

A proprietary blend of *Magnolia* and *Ziziphus* extracts assists with sleep: an open-label assessment

James LaValle^{1*}, Maureen Pelletier¹, Laura LaValle¹, Marilyn Barrett², Uwe Koetter³,
Deanne Dolnick^{4§}

¹ LaValle Metabolic Institute, Cincinnati OH, USA

²Pharmacognosy Consulting, Mill Valley CA, USA

³Dr. Koetter Consulting, Uttwil, Switzerland

⁴Next Pharmaceuticals, Salinas CA, USA

*Principal Investigator

§Corresponding author

E-mail addresses:

JLV: jlavalle@Lmihealth.com

MP: mpelletier@Lmihealth.com

LLV: llavalle@Lmihealth.com

MB: marilyn@pharmacognosy.com

UK: koettu@mac.com

DD: ddolnick@nextpharmaceuticals.com

Abstract

Background

Magnolia officinalis bark and *Ziziphus spinosa* seed have a history of use in traditional Asian medicine for mild anxiety, nervousness and sleep-related problems.

Methods

A proprietary blend of extracts of *Magnolia officinalis* bark and *Ziziphus spinosa* seed (Seditol[®]) was tested for tolerability and efficacy in 295 volunteers with mild to moderate sleep difficulties. A questionnaire was used for the participants to self-report tolerance and efficacy following a minimum of two weeks of treatment with one capsule one hour before bedtime.

Results

None of the participants reported any significant adverse events. Of the 18 participants (6.4%) that had mild complaints, the most common concern (8 individuals) was of feeling groggy the next morning. Just over half of the participants (53.1%) received one bottle of Seditol and filled out one questionnaire. Just under half of the participants (46.9%) requested at least one additional bottle of Seditol and filled out more than one questionnaire (from 2 to 20; average 4.2 questionnaires). Of the individuals filling out just one questionnaire, the product was considered relaxing by 86.9%, assisting in a restful sleep by 82.8% and effective in reducing fatigue due to lack of sleep by 82.8%. In the group that returned more than one questionnaire, the scores were higher. However the differences between the two groups were not significant.

Conclusions

A proprietary blend of extracts of *Magnolia officinalis* bark and *Ziziphus spinosa* seed was well tolerated and found to effectively assist individuals with mild to moderate sleep difficulties.

Background

Insomnia is defined as difficulty falling asleep, difficulty staying asleep, or non-restorative sleep.[1] Approximately 30% of adults are thought to have one or more of the above symptoms at some time in their lives. Insomnia lasting for a period of days is often the result of acute and transient stress; and is a normal phenomenon. Insomnia lasting more than a few weeks can be related to other health issues.[2] Insomnia is thought to be caused by hyperarousal during the day due to worry and a preoccupation with stresses. This hyperarousal can cause an over activation of the hypothalamic-pituitary-adrenal (HPA) axis.[1]

Treatment for insomnia often begins with behavioral habits surrounding sleep. As a next step, over the counter prescriptions which contain anti-histamines such as diphenhydramine or doxylamine are available. These medications are undesirable as they may lose effectiveness over time due to tolerance and can cause grogginess the next morning. The most common FDA-approved prescriptions medications are benzodiazepine receptor agonists (benzodiazepines and non-benzodiazepines) which modulate GABA_A activity. Benzodiazepines such as triazolam (Halcion®) are best for short-term treatment, as long-term use may lead to adverse effects and withdrawal phenomena. Non-benzodiazepine receptor agonists such as zolpidem (Ambien®) are better choices. However some individuals may experience short term amnesia with zolpidem. Another option is a selective melatonin receptor agonist, ramelteon (Rozerem®), which has recently been approved by the FDA.[3]

Increasingly, patients are looking for alternatives to prescription drugs. A variety of preparations are available in the US market as dietary supplements; containing ingredients such as valerian, hops, kava and melatonin.[3]

We sought to examine the tolerability and efficacy of a combination of *Magnolia officinalis* bark extract and *Ziziphus spinosa* seed extract, in a proprietary product known as Seditol. Both *Magnolia* and *Ziziphus* preparations are used in traditional Asian medicine. Both are listed in the Pharmacopeia of the Peoples Republic of China (English Edition, 2005). Additionally, *Magnolia* bark is listed in the Japanese Pharmacopeia XIV (English Edition, 2001).

This study is an open-label, single-center, observational survey that included people with sleep difficulties, whose purpose was to obtain a subjective evaluation of the tolerability and effectiveness of a combination of *M. officinalis* bark and *Z. spinosa* seed extracts.

Methods

Test Material

Seditol is a proprietary blend of a patented extract of the bark of *Magnolia officinalis* Rehder & Wilson [Magnoliaceae] and an extract of the seeds of *Ziziphus spinosa* (Buhge) Hu ex. Chen.(syn. *Ziziphus jujube* var. *spinosa* (Bunge) Hu ex HF Chow) [Rhamnaceae].The magnolia extract is the subject of two US patents (Nos. 6,582,735 and 6,814,987) describing composition and methods of preventing, treating in managing sleeplessness, restlessness and weight gain due to stress or lack of sleep. Seditol is

characterized as containing a minimum of 2.7% honokiol, an active constituent of *Magnolia officinalis* bark and 0.1% spinosin, a chemical marker of quality for *Ziziphus spinosa* seed.

Study Design

This study is an open-label, single-center, observational survey that included people with sleep difficulties, whose purpose was to obtain a subjective evaluation of the tolerability and effectiveness of Seditol. Patients at the LaValle Metabolic Institute in Cincinnati, OH, filled out a General Health Questionnaire which detailed all aspects of their health, including sleep patterns. Participants were given the opportunity to be included in the study if they complained of difficulty sleeping. Specifically, if they had difficulty falling asleep, woke one to three times in the middle of the night and/or felt tired during the day due to a lack of sleep. Patients were excluded from participation in the study if they were under the age of 18, had allergies and/or if they were pregnant. Participants granted written permission before inclusion into the study.

Those that participated were instructed to take one 365 mg capsule Seditol one hour before going to bed, every night, for at least two weeks. They were instructed to take the capsule with a glass of water, to notify the investigator if they experienced any adverse reaction, to maintain their normal diet and exercise, to avoid alcoholic beverages, to keep the medication out of reach of children, and to avoid taking prescription drugs without the consent of their physician at the LaValle Institute.

They were instructed to answer a questionnaire regarding their experience with Seditol after taking the product for at least two weeks.

Tolerance was assessed using an open-ended question included in the questionnaire, “Did you dislike anything about Seditol?” The participants were also instructed to contact the clinic if they experienced any adverse events.

Efficacy was assessed in the questionnaire with three questions answered using a preset scale, as well as an open-ended question. The participants were asked to rate how “relaxed Seditol made them feel”, “restful a sleep they had after taking Seditol” and how “effective Seditol was in helping to reduce fatigue due to lack of sleep”. They were asked to circle a number on a 5-point scale, where a “5” meant extremely and a “1” meant not at all. The open-ended question was “Did you notice any additional beneficial effects of Seditol?”

A descriptive analysis of the results was conducted computing averages, medians and standard deviations.

Results

Study Population

A total of 295 individuals participated and they returned a total of 740 questionnaires. Twenty two (22) individuals were excluded from the effectiveness analysis due to incomplete enrollment data or ineligibility. Thus the safety population included 295

individuals and the effectiveness data came from 273 individuals. The efficacy population included 208 women (76.2% of the participants) and 65 men (23.8% of the participants) (Table 1). Their ages ranged from 18 to 87, with an average of 48.5 ± 11.3 years and a median of 49 years. Most of the participants (90%) were 35 years old, or older (n=236).

The body weight of the participants ranged from 105 to 414 pounds (average 165 ± 46). The average weight of the women was 149.5 ± 30.6 pounds and the average weight of the men was 214.8 ± 49.9 . According to their body mass index (BMI) (n=245) 44.1% of the participants were normal weight, 2.9% were underweight, 33.5% were overweight, and 19.6 % were considered obese (<http://www.nhlbisupport.com/bmi/>). The average BMI for the women was 24.9 ± 4.6 , just inside the BMI for normal weight (BMI up to 24.9). The BMI's for the participating men were on average heavier than that of the women. The average BMI for the men was 29.8 ± 6.0 , just inside the cut off for overweight, on the borderline of obese (cut off BMI 29.9).

Information as to whether or not the participants had previously used relaxants and/or sleeping pills was provided by 267 individuals. The population with prior use was 27.7% of the total (62 women and 12 men).

Tolerability

A total of 295 individuals took Seditol and made up the group providing information on acceptability of the product. Slightly less than half of these participants (43.4%; n=128) returned to the clinic requesting more Seditol. The latter individuals took Seditol for a

longer period of time: an average of 4.2 months with a range of 2 to 20 months. During that time, no significant adverse events were reported by any of the participants.

When asked in the open-ended question, “did you dislike anything about Seditol?” Two hundred sixty two individuals (89%) did not report any dislikes. Forty (14%) individuals responded to the question with a comment. Eighteen (6%) individuals responded with a mild unfavorable event: a feeling of grogginess in the morning (8; 2.7%), bad dreams (4; 1.4%), headaches (3; 1.0%), and there was one comment each of dry mouth, joint pain, and drowsy at night. Nineteen of the remarks were regarding the effectiveness of Seditol: did not work (13); bad taste (2); takes a while to work (2); doesn’t work long enough, discontinued taking before the end of 2 weeks. One person didn’t like the blue color and another wanted the product to be more readily available.

Effectiveness

Before receiving Seditol, the volunteers rated themselves as having mild to moderate difficulties with sleep in a general questionnaire and in their visit with the clinic health provider. The sleep difficulties included falling asleep, waking one to three times in the middle of the night and/or felt tired during the day due to a lack of sleep. The most common of these complaints was waking in the night. When the population was partitioned according to age, those 34 years old and younger had the greatest difficulty falling asleep, while those 35 years old and older complained most about sleeping through the night. When the population was subdivided by their BMI or by their sex, there was no difference between the groups in difficulties with sleep.

Just over half of the participants included in the effectiveness analysis (53.1%; 145 of 273) received one bottle of Seditol and filled out one questionnaire. Just under half of the participants (46.9%; n=128) requested at least one additional bottle of Seditol and filled out more than one questionnaire. The number of questionnaires filled out by these individuals ranged from 2 to 20, the average was 4.2 each and the total was 539.

The participants scored the effects of Seditol on a scale of 1 to 5, with 5 being the best possible. Of those 145 individuals that only returned one questionnaire after taking Seditol: the average score for how “relaxed Seditol made them feel” was 3.39, the average score for how “restful a sleep they had after taking Seditol” was 3.60 and that for how “effective Seditol was in helping to reduce fatigue due to lack of sleep” was 3.45 (Table 2). Of those who returned more than one questionnaire, the average scores for relaxation, restfulness and effectiveness were higher at 3.83, 3.83 and 3.80. However the differences in scores between the two groups were not significant.

The product was considered to be beneficial if the subject rated it with a score of 3 or higher. Accordingly, of the 145 individuals that only returned one questionnaire; 86.9% rated Seditol as relaxing, 82.8% rated it as assisting in a restful sleep and 82.8% rated it as effective in reducing fatigue. In the group that returned more than one questionnaire; 96.7% of the responses to the question regarding relaxation, 94.1% of the responses regarding a restful sleep and 94.2% of the responses regarding effectiveness in reducing fatigue were positive. There were no significant differences in responses between those who filled out one questionnaire and those who filled out multiple questionnaires.

There were no significant differences in the responses to the questionnaire when comparing women and men. There were also no differences when comparing those who had previously taken relaxants and/or sleeping pills to those who had not.

Fifty individuals responded to the open-ended question regarding benefits. Of those, half (50%) responded that they slept better, or now slept through the night. The other comments were that they felt more relaxed (12%), had more energy (10%), fell asleep more easily (8%), did not wake feeling groggy (8%), felt refreshed (6%), had better dreams (2%), preferred Seditol to other supplements (2%) and were generally pleased (2%).

Discussion

Seditol was tolerated well by all participants. There were no significant adverse events and 87% of individuals did not report any dislikes. The most commonly reported problem was of feeling groggy in the morning; reported by 2.6% of the participants. The botanical ingredients in Seditol have been rated as to their safety in a reference titled, *The American Herbal Products Association's Botanical Safety Handbook*. This book lists both *Magnolia officinalis* Rehd. et Wils. bark and *Ziziphus spinosa* Hu seed as Class 2b: not to be used during pregnancy.[4]

A single-dose oral toxicity test was conducted in rats given 5000 mg Seditol/kg body weight. A group of 10 male and female Sprague Dawley rats were given Seditol and observed for 14-days. Clinical abnormalities observed included transient incidence of

mucoid stools, congested breathing, rales and dark material around the facial area. No significant gross internal findings were observed at necropsy on day 14. The acute oral LD₅₀ was estimated to be greater than 5g/kg in the rat. [5]

The safety of Magnolia bark extracts has been determined in genotoxic studies *in vitro* with strains of *Salmonella typhimurium* and *Escherichia coli*, Chinese hamster ovary cells, V79 cells from Chinese hamster lung tissue and *in vivo* in the immature erythrocytes of mice. [6,7]. Magnolia bark extract has also been reported to be safely consumed in 21-day and 90-day subchronic toxicity studies in rats with doses up to 240 mg extract/kg body weight. [8] Similar safety studies on *Ziziphus* seed extracts were not available in the literature.

In this study, Seditol was considered beneficial by over 80% of the participants who took it for the first time. Significantly, 47% of the total participants returned to the clinic to request an additional supply. Seditol contains extracts of *Magnolia officinalis* bark and *Ziziphus spinosa* seed, which have been traditionally used in Asia for mild anxiety, nervousness and sleep-related problems.[9,10] In addition to traditional use, animal and *in vitro* studies provide further evidence for the activity of these extracts.

Two constituents of Magnolia bark extract, magnolol and honokiol, have been identified as having anxiolytic activity in the elevated plus maze test in mice. It was demonstrated that the treatment effects improved gradually over time, with no further improvement after 7 days.[11] Honokiol, was more active than magnolol, and demonstrated activity in

the plus maze test with a dose of 0.2 mg/kg for 7 days. Importantly, honokiol, which exhibited activity in mice at a dose similar to that of diazepam (a benzodiazepine), did not exhibit the side effects known to be produced by this class of drugs.[12,13]

Benzodiazepine drugs reduce anxiety and induce sleep through interactions with the GABA_A receptor. *In vitro* receptor binding studies suggest that honokiol and magnolol interact with the GABA_A receptor and this may explain the anxiolytic action of the magnolia extract. [14,15,16] A constituent identified in another species of Magnolia, obovatol from *Magnolia obovata*, has shown similar anxiolytic activity in the elevated plus maze test in mice and also is reported to interact with the GABA_A receptor. [17]

Animal and *in vitro* studies indicate that extracts of *Ziziphus spinosa* seed have anxiolytic, sedative and hypnotic effects. A traditional Chinese formula (Suanzaoren), in which *Ziziphus* is considered the key ingredient, caused sedative activity (spontaneous motion assay) and hypnotic activity (sleep) when administered orally to mice.[10] An extract of *Ziziphus* seeds demonstrated anxiolytic activity in the black and white test as well as the elevated plus maze assay. [18] Activity guided fractionation identified spinosin as an active chemical constituent of *Z. spinosa*. [10] Spinosin augmented pentobarbital-induced sleep, increasing sleep time and reducing sleep latency in mice. Further studies in mice indicated that spinosin might act through a serotonergic mechanism. [19] Other research on *Ziziphus* identified sanjoinine A, another constituent of the seeds, as active in augmenting pentobarbital-induced sleeping behavior through a GABA-ergic mechanism.[20] *In vitro* receptor binding studies with a *Z. spinosa* seed

extract demonstrated an interaction with serotonin receptors (5-HT_{1A} and 5-HT₂) and GABA_A receptors.[21]

Conclusion

In conclusion, in this open label study with 295 volunteers, Seditol was found to be well tolerated. Seditol was also found to effectively assist individuals with mild to moderate sleep difficulties.

Competing Interests

This research was supported by Next Pharmaceuticals, Salinas, CA. Dietary supplements supplied by Next Pharmaceuticals are offered for sale at the LaValle Metabolic Institute. MB and UK are consultants to Next Pharmaceuticals.

Authors contributions

JLV was the principal investigator. JLV, MP, LLV and DD designed, coordinated and executed the study. MB and UK conducted the analysis and interpretation of the data. MB, UK and DD drafted the manuscript.

References

1. Roth T: **Insomnia: definition, prevalence, etiology, and consequences.** *J Clin Sleep Med.* 2007, 3(5 Suppl):S7-10.
2. Wing YK: **Herbal treatment of insomnia.** *Hong Kong Med J.* 2001,7(4):392-402.
3. Ramakrishnan K, Scheid DC: **Treatment options for insomnia.** *Am Fam Physician.* 2007, 76(4):517-26.
4. McGuffin M, Hobbs C, Upton R, Goldberg A: *American Herbal Products Association's Botanical Safety Handbook.* Boca Raton, CRC Press 1997.

5. Rodabaugh DD: An Acute oral toxicity study in rats with NP04-1 (Seditol™). *Final Report Study No. 3517.10*. Charles River Laboratories, Inc, Spencerville, Ohio. March 26, 2004.
6. Li N, Song Y, Zhang W, Wang W, Chen J, Wong AW, Roberts A: **Evaluation of the in vitro and in vivo genotoxicity of magnolia bark extract.** *Regul Toxicol Pharmacol.* 2007, 49(3):154-9.
7. Zhang B, Maniatis T, Song Y, Zhang W, Zhang X, Li N, Chen J, Wong AW, Roberts A: **Evaluation of magnolia bark extract in chromosomal aberration assays.** *Mutat Res.* 2008, 654(2):133-7.
8. Liu Z, Zhang X, Cui W, Zhang X, Li N, Chen J, Wong AW, Roberts A: **Evaluation of short-term and subchronic toxicity of magnolia bark extract in rats.** *Regul Toxicol Pharmacol.* 2007, 49(3):160-71.
9. Kuribara H, Kishi E, Hattori N, Okada M, Maruyama Y: **The anxiolytic effect of two oriental herbal drugs in Japan attributed to honokiol from magnolia bark.** *J Pharm Pharmacol.* 2000, 52:1425-1429
10. Li YJ, Bi KS: **Study on the therapeutic material basis of traditional Chinese medicinal preparation suanzaoren decoction.** *Chem Pharm Bull (Tokyo)* 2006, 54: 847-851
11. Maruyama Y, Kuribara H, Morita M, Yuzurihara M, Weintraub ST: **Identification of magnolol and honokiol as anxiolytic agents in extracts of saiboku-to, an oriental herbal medicine.** *J Nat Prod.* 1998, 61:135-138

12. Kuribara H, Kishi E, Hattori N, Yuzurihara M, Maruyama Y: **Application of the elevated plus-maze test in mice for evaluation of the content of honokiol in water extracts of magnolia.** *Phytother Res.* 1999, 13:593-596
13. Kuribara H, Stavinoha WB, Maruyama Y: **Honokiol, a putative anxiolytic agent extracted from magnolia bark, has no diazepam-like side-effects in mice.** *J Pharm Pharmacol.* 1999, 51:97-103
14. Squires RF, Ai J, Witt MR, Kahnberg P, Saederup E, Sterner O, Nielsen M: **Honokiol and magnolol increase the number of [³H] muscimol binding sites three-fold in rat forebrain membranes in vitro using a filtration assay, by allosterically increasing the affinities of low-affinity sites.** *Neurochem Res.* 1999, 24:1593-1602
15. Ai J, Wang X, Nielsen M: **Honokiol and magnolol selectively interact with GABA_A receptor subtypes in vitro.** *Pharmacology* 2001, 63: 34-41
16. Kim HJ, Baburin I, Khom S, Hering S, Hamburger M: **HPLC-based activity profiling approach for the discovery of GABA_A receptor ligands using an automated two microelectrode voltage clamp assay on *Xenopus* oocytes.** *Planta Med.* 2008, 74(5):521-6.
17. Seo JJ, Lee SH, Lee YS, Kwon BM, Ma Y, Hwang BY, Hong JT, Oh KW: **Anxiolytic-like effects of obovatol isolated from *Magnolia obovata*: involvement of GABA/benzodiazepine receptors complex.** *Prog Neuropsychopharmacol Biol Psychiatry.* 2007, 31(7):1363-9.
18. Peng WH, Hsieh MT, Lee YS, Lin YC, Liao J: **Anxiolytic effect of seed of *Ziziphus jujuba* in mouse models of anxiety.** *J Ethnopharmacol.* 2000, 72(3):435-41.

19. Wang LE, Bai YJ, Shi XR, Cui XY, Cui SY, Zhang F, Zhang QY, Zhao YY, Zhang YH: **Spinosin, a C-glycoside flavonoid from semen Ziziphi Spinozae, potentiated pentobarbital-induced sleep via the serotonergic system.** *Pharmacol Biochem Behav.* 2008, 90(3):399-403.
20. Ma Y, Han H, Eun JS, Kim HC, Hong JT, Oh KW: **Sanjoinine A isolated from Ziziphi Spinosi Semen augments pentobarbital-induced sleeping behaviors through the modification of GABA-ergic systems.** *Biol Pharm Bull.* 2007, 30(9):1748-53.
21. Liao JF, Jan YM, Huang SY, Wang HH, Yu LL, Chen CF: **Evaluation with receptor binding assay on the water extracts of ten CNS-active Chinese herbal drugs.** *Proc Natl Sci Counc Repub China B* 1995, 19:151-158

Tables

Table 1 - Participants

	Women	Men	Total
Number	208	65	273
Age	48.3 ± 10.8	49.2 ± 12.7	48.5 ± 11.3
BMI	24.9 ± 4.6	29.8 ± 6.0	26.1 ± 5.4
Single questionnaire	113 (77.9%)	32 (22.1%)	145 (53.1%)
Multiple questionnaires	95 (74.2%)	33 (25.8%)	128 (46.9%)

Characterization of the participants included in the efficacy analysis. Age and BMI are presented as averages plus/minus standard deviations. The number of individuals filling out single or multiple questionnaires are given along with the percentage of each group as a total of the efficacy population.

Table 2 - Questionnaire Responses

A. Single Questionnaire Response

	Women	Men	Total
Relaxed	3.35	3.53	3.39
Restful Sleep	3.55	3.77	3.60
Effective in Reducing Fatigue	3.38	3.71	3.45

B. Multiple Questionnaire Responses

	Women	Men	Total
Relaxed	3.83	3.86	3.83
Restful Sleep	3.81	3.89	3.83
Effective in Reducing Fatigue	3.79	3.83	3.80

The participants were asked to rate how “relaxed Seditol made them feel”, “restful a sleep they had after taking Seditol” and how “effective Seditol was in helping to reduce fatigue due to lack of sleep” using a 5-point scale, where a “5” meant extremely and a “1”

meant not at all. The average scores in response to the questionnaire are listed above, separated by those who filled out one questionnaire and those who filled more than one questionnaire.