BIOMOLECULES & THERAPEUTICS

Review
Biomol Ther 19(3), 274-281 (2011)

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-amino butyric 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; Suntsova *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

www.biomolther.org

Open Access **DOI: 10.4062/biomolther.2011.19.3.274**

pISSN: 1976-9148 eISSN: 2005-4483

Received Apr 15, 2011 **Revised** Jul 4, 2011 **Accepted** Jul 4, 2011

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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)

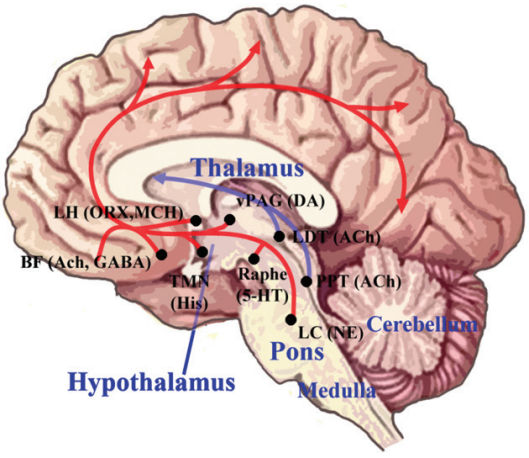

Fig. 1. Neurotransmitters that regulate sleep/wakefulness in brain regions. 1) Acetylcholine from the midbrain-pons (mesopontine) and the basal forebrain. 2) Norepinephrine and serotonin from the locus coeruleus and dorsal raphe. 3) Dopamine from the midbrain periaqueductal gray. 4) Histamine from the posterior hypothalamus. 5) Orexin from the lateral hypothalamus.

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 (Hayaishi, 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 predomi-

Table 1. Herbs used as insomnia aids in western countries

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

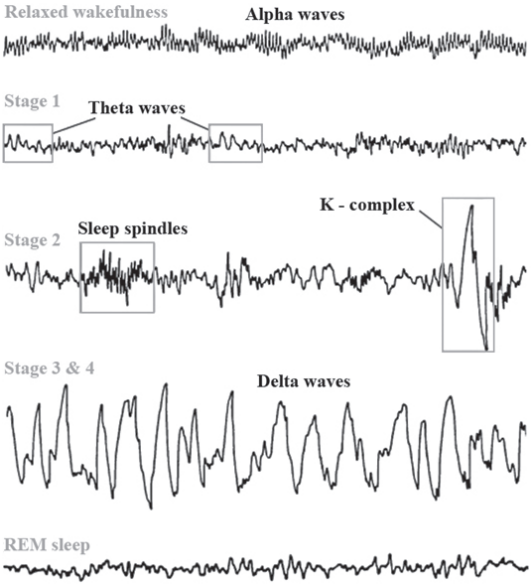

Fig. 2. EEG recording during sleep stages. The waking state with the eyes open is characterized by high frequency [15-60 Hz] and low-amplitude activity [-30 μV]. This pattern is called beta activity. Descent into stage 1 non-REM sleep is characterized by decreasing EEG frequency [4-8 Hz] and decreasing 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)].

nant EEG pattern is a low voltage, mixed frequency activity (10-30 μV and 16-25 Hz). Stage 2 NREM sleep is defined by the appearance of steep 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) or slow-wave sleep. REM sleep consists of relatively low voltage, mixed-frequency EEG activity, somewhat similar to stage 1 or wakefulness, with the appearance of episodic rapid eye movement (Fig. 2) (Steinfels *et al*., 1980; Armitage, 1995). For this reason, REM sleep has been called paradoxical sleep. One of the prime characteristics of REM sleep is a low level of muscle tone. In contrast to the diffuse brain structures involved in NREM sleep, the neuroanatomy of REM-active structures is relatively circumscribed. As previously mentioned, the primary oscillator that drives REM sleep appears to be located in the pontine tegmentum (PT). REM-on cholinergic neurons in the pedunculopontine tegmental (PPT) and laterodorsal tegmental (LDT) nuclei have high charge rates during wakefulness and REM sleep, and low discharge rates during NREM sleep. The norepinephrine and serotonin REM-off cells, which are excited by orexin neurons during wakefulness, start to wane in activity, which gradually release the cholinergic REM-on cells from their inhibitory effects (Gilbert and Lydic, 1994; Harris, 2005).

INSOMNIA

Insomnia is a widespread health complaint, and is one of the most common sleeping disorders. Insomnia is defined as a condition of unsatisfactory quality and inadequate quantity of sleep; it is characterized by difficulty initiating or maintaining sleep and early final waking. Insomnia occurs in 30-50% of people over 60 years old (Avidan, 2005). Gender differences exist as well, with older women being more likely to complain of insomnia than older men. The consequences of disturbed sleep are well known and may include difficulty sustaining attention and slowed response time. These consequences can be more pronounced in older adults and may even be misinterpreted as symptoms of dementia and Alzheimer's disease (Wu *et al*., 2010). Primary insomnia is sleeplessness that is not attributable to a medical, psychiatric, or environmental cause. The etiology of primary insomnia relates in part to psychological conditioning processes. Secondary insomnia is a symptom caused by medical, psychiatric, or environmental factors. According to the International Classification of Sleep Disorders, persistent insomnia of more than 4 weeks duration is regarded as significant insomnia (Bailes *et al*., 2009; Naude *et al*., 2010) . The causes of insomnia include psychiatric disorders; social disturbances; physical problems such as cardiopulmonary failure and chronic pain; drugs and foods such as caffeine, nicotine, alcohol, and amphetamines; as well as an irregular sleep-wake cycle. Approximately 35 percent of the adult population has insomnia during the course of a year. Up to seven percent indicate that insomnia is chronic, severe, or both 7-9. In contrast to the occasional sleepless night experienced by most people, insomnia may be a persistent or recurrent problem with serious complications, such as anxiety and depression (Doi *et al*., 2000; Eytan *et al*., 2011).

The economic burden of insomnia is very high, with the largest proportion of all expenses (76%) attributed to insomnia-related work absences and reduced productivity. As the economic burden of untreated insomnia is much higher than that of treating insomnia, future clinical trials should evaluate the cost-benefits, cost-utility, and cost-effectiveness of insomnia therapies (Daley *et al*., 2009). Effective treatments for insomnia include short and long acting benzodiazepines, although many of these are associated with adverse effects, daytime sedation (hangover) and dependence with continued use (Blatter *et al*., 1988). More modern drugs such as zolpidem, zopiclone and zaleplon avoid some of the adverse effects of benzodiazepines by selective binding to receptor sites (Meier *et al*., 1988; Ohta, 1996). Some individuals with insomnia or trouble sleeping use CAM therapies to treat their condition. In this review, we will demonstrate that widely available wake-promoting and sleep-promoting herbs, most of which have commonly been used in Europe and the USA. We also like to focus attention on some herbs that have traditionally been used to treat insomnia in oriental countries.

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 jujubae* 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 of St John's wort in treating depression and the suggestion that it may modulate REM and deep sleep; however, further study on the potential hypnotic properties of St John's wort is necessary (Sharpley *et al.*, 1998). Hypericin and pseudohypericin, are postulated to be the main active ingredients of St John's wort. The crude extract has significant in vitro receptor affinity for GABA, benzodiazepines, inositol triphosphate, and monoamine oxidase A and B (Butterweck, 2003; Kubin *et al.*, 2005). Chronic treatment with hypericum may also downregulate β_1- adrenoceptors and upregulate post-synaptic 5-HT_{1A} and 5-HT_2 receptors (Teufel-Mayer and Gleitz, 1997; Tadros *et al.*, 2009). In general, St John's wort is well tolerated, with minimal side-effects, including sedation, dry mouth, dizziness, gastrointestinal upset, restlessness, and hypersensitivity (Dugoua *et al.*, 2006). Potential drug interactions with serotonin reuptake inhibitors and monoamine oxidase inhibitors have been reported (Bennett *et al.*, 1998). It would be interesting to see whether Asian hypericums share similar psychotropic properties with those reported for St John's wort. Today, some people use St. John's wort to treat mild to moderate depression, anxiety and sleep disorders.

Kava Kava (*Piper methysticum*) is a large shrub cultivated in the South Pacific islands. Kava is the term used for both the plant and the beverage made from it. The beverage is prepared from the root of the *P. methysticum* shrub, also called the pepper plant. Recently, kava kava, in various preparations, has become popular in the United States and Europe, where it is generally sold as an herbal supplement to treat anxiety, stress and sleep disorders, often the underlying causes of insomnia (Wheatley, 2001b; Larzelere and Wiseman, 2002). 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 resinous 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.*, 2007). Valerian has been shown to have sleep-inducing, anxiolytic, and tranquilizing effects in *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 (Balderer 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,

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 neurasthenia, insomnia, and even schizophrenia (Huang *et al.*, 1991). The active biochemical ingredient of the herbal formula is unknown. Jujube contains stepharine, *N*-nor-nuciferine, asimilobine, and two kinds of *Zizyphus* saponin.

Arillus Longan is commonly consumed as the dried fruit of *Euphoria longana* (Family: Sapindaceae). The pulp of the dried fruit, as well as fresh Longanae Arillus, has been consumed for the treatment of anxiety and insomnia in Asian countries. In a pharmacological study, the extract of Longanae Arillus was proven to have anxiolytic activity (Okuyama *et al.*, 1999). The methanol extract of Longanae 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 quinquefolius* (American ginseng), and *Panax vietnamensis* (Vietnamese ginseng) are reported to have sleep-modulating effects. Constituents of most ginseng species include ginsenosides, polysaccharides, peptides, polyacetylenic 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* extracts 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 vietnamensis*, 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 bind to the benzodiazepine site 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 Longanae Arillus appear promising for the treatment of insomnia. Oriental botanical herbs especially, have not yet been fully studied for clinical use.

ACKNOWLEDGMENTS

This research was supported by the Medical Research Center program (2010-0029480) and by Priority Research Centers Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2009-0094035).

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