Herbs for the Treatment of Insomnia

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Abstract
Pharmacological approaches have been included in conventional medical treatment for insomnia or sleep disorders. However, long-term use of frequently prescribed medications can often lead to habituation, critical withdrawal symptoms and/or side effects. Some individuals with insomnia or trouble sleeping have used complementary and alternative medicine (CAM) therapies to treat their conditions. Recently, CAMs or herbs have been attractive alternative medications to many patients with sleep disorders who may be averse to using conventional drugs. We reviewed the most widely available sleep-promoting herbs commonly used in the western and oriental countries.

Key Words: Insomnia, Sleep, Complementary, Alternative, Medicine, Herbal treatments

SLEEP PHYSIOLOGY

The need for the proper quantity and quality of sleep is a biological drive similar to those of hunger and thirst. Humans sleep for approximately one-third of their lives. Nevertheless, sleep still remains one of mysteries despite several decades of research. Sleep is an essential part of life, but its exact role has not been elucidated. However, it is well known that sleep plays an important role in the restoration of physical and mental functioning. Recent research has led to a substantially improved understanding of both normal and altered sleep patterns, and their impact on health (Stanley, 2003). Generally, sleep is defined behaviorally by four criteria as follows: 1) reduced motor activity, 2) decreased response to stimulation, 3) stereotypic postures such as lying down with eyes closed, and 4) relatively easy reversibility (distinguishing it from a coma). Physiological activities during sleep can be conveniently monitored by electrical recording with an electroencephalogram (EEG) (Dijk, 2010; Edwards et al., 2010).

The hypothesis of a hypnogenic mechanism localized in the mammalian hypothalamic preoptic area (POA) was proposed 70 years ago. Von Economo proposed that sleep is regulated by opposing wake-promoting and sleep-promoting mechanisms localized in the hypothalamus (Saper et al., 2001). This hypothesis has been confirmed by findings that experimental POA lesions suppress sleep, and that electrical, chemical and thermal POA stimulation induced sleep (McGinty and Szymusiak, 2001). There is a population in the anterior hypothalamus that shows increased metabolic activities during sleep. Many sleep-promoting substances act in the POA. These neurons are concentrated in the ventrolateral POA (VLPO) and produce the inhibitory amino acid, γ-aminobutyric acid (GABA), and the inhibitory neuropeptide, galanin. At sleep onset, these neurons become active and inhibit ascending arousal systems of the brain stem, posterior hypothalamus, and basal forebrain (Fig. 1). In addition, the numbers of c-Fos/GAD double-labeled neurons increased following sleep, compared with waking, in dorsal and lateral POA sites, as well as in the rostral median preoptic nucleus (MnPN) and VLPO (Szymusiak and McGinty, 2008; Sun'tsova et al., 2009). Sleep-active neurons were found throughout the lateral POA and in the adjacent basal forebrain. Therefore, most of the available evidence suggests that sleep-active neurons are distributed in the median, dorsal, and ventrolateral POA as well as in the adjacent basal forebrain (Szymusiak et al., 2001). Neurotransmitters/neuromodulators responsible for maintaining wakefulness include norepinephrine (NE), dopamine (DA), serotonin (5-HT), acetylcholine (ACh), excitatory amino acids, hypocretin (orexin), and histamine, while those responsible for inducing sleep are GABA, adenosine, glycine and melatonin (Mendelson, 2001; Monti and Jantos, 2004) (Table 1). There are descending pathways from the VLPO to neuronal populations...
that have been found to promote wakefulness, including the serotonergic neurons of the dorsal raphe nucleus (DRN), noradrenergic cell groups in the locus coeruleus (LC), the histaminergic populations in the tuberomammillary nucleus (TMN) of the posterior hypothalamus (PH), and to additional regions of the hypothalamus (Sherin et al., 1998; Steininger et al., 1999; Takahashi et al., 2010). The wake-promoting roles of the DRN, LC, PH, and TM cell groups as well as the PH have been demonstrated by many methods (Perez and Benedito, 1997; Shouse et al., 2000).

**SLEEP ARCHITECTURE**

Most sleep-active neurons in all sites slowly discharge during waking. Increase in discharge anticipated EEG synchronization at sleep onset by a few seconds in each site. The sleep in most mammals is divided into two major types of sleep, rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep (McCarley, 2007). Humans usually fall asleep by entering NREM sleep, a phase accompanied by characteristic changes in the EEG. The next stage is REM sleep, which is characterized not only by REM but also by a complete inhibition of skeletal muscle tone. Before commencing on a description of sleep architecture, it is important to define three terms used to characterize the EEG: frequency, amplitude, and morphology (Lanquart et al., 1996). During NREM sleep neuronal activity is low, and metabolic rate and brain temperature are at their lowest. According to a simplified model, the onset of NREM sleep is driven by VLPO area neurons that exert an inhibitory effect on TMN histaminergic neurons (Liu et al., 2010). Consistent with this hypothesis is the finding that VLPO and TMN neurons exhibit opposite patterns of activity during the sleep-wake cycle (Hayashi, 2000). In contrast to the VLPO neurons, which are active during sleep, the TMN neurons are persistently active during wakefulness, reduce their firing during NREM sleep, and become inactive during REM sleep (Ramesh et al., 2004).

In addition, sleep is staged by determining the predominant pattern in 10-30 second “epochs” of EEG, muscle, and eye movement activity. Stage 1 NREM sleep represents very light sleep, from which one can be easily aroused. The predomin-

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**Table 1.** Herbs used as insomnia aids in western countries

<table>
<thead>
<tr>
<th>Name</th>
<th>Traditional usage</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lemon balm *</td>
<td>Remedy for sleep problems</td>
<td>Inhibits the breakdown of the sedative neurotransmitter GABA and possibly acetylcholine (Awad et al., 2007; Yoo et al., 2011)</td>
</tr>
<tr>
<td>Valerian *</td>
<td>Remedy for sleep problems</td>
<td>Increases the brain levels of GABAa (Trauner et al., 2008; Benke et al., 2009)</td>
</tr>
<tr>
<td>Hops *</td>
<td>Beer brewing, sleep aid</td>
<td>Slows down the breakdown of GABA and acts via the melatonin receptors (Awad et al., 2007)</td>
</tr>
<tr>
<td>Passionflower *</td>
<td>Treatment of anxiety</td>
<td>Action similar to benzodiazepine drugs (Carrasco et al., 2009)</td>
</tr>
<tr>
<td>Kava kava *</td>
<td>Treat anxiety, sleep aid.</td>
<td>Not well understood - affects the enzyme CYP2D6, vulnerable to liver damage from use of kava (banned in many countries) (Gurley et al., 2008)</td>
</tr>
<tr>
<td>Sprouted oats *</td>
<td>Treat anxiety and worry</td>
<td>No studies of its use</td>
</tr>
<tr>
<td>Lavender *</td>
<td>Remedy for insomnia</td>
<td>Not well understood</td>
</tr>
<tr>
<td>Chamomile *</td>
<td>Common tea</td>
<td>Action similar to the benzodiazepine drugs (Shinomiya et al., 2005)</td>
</tr>
<tr>
<td>St. John’s wort *</td>
<td>Depression, insomnia</td>
<td>Increases brain levels of GABA (Gobbi et al., 2001; Langosch et al., 2002)</td>
</tr>
<tr>
<td>Jasmine *</td>
<td>Common tea</td>
<td>Contains L-theanine, an amino acid which relieves anxiety and stress, but is not sedative by itself (Kuroda et al., 2005).</td>
</tr>
</tbody>
</table>

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\* spp: species

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REM sleep is characterized by slower waves at 2-4 Hz [100-150 μV], which occur periodically and last for a few seconds. Stage 3 non-REM sleep is characterized by 10-12 Hz oscillations [50-150 Hz] called spindles, which gradually release the cholinergic REM-on cells from orexin neurons during wakefulness, start to wane in activity, and low discharge rates during NREM sleep. The laterodorsal tegmental (LDT) nuclei have high charge rates during wakefulness and low-amplitude activity [-30 μV and 16-25 Hz]. Stage 2 NREM sleep is defined by the appearance of sleep spindles (12-14 Hz) or K-complexes on EEG. The majority of a typical night’s sleep is spent in stage 2. Stages 3 and 4 of NREM sleep are often referred to collectively as delta sleep (0.5-2.0 Hz [100-200 μV]). Stage 4 sleep is defined by slow waves at 0.5-2 Hz [100-200 μV]. [Modified from (Allison and Goff, 1972)].

Fig. 2. EEG recording during sleep stages. The waking state with the eyes open is characterized by high frequency [15-60 Hz] and low-amplitude activity [≤30 μV]. This pattern is called beta activity. Descent into stage 1 non-REM sleep is characterized by decreasing EEG frequency [4-8 Hz] and decreasing amplitude [50-100 μV], called theta waves. Descent into stage 2 non-REM sleep is characterized by 10-12 Hz oscillations [50-150 Hz] called spindles, which occur periodically and last for a few seconds. Stage 3 non-REM sleep is characterized by slower waves at 2-4 Hz [100-150 μV]. Stage 4 sleep is defined by slow waves at 0.5-2 Hz [100-200 μV]. [Modified from (Allison and Goff, 1972)].

HERBS AS SLEEP AIDS

Difficulties with daytime performance or unwanted sleepiness are often manifestations of sleep stage disruption or insufficient sleep. The majority of people seen in North American Sleep Disorder Centers presents with excessive daytime sleepiness. Conventional treatment for insomnia includes drugs that exert a depressant effect on the central nervous systems (CNS) and psychological therapy. Most of the drugs prescribed for insomnia involve some risk of overdose, tol-
erance, habituation, and addiction (Cheng et al., 2010). As alternative therapies, herbal products and other agents with sedative-hypnotic effects are increasingly sought after by the general population. These therapies are less likely to have the drawbacks of conventional drugs. How the efficacy of alternative therapies compares to conventional therapies warrants further investigation. Over-the-counter sleep aids are becoming popular as an alternative to prescription hypnotics. Surveys of young adults indicate that approximately 10 percent used nonprescription medications in the past year to improve sleep. Patients reported self-medicating with herbs, hormones, and amino acids in an effort to improve sleep, and avoided the unacceptable side effects of prescription medications. The most commonly used botanical sleep aids were introduced in Europe and the USA (Escourrou et al., 2000; Pearson et al., 2006). However, Zizyphus jujuba, Fructus jubae and Arillus Longan are Chinese herbs used in the treatment of insomnia (Table 1).

St John’s wort (Hypericum perforatum) is the most popular and well-studied herbal treatment for psychiatric problems in the West in recent years. H. perforatum has long been used as a remedy for wound healing, mild sedation, and pain relief (Barnes et al., 2001). Its flowers, leaves, bark, fruit, seeds, stems, and roots have all been used to treat insomnia and depression. However, two recent large-scale randomized controlled studies reported conflicting results on the efficacy of St John’s wort in treating depression. The use of St John’s wort as a hypnotic has not been systematically studied. A cross-over double-blind placebo-controlled study of high-dose hypericum extract in 12 elderly healthy volunteers suggested that St John’s wort induced an increase in deep sleep, but had no effect on other sleep parameters. Based on the results that St John’s wort increased deep sleep spindle density with activity comparable to tranquilizers and improved subjective parameters of sleep quality. Kava also decreased sleep latency, duration of wake phase, and sleep stage 1. Several relatively short-term clinical studies provide favorable evidence that kava kava is effective in treating anxiety and insomnia (Wheatley, 2001a; Meolie et al., 2005). Because of the increasing use of kava preparations, possible side effects are a concern. Valerian (Valeriana officinalis), from the plant family Valerianaceae, has been a popular Western botanical medicine used for its mild sedative and tranquilizing effects since the 17th century. The use of the rhizome and roots of V. officinalis as an anxiolytic and sleep aid dates back 1,000 years (Pallesen et al., 2002). In 1996, valerian was one of the 25 best-selling herbs in the United States (Chung and Lee, 2002; Koetter et al., 2007). In most countries, it is marketed as an over-the-counter product for this purpose. The U.S. Food and Drug Administration (FDA) rates valerian as a generally recognized as safe (GRAS) herb. Valerian contains valepotriates, valerenic acid, and unidentified aqueous constituents that contribute to the sedative properties of valerian. Valerenic acid is a sesquiterpene compound, which may represent an active compound and is used in standardization. Valerian root also contains 0.3-0.7 percent of a pungent volatile oil that contains bornyl acetate and the sesquiterpene derivatives of valerenic acid (Khom et al., 2000). Valerian has been shown to have sleep-inducing, anxiolytic, and tranquilizing effects in vivo animal studies and clinical trials. In clinical studies, valerian extract at bedtime led to improve sleep quality, decrease sleep latency, and reduced the number of night awakenings. From two other clinical studies, valerian before bed also improved insomnia (Koetter et al., 2007; Taibi et al., 2009). One EEG study reported that a dried extract of valerian, taken three times daily, improved delta sleep and decreased stage 1 sleep with repeated rather than single-dose administration (Balderon and Borbely, 1985). In general, clinical studies with valerian extract show that it has mild hypnotic effects and that it improves sleep quality. Animal studies suggest that valerian has a similar behavioral effect to that of benzodiazepines. More recent research suggests that GABA and serotonin may contribute to the activity of valerian extracts (Dietz et al., 2005; Benke et al., 2009).

Passion flower (Passiflora incarnata) consists of the dried flowering and fruiting top of a perennial climbing vine (Family: Passifloraceae). Although studies proving its efficacy are lacking, it is usually used for insomnia (Wheatley, 2005). Active components of passion flower may include indole alkaloids,

The active constituents are the kavalactones or kavapyrones, including kawain, dihydrokawain, methysticin, and dihydromethysticin; the CNS activity of kava kava is due to this group of resinosin compounds (Cheng et al., 1988; Dinh et al., 2001; Xuan et al., 2008). Research indicates that kava kava acts as a central nervous system depressant, and possesses muscle relaxant and analgesic effects in animals (Abebe, 2002). In several clinical trials, mainly conducted with a dose of 300 mg kava extract per day, kava has been employed successfully for the treatment of anxiety disorders (Gale and Oakley-Browne, 2004; Geier and Konstantinowicz, 2004). While the underlying mechanism is not entirely clear, it is possible that kava kava acts indirectly on GABA and benzodiazepine binding sites in the brain (Yuan et al., 2002). The effectiveness of kava kava as a sleep aid has also been studied. It was found that kava extract increased sleep spindle density with activity comparable to tranquilizers and improved subjective parameters of sleep quality. Kava also decreased sleep latency, duration of wake phase, and sleep stage 1. Several relatively short-term clinical studies provide favorable evidence that kava kava is effective in treating anxiety and insomnia (Wheatley, 2001a; Meolie et al., 2005). Because of the increasing use of kava preparations, possible side effects are a concern. Valerian (Valeriana officinalis), from the plant family Valerianaceae, has been a popular Western botanical medicine used for its mild sedative and tranquilizing effects since the 17th century. The use of the rhizome and roots of V. officinalis as an anxiolytic and sleep aid dates back 1,000 years (Pallesen et al., 2002). In 1996, valerian was one of the 25 best-selling herbs in the United States (Chung and Lee, 2002; Koetter et al., 2007). In most countries, it is marketed as an over-the-counter product for this purpose. The U.S. Food and Drug Administration (FDA) rates valerian as a generally recognized as safe (GRAS) herb. Valerian contains valepotriates, valerenic acid, and unidentified aqueous constituents that contribute to the sedative properties of valerian. Valerenic acid is a sesquiterpene compound, which may represent an active compound and is used in standardization. Valerian root also contains 0.3-0.7 percent of a pungent volatile oil that contains bornyl acetate and the sesquiterpene derivatives of valerenic acid (Khom et al., 2000). Valerian has been shown to have sleep-inducing, anxiolytic, and tranquilizing effects in vivo animal studies and clinical trials. In clinical studies, valerian extract at bedtime led to improve sleep quality, decrease sleep latency, and reduced the number of night awakenings. From two other clinical studies, valerian before bed also improved insomnia (Koetter et al., 2007; Taibi et al., 2009). One EEG study reported that a dried extract of valerian, taken three times daily, improved delta sleep and decreased stage 1 sleep with repeated rather than single-dose administration (Balderon and Borbely, 1985). In general, clinical studies with valerian extract show that it has mild hypnotic effects and that it improves sleep quality. Animal studies suggest that valerian has a similar behavioral effect to that of benzodiazepines. More recent research suggests that GABA and serotonin may contribute to the activity of valerian extracts (Dietz et al., 2005; Benke et al., 2009).

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maltol, ethyl-maltol, and flavonoids (Wheatley, 2005). When administered intraperitoneally to rats, passion flower extract significantly prolonged sleeping time (Krenn, 2002). The principal flavonoid, chrysin, was demonstrated to have benzodiazepine receptor activity (Nassiri-Asl et al., 2007). The usual daily dose is 4-8 g taken as a tea. Because alkaloid compounds are uterine stimulants, passion flower extract is not recommended for pregnant women (Soulimani et al., 1997).

Semen Zizyphi Spinosae is one of the most common ancient Chinese remedies for the treatment of insomnia. This herb is the dried ripe seed of the Zizyphus jujube (Family: Rhamnaceae). It has been used as an analgesic, tranquilizer and as an anticonvulsant. Animal studies suggest that it protects cerebral ischemic injuries, has hypnotic effects in rats, modulates stress-induced sleep changes in mice, and enhances total sleep time and slow wave sleep in rabbits. It is a common ingredient of traditional herbal formulas used in treating insomnia. Its extract of zizyphi contains pharmacologically active compounds such as flavones, alkaloids and triterpenes (Lee et al., 1996; Cheng, 2000). The hypnotic effect of semen zizyphi spinosi was postulated to be due to the anti-cholinergic and anti-histaminergic actions of betulic acid, an active compound of this herb. However, peptide alkaloids from semen zizyphi spinosi increased total sleeping time through modulation of GABAergic systems (Ma et al., 2007). In vitro analysis suggests an affinity for 5HT1a, 5HT2, and GABA receptors (Yi et al., 2007). Side effects consisting of gastrointestinal symptoms, dizziness and skin rash were reported.

Fructus Jujubae is the dried ripe fruit of Zizyphus jujube (Family: Rhamnaceae). The use of this fruit has a long tradition and a traditional herbal formula, ‘liquorice, wheat and jujuba soup’, which was first recorded during the Han dynasty (Wang et al., 1995). This has been a common prescription for treating mental problems including neuroasthenia, insomnia, and even schizophrenia (Huang et al., 1991). The active biochemical ingredient of the herbal formula is unknown. Jujube contains stepharine, N-nor-nuxerrine, asimilobine, and two kinds of Zizyphus saponin.

Aralius Longan is commonly consumed as the dried fruit of Euphoria longana (Family: Sapindaceae). The pulp of the dried fruit, as well as fresh Longanaceae Arillus, has been consumed for the treatment of anxiety and insomnia in Asian countries. In a pharmacological study, the extract of Longanaceae Arillus was proven to have anxiolytic activity (Okuyama et al., 1999). The methanol extract of Longanaceae Arillus prolonged sleep time and reduced sleep latency induced by pentobarbital. The extract itself does not induce sleep, but modulates GABAergic systems (Ma et al., 2009). Phytochemicals were extracted with 70% methanol from peel, pulp, and seed tissues of longan fruit, and the major components were identified as gallic acid, corilagin (ellagitannin), and ellagic acid (Rangkadilok et al., 2005).

Ginseng may be, at least in part, related to maintaining normal sleep and wakefulness. Of the several species of ginseng, Panax ginseng (Korean or Asian ginseng), Panax quinquefoi-lius (American ginseng), and Panax vietnamensis (Vietnamese ginseng) are reported to have sleep-modulating effects. Constituents of most ginseng species include ginsenosides, polysaccharides, peptides, polycyclic alcohols, and fatty acids (Kaku et al., 1975). Ginseng has an inhibitory effect on the CNS and may modulate neurotransmission. A mixture of the ginsenosides Rb1, Rb2, and Rc from Panax ginseng ex-tracts prolonged the duration of hexobarbital-induced “sleep” in mice (Takagi et al., 1972). Rhee et al. reported that Panax ginseng extract decreased the amount of wakefulness during a 12-hour light period and increased the amount of slow wave sleep (Rhee et al., 1990). In addition, red ginseng extract increased total sleep and NREM sleep (Ma et al., 2008; Yang et al., 2010), and it was reported that Panax ginseng extract normalized the disturbances in sleep-waking states caused by food deprivation in rats (Lee et al., 1990). Majonosides R2, a major saponin isolated exclusively from Panax vietnamera- sis, restored the hypnotic activity of pentobarbital, which was decreased by two models of psychological stress (Nguyen et al., 1996). In a recent double-blind study investigating the influence of ginseng on the quality of life of urban dwellers, a daily dose of 40 mg ginseng extract for 12 weeks significantly improved quality of life, including sleep (Hartley et al., 2004).

There is evidence to suggest that regulation of GABAergic neurotransmission is one mechanism for the CNS-depressant action of ginseng extract and ginsenosides. Ginsenosides have been reported to compete with agonists for binding to GABA_a and GABA_b receptors (Kimura et al., 1994). There are few reports of severe side-effects secondary to ginseng, despite the fact that over six million people ingest it regularly in the United States (Kabalak et al., 2004). The most common reported side effects are nervousness and excitation, but these diminish with continued use or dosage reduction. On the basis of its long-term usage and the relative infrequency of reported significant side effects, it is safe to conclude that ginseng is not associated with serious adverse reactions (Choi et al., 1999; Vazquez and Aguera-Ortiz, 2002). Because the possibility of hormone-like or hormone-inducing effects cannot be ruled out, some authors suggest limiting treatment to three months. Moreover, some participants reported less sleep and poor quality of sleep following ginseng use.

CONCLUSION

Recently, there has been great interest in alternative or complementary medicine, both locally and internationally. In the CNS, alkaloids and flavones to benzodiazepine sites on the GABA_a receptors resulting in sedation, anxiolytic or anti-convulsant effects. The use of herbs in the treatment of psychiatric problems including insomnia is not exclusive to oriental countries. Therefore, this review covered both western and oriental herbs used in the treatment of insomnia. The difference between the western and oriental use of herbs is that western herbs are more often used singly, while herbs used in oriental countries are usually in combined formulas. Western herbs for the treatment of insomnia have been studied more extensively than oriental herbs, both pre-clinically and clinically. Thus, more basic and clinical studies for oriental herbs are required to demonstrate their efficacy and safety. The modern scientific approach to research, using randomized controlled studies, with standardized dosages and measurements (both subjective and objective) is necessary, and careful monitoring of any adverse effects and potential drug interactions is essential. Some individual TCM herbs, such as Semen zizyphi spinosae, Fructus zizyphi jujubae, and Longanaceae Arillus appear promising for the treatment of insomnia. Oriental botanical herbs especially, have not yet been fully studied for clinical use.
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