_B in platelets.

Neither an acute dose of dihydromethysticin (100 mg/kg) or chronic doses of kavain altered levels of dopamine, serotonin, or their metabolites in the striatum and cortex of rats.[48] Kavalactones have complex and mixed effects on monoamine levels in the nucleus accumbens, depending both on which kavalactone is used and at what dose.[49] Short term increases in dopamine and decreases in serotonin were reported.

Effects

Neuromuscular

Kava has direct neuromuscular relaxing effects through a mechanism similar to those 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.[50] 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.[51,52] 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.[53] 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.[54]

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.[55] 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 it's potential for improving sleep, only two studies to date has formally investigated this. One study found six-week, daily treatment with kava reduced stress-induced insomnia.[56] The other study similarly found kava extract to improve anxiety-related sleep problems, ameliorating quality and restorative aspects of sleep.[57]

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.[58] 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.[59] 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.[60,61] Long-term aboriginal Australian users of kava showed mild elevation of certain liver enzymes which were reversible.[62] There is evidence that the extraction process using acetone is partly responsible for the hepatotoxic effect.[63] 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 their hepatic effects are known.

A scaly skin eruption called kava dermopathy has been reported to occur from kava use.[64] 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.[65] 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 (passifloracea) which have sedative and anxiolytic effects. The one 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.[1]

Chemical Constituents

There are 3 categories of constituents in passionflower: flavonoids, maltol, and indole alkaloids. The greatest accumulation of flavonoids occurs in the leaves.[66] The indole alkaloids are small amounts (up to 0.01 percent), including harman, harmine, harmaline, and harmalol.[5]

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 fluniztrazepam.[67] Behavioral assays suggest that chrysin acts as a partial agonist at central benzodiazepine receptors.[68] Anxiolytic effects of chrysin are blocked by flumazenil, arguing for a benzodiazepine mechanism.[69] However, chrysin antagonized the electrophysiological effects of GABA at $GABA_A$ receptors.[70] 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 neuropharmacolgocal 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.[71] 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.[71] The anxiolytic and sedative activity occur in a dose-dependent continuum.[19] Passiflora edulis has sedative effects as well.[72] Chronic administration of passionflower flavonoids produced anxiolytic effects and prevented the incurrence of diazepam-dependence.[73] A small, controlled trial showed passionflower extract improved anxiety in Generalized Anxiety Disorder better than placebo.[74] 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.[75]

The cognitive effects of passionflower have not been examined in humans.

Anti-seizure

Central, but not peripheral, injections of chrysin significantly reduced chemically-induced (pentylenetetrazol) seizures in mice.[76] 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.[77] 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 nobile*), both of which are members of the *Asteracea* 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 dried and often used to make a tea.

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.[78]

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 $GABA_A$ channel.[79] However, others report an antagonistic effect at GABA channels, which are insensitive to flumazenil.[70] While another study confirmed a sedative effect of apigenin in mice, it also failed to reverse the effect with flumazenil.[69]

Apigenin showed anxiolytic effects in mice, but no anti-seizure effects.[79] 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 it's 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.[80] Controlled trials of its effects have not been reported.

Hops

Hop (*Humulus lupulus*) is a flowering vine that grows in Europe, Western Asia, and North America.[1] 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.[81] In humans, one study found no CNS depressant effects when administered orally.[82] 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.[83] Its pharmacological and behavioral effects have not been established in animals or humans. It does contain the flavonoids baicalin and baicalein, and the amino acid glutamine, so GABAergic mechanisms are possible.[84] One methodologically-controlled study in humans showed anxiolytic effects.[85]

Lemon Balm

Lemon balm (*Melissa officianalis*) is flowering perennial plant, and a member of the mint family.[1] In mice, lemon balm has sedative effects and analgesic activity.[86] 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.[87] 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.[88,89] However, it also has potential for the treatment of sleep disorders.

Several active constituents have been identified in St. John's wort.[90] 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.[91,92] 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.[93,94]

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.

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