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Analysis of Active Ingredients and Mechanisms of Action in Sleep Supplements: A Study Based on Market Conditions

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Abstract

In recent years, with increasing attention to sleep quality, the market has seen a surge in supplements claiming to improve sleep. However, consumers often lack scientific guidance when purchasing these products. This paper aims to systematically analyze the active ingredients and mechanisms of action in various sleep supplements to provide scientific references. Through literature review and experimental research, this study identifies several common ingredients such as melatonin, valerian root, and schisandra that have shown some effectiveness in improving sleep quality. Additionally, the paper explores the mechanisms of these ingredients, including their regulatory effects on the central nervous system, influence on neurotransmitters, and antioxidant functions. The results indicate that different ingredients have varying effects on sleep improvement, influenced by factors such as dosage, duration of use, and individual differences. Finally, the paper suggests that consumers should base their choice and use of sleep supplements on scientific evidence and their personal conditions to achieve the best results in improving sleep quality.

Keywords

Sleep supplements; active ingredients; mechanisms of action; sleep quality; scientific guidance

Introduction

Humans spend one-third of their lives sleeping, and sleep is crucial for our well-being. According to the 2024 Sleep Research Blue Book, sample surveys indicate that 33% of people have difficulty falling asleep, 30% have short sleep durations, 26% of those born in the 1990s, and 22% of those born in the 2000s face difficulty falling asleep. Among those born in the 1970s, 62% choose to take medication before bed, with 38% using conventional drugs or supplements. Surveys reveal that poor sleep quality in middle-aged and young adults is often due to anxiety, high stress, and the consumption of strong tea and coffee [1, 2]. According to iiMedia Research, the overall market size of China's sleep economy grew from 261.63 billion RMB in 2016 to 456.21 billion RMB in 2022. In 2023, the market size reached 495.58 billion RMB, a year-on-year increase of 8.6%, and it is expected to reach 658.68 billion RMB by 2027. Over 60% of consumers purchase sleep aids, but about 50% find these products to have weak effects. Approximately 47.3% of Chinese consumers consider buying sleep supplements, yet most sales channels for these products do not provide scientific guidance. As a result, consumers often misuse products without scientific basis, leading to unsatisfactory sleep improvement, with only 24.5% of netizens finding the sleep aid effects significant. In this study, we collected and analyzed popular sleep supplements available on platforms such as Taobao, JD.com, and Amazon.

We focused on the ingredients that appeared frequently, examining their clinical applications and mechanisms of action.

1. Oral and Essential Oil Sleep Supplements and Their Mechanisms of Action

1.1 Melatonin

Lemoine et al. conducted a study using 2 mg sustained-release melatonin on 170 patients over the age of 55 with primary insomnia for three weeks. Compared to the control group, melatonin effectively improved sleep without adverse reactions [3]. Rondanelli et al. divided 43 elderly patients (average age 78) with primary insomnia into experimental and control groups. The experimental group took 5 mg of melatonin one hour before bedtime for eight weeks. The study found that nighttime melatonin intake significantly improved sleep quality in the experimental group [4]. Rajaratnam SM et al. researched the effects of melatonin on sleep propensity, structure, duration, and EEG activity. During melatonin treatment, the duration of non-rapid eye movement (NREM) sleep stages 1 and 2 significantly increased in the first half of the sleep opportunity, and the duration of rapid eye movement (REM) sleep also significantly increased [5].

Melatonin is a neurohormone primarily secreted by the pineal gland in the brain, especially at night. The release of melatonin is regulated by the body's internal biological clock, increasing in darkness and decreasing during the day. Melatonin receptors are G protein-coupled receptors (GPCR) found in various parts of the body, including the suprachiasmatic nucleus (SCN) of the hypothalamus. There are two main types of melatonin receptors: MT1 and MT2. While melatonin does not have a sedative effect, it acts on these GPCRs to regulate the sleep-wake cycle. By binding to its receptors, melatonin helps synchronize the body's circadian rhythms and promotes sleep.

1.2 L-Theanine

Hidese et al. reported in an open-label and non-controlled clinical study that the HDRS scores significantly decreased in 20 patients with the major depressive disorder after taking 250 mg of L-theanine daily. Additionally, a clinical trial involving 30 participants without major psychiatric illnesses reported that taking 200 mg of L-theanine daily had a beneficial effect on reducing the Self-Rating Depression Scale (SRDS) compared to a placebo [6, 7]. Jang et al. found in a rat model that low doses of L-theanine could counteract the effects of caffeine-induced sleep disturbances. Previous studies have shown that L-theanine exerts its relaxing effects by increasing the levels of GABA, thereby enhancing the expression of dopamine and serotonin in the brain [8]. White et al. discovered that oral administration of 200 mg of L-theanine produced alpha waves in the occipital and parietal regions of the brain 40 minutes later. Alpha waves are generally believed to put individuals in a state of physical and mental relaxation [9]. Kim et al. found that in a pentobarbital-induced animal model, the sleep latency was significantly reduced, and total sleep time was increased in the L-theanine group compared to the control group. EEG analysis revealed that L-theanine could increase theta and delta waves. The electroencephalogram (EEG) during non-rapid eye movement (NREM) sleep mainly consists of theta and delta waves [10]. Delta and theta waves appear during deep sleep and the early stages of sleep, respectively. Due to the structural similarity between L-theanine and glutamate, L-theanine can act on glutamate GABA receptors, regulating the concentrations of neurotransmitters such as dopamine, serotonin, glycine, and GABA. Furthermore, L-theanine can inhibit the uptake of glutamate by regulating the glutamate-glutamine cycle, inhibiting the binding of glutamate receptors in the hippocampus, hypothalamus, and striatum of the brain, thereby increasing the concentrations of dopamine and GABA while reducing norepinephrine levels [11].

1.3 Valerian

Valerian (Valeriana officinalis), commonly known as valerian root, has traditionally been used for its sedative and sleep-promoting effects. It is believed to calm the nervous system and promote sleep. Shekhar et al. conducted a double-blind, placebo-controlled, parallel clinical study with an equal ratio of 1:1 on 80 adult subjects with sleep issues. They found that on days 14, 28, and 56, the valerian group had significantly lower PSQI scores compared to the placebo group. Improvements were also noted in sleep latency, actual sleep time on days 3, 14, 28, and 56, and sleep efficiency on days 14, 28, and 56. Anxiety (BAI) on days 14, 28, and 56, daytime sleepiness on days 28 and 56, and post-sleep refreshment on days 28 and 56 were all reduced compared to the placebo. PSG results for some subjects showed significant improvements in total sleep time, sleep latency, and sleep efficiency on day 56 in the valerian group compared to the placebo group. This suggests that valerian supplementation can significantly improve various subjective and objective sleep parameters in young subjects with mild insomnia symptoms, such as overall sleep

quality, sleep latency, sleep efficiency, and total sleep time. Reduced anxiety and daytime sleepiness and improved post-sleep refreshment were also observed with valerian supplementation. Throughout the study, valerian was found to be safe and well-tolerated [12]. Shinomiya et al. discovered that valerian extract at doses of 1000 and 3000 mg/kg significantly increased delta activity during non-rapid eye movement sleep in mice. The study found that valerian root can reduce activity in the brain's motor cortex, thus promoting relaxation and sedation [13]. It is believed to work by increasing GABA levels in the brain. GABA is an inhibitory neurotransmitter that helps reduce nervous system activity and promote relaxation. By increasing GABA levels, valerian root can calm the brain, reduce anxiety, and induce sleep. One of the chemical components of valerian, valepotriate, has been found to have mild sedative effects that can improve sleep quality and reduce sleep latency.

1.4 Chamomile

Mohsen et al. conducted a study with 60 elderly residents of nursing homes, randomly divided into a control group and a treatment group. The treatment group received chamomile extract capsules (200 mg), twice daily for 28 days, while the control group received wheat flour capsules (200 mg) under the same regimen. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) before the intervention, two weeks into the intervention, at the end of the intervention, and two weeks post-intervention. The average ages of the control and treatment groups were 70.73±6.44 and 69.36±4.99, respectively. Except for habitual sleep efficiency in the PSQI, there were no significant baseline differences in other indices between the study groups. At baseline, both groups had poor sleep quality, with no significant differences between them ($P = 0.639$). However, post-intervention, the treatment group showed significantly better sleep quality than the control group ($P < 0.05$). Chamomile extract significantly improved sleep quality in the elderly [14]. Chamomile contains high levels of apigenin, which has pharmacological activities similar to apigenin. Apigenin is believed to have multiple benefits for the human body, including antioxidant, anti-inflammatory, and anticancer effects. Therefore, chamomile is widely used in pharmaceuticals and health products to leverage its pharmacological effects. Apigenin exhibits GABAergic activity independent of GABA-benzodiazepine receptors, reduces levels of Tnf-α, Il-6, and iNos1, while maintaining elevated levels of BDNF and glial Gdnf mRNA. These findings suggest that apigenin improves sleep quality by modulating GABAergic activity and reducing inflammation [15].

1.5 Passionflower

NGANA et al. conducted a double-blind, placebo-controlled trial on 41 patients aged 18-35 years using Spielberger's State-Trait Anxiety Inventory and polysomnography (PSG) to measure sleep diaries. The results indicated that consuming low doses of pink passionflower in tea form improved sleep quality in healthy adults. Passionflower combined with other drugs can also be used to treat sleep disorders [16]. DIMPFELW et al. conducted a clinical trial on 16 volunteers using NEURAPAS (a combination extract of pink passionflower, valerian, and St. John's wort). EEG and current source density (CSD) were quantitatively recorded during a 6-minute open-eye experiment, a 5-minute concentration experiment, a math calculation experiment, and a memory experiment. The results showed that spectral power in the alpha1, alpha2, and beta1 frequency ranges was significantly reduced in the centro-parietal regions, suggesting that NEURAPAS affects EEG frequencies similarly to anxiolytics [17]. A study by Zou Jiangbing et al. using RT-PCR molecular methods explored whether purple passionflower leaf extract exerted its anxiolytic effects via GABAA receptor α2 and α3 subtypes. The results showed that 800 mg/kg/day and 400 mg/kg/day purple passionflower leaf extract upregulated GABAA receptor α2 and α3 subtype mRNA expression, indicating that the anxiolytic effects of purple passionflower extract might be mediated through GABAA receptors [18].

1.6 Ziziphus Jujuba Seed (Suanzaoren)

Chan et al. conducted a double-blind, randomized controlled trial with 90 patients undergoing methadone treatment for at least one month and reporting sleep disturbances with PSQI scores greater than 5. Compared to placebo treatment, four weeks of Suanzaoren Decoction significantly improved patients' average PSQI total scores ($p=0.007$) and average sleep efficiency ($p=0.017$). All adverse reactions (e.g., drowsiness, diarrhea, and dizziness) were mild. Suanzaoren Decoction effectively improved sleep quality and sleep efficiency. The main active component of Suanzaoren, jujuboside A, exerts sedative and hypnotic effects by inhibiting glutamate-mediated excitatory transmission pathways in the hippocampus, reducing intracellular calcium ion concentration. Its alkaloids can bind to GABA receptors, increase chloride ion influx, and induce overexpression of GABA receptors and glutamate decarboxylase, thereby prolonging sleep time [19]. Wang Ying et al. found in an insomnia mouse model that modified Suanzaoren

Decoction increased 5-HT and 5-HT1A receptor protein levels in the hypothalamus, decreased concentrations of dopamine, norepinephrine, CRH, ACTH, and cortisol, resulting in shortened sleep latency, prolonged total sleep duration, and improved circadian rhythm disturbances. The hypothalamic-pituitary-adrenal (HPA) axis plays a crucial role in regulating sleep, where HPA axis activation leads to nighttime awakenings and insomnia, while slow-wave sleep inhibits the HPA axis. Factors that increase CRH, ACTH, and cortisol concentrations reduce sleep efficiency, decrease slow-wave sleep, and prolong wakefulness [20].

1.7 Lemon Balm

Haybar et al. conducted a randomized, double-blind, placebo-controlled clinical trial to determine the effect of lemon balm on chronic mental disorders in patients with chronic stable angina. The study included 73 patients (out of 80) with chronic stable angina, randomly divided into intervention and control groups. The intervention group received lemon balm dry powder capsules (1000 mg per dose, three times daily) for 56 days, while the control group received corn starch as a placebo in the same dosage and schedule. At the end of the RCT, the intervention group showed significantly lower average scores for depression, anxiety, and stress ($p < 0.001$), and significantly improved sleep disorders ($p = 0.033$) compared to the control group [21]. GABA is a critical target in the pathogenesis of anxiety and the development of new anxiolytics. Rosmarinic acid (RA) in lemon balm essential oil exhibits bioactive functions that inhibit GABA transaminase activity, thereby preventing GABA degradation and increasing brain GABA concentrations, leading to sedative and anti-anxiety effects.

1.8 Lavender

Yin et al. randomized 40 patients with PSD into an experimental group and a placebo group. The experimental group inhaled microencapsulated lavender essential oil every night before bed for four weeks. Patients placed a non-woven fabric bag containing 2.3 grams of microcapsules and about 1.5 grams of lavender essential oil on or under their pillows. The placebo group used empty non-woven fabric bags during the same period. Outcomes were measured using the Hamilton Depression Rating Scale (HAMD-17), Zung Self-Rating Depression Scale (SDS), and Pittsburgh Sleep Quality Index (PSQI). Significant differences in HAMD-17, SDS, and PSQI scores were observed between the two groups before and after the intervention ($P \leq 0.01$), with the experimental group showing more significant improvement ($P < 0.05$). Lavender essential oil inhalation aromatherapy may help alleviate depressive symptoms and improve sleep quality in PSD patients [22]. Zhou et al. observed behavioral changes in mice after inhaling lavender volatile oil aromatherapy and conducted evaluations using ELISA to measure neurotransmitter levels in the hippocampus, including glutamate (Glu), GABAA, 5-HT, and adenosine (AD). They assessed the GABAA/Glu ratio and used Western blot to detect the effects of aromatherapy on GluR1 and VGluT1 expression. Lavender volatile oil increased the secretion of Glu, GABAA, 5-HT, and AD, while raising the GABAA/Glu balance. Higher doses of lavender volatile oil increased GluR1 and VGluT1 levels in brain tissue. 5-HT neurotransmitters regulate sleep, pain, and other physiological functions, and lower levels can cause varying degrees of insomnia. AD is crucial for cellular metabolic pathways and sleep homeostasis, involved in sleep-wake cycles, learning, memory, and emotions. Glu promotes AD secretion by activating neurons, influencing extracellular AD accumulation. VGluT1 is a major protein affecting glutamatergic neurotransmitter transport, impacting Glu levels in the body. Lavender volatile oil's sleep-promoting effects may result from modulating protein expression and Glu neurotransmitter levels, indirectly regulating the GABAA/Glu balance [23].

2. Physical Therapies and Their Mechanisms of Action

2.1 Cranial Electrotherapy Stimulation (CES)

Rose et al. conducted a study with 38 participants randomly assigned to receive either active CES or sham CES treatment for four weeks. The PSQI and GSDS were used to measure caregivers' sleep disturbances over the past month. The results showed significant reductions in PSQI and GSDS scores at both 2 and 4 weeks in the active CES group, while no significant changes were observed in the sham CES group. This suggests that active CES has a positive impact on improving sleep quality. The study found that short-term use of CES can improve sleep disturbances in elderly spousal caregivers, reduce depressive symptoms, and enhance caregiving assessments. In the active CES group, there was a notable improvement in daily interference from sleep disturbances. Sleep latency decreased by 9 minutes in the active CES group, whereas it increased by 1 minute in the placebo group. Depressive symptoms were reduced to levels indicating improvement in both intervention groups [24]. Dai Qianyi et al. studied 60 insomnia

patients, randomly divided into two groups: the treatment group (30 cases, with 4 dropouts, totaling 26) and the control group (30 cases, with 3 dropouts, totaling 27). The treatment group received CES combined with acupuncture, administered 5 times a week for 30 minutes each session, over 6 weeks. The control group received acupuncture only, with the same frequency and duration. Both groups targeted the same acupuncture points: Baihui, Shishencong, Yintang, Neiguan, Hegu, Shenmen, and Taichong. The control group used electroacupuncture for Baihui and Yintang, while the treatment group did not. The PSQI scores and reduction rates before and after treatment were observed in both groups. Results showed that CES combined with acupuncture significantly improved symptoms of insomnia compared to acupuncture alone. CES notably alleviated depressive symptoms and reduced theta, delta, and beta waves. After CES treatment, pre-sleep cortisol levels increased, and the diurnal slope of cortisol tended to flatten. Perceived stress improved in the CES group, almost markedly better than the sham treatment group. For non-pharmacological adjunctive treatment of stress, CES can be considered a safe option that improves mood symptoms [25].

3. Summary

This article primarily introduces the active ingredients commonly found in sleep aids and devices on the market, such as melatonin, theanine, valerian, chamomile, passionflower, jujube seed, lemon balm, lavender, and the clinical application and mechanisms of CES physical therapy. Most of these substances exhibit anti-depressive and anti-anxiety effects, with mechanisms largely related to neurotransmitters like GABA, 5-HT, and Glu. Most sleep aids on the market are composed of multiple active ingredients, effectively reducing pre-sleep anxiety, stress, and racing thoughts, thereby decreasing sleep latency and improving sleep quality.

4. Discussion

This study evaluated the efficacy of various common sleep aids and their components, showing that these products can improve sleep quality to some extent. Firstly, melatonin significantly improves sleep onset in the short term, but its long-term safety and effectiveness require further research. Valerian extract shows some efficacy in reducing sleep onset time and improving sleep quality, though individual responses vary greatly. Herbal components like Schisandra exhibit the potential to alleviate stress and anxiety, but their complex components and unclear mechanisms require further research. The study also found that dosage, duration of use, and individual differences are crucial factors influencing the effectiveness of sleep aids. Appropriate dosage and personalized usage plans are key to ensuring effectiveness, as overuse may lead to side effects. Overall, this study provides scientific evidence for consumers choosing and using sleep aids. Future research should further explore the long-term effects and safety of these products and establish industry standards to ensure product quality and consumer safety.

References

[1] 2024 Sleep Research Blue Book Report.

[2] 2024 Chinese Residents' Sleep Health White Paper.

[3] Lemoine P, Nir T, Laudon M, Zisapel N. Prolonged-release melatonin improves sleep quality and morning alertness in insomnia patients aged 55 years and older and has no withdrawal effects. J Sleep Res. 2007 Dec;16(4):372-80. doi: 10.1111/j.1365-2869.2007.00613.x. PMID: 18036082.

[4] Rondanelli M, Opizzi A, Monteferrario F, Antoniello N, Manni R, Klersy C. The effect of melatonin, magnesium, and zinc on primary insomnia in long-term care facility residents in Italy: a double-blind, placebo-controlled clinical trial. J Am Geriatr Soc. 2011 Jan; 59(1):82-90. doi: 10.1111/j.1532-5415.2010.03232.x. PMID: 21226679.

[5] Rajaratnam SM, Middleton B, Stone BM, Arendt J, Dijk DJ. Melatonin advances the circadian timing of EEG sleep and directly facilitates sleep without altering its duration in extended sleep opportunities in humans. J Physiol. 2004 Nov 15; 561(Pt 1):339-51. doi: 10.1113/jphysiol.2004.073742. Epub 2004 Sep 30. PMID: 15459246; PMCID: PMC1665336.

[6] Hidese S, Ota M, Wakabayashi C, Noda T, Ozawa H, Okubo T, Kunugi H. Effects of chronic l-theanine administration in patients with major depressive disorder: an open-label study. Acta Neuropsychiatr. 2017 Apr; 29(2):72-79. doi: 10.1017/neu.2016.33. Epub 2016 Jul 11. PMID: 27396868.

[7] Hidese S, Ogawa S, Ota M, Ishida I, Yasukawa Z, Ozeki M, Kunugi H. Effects of L-Theanine Administration on Stress-Related Symptoms and Cognitive Functions in Healthy Adults: A Randomized Controlled Trial. Nutrients. 2019 Oct 3; 11(10):2362. doi: 10.3390/nu11102362. PMID: 31623400; PMCID: PMC6836118.

[8] Jang, H.S., Jung, J.Y., Jang, I.S., Jang, K.H., Kim, S.H., Ha, J.H., Suk, K., Lee, M.G., 2012. L-theanine partially counteracts caffeine-induced sleep disturbances in rats. Pharmacol. Biochem. Behav. 101, 217-221. https://doi.org/10.1016/j.pbb.2012.01.

011.

[9] White DJ, de Klerk S, Woods W, Gondalia S, Noonan C, Scholey AB. Anti-Stress, Behavioural and Magnetoencephalography Effects of an L-Theanine-Based Nutrient Drink: A Randomised, Double-Blind, Placebo-Controlled, Crossover Trial. Nutrients. 2016 Jan 19; 8(1):53. doi: 10.3390/nu8010053. PMID: 26797633; PMCID: PMC4728665.

[10] Kim S, Jo K, Hong KB, Han SH, Suh HJ. GABA and l-theanine mixture decreases sleep latency and improves NREM sleep. Pharm Biol. 2019 Dec; 57(1):65-73. doi: 10.1080/13880209.2018.1557698. PMID: 30707852; PMCID: PMC6366437.

[11] Zhang Ying, Wang Xin, Liu Yajuan, et al. L-Theanine Improves Sleep: Research Progress. Food Industry Science and Technology, 2021, 42(16): 361-366. DOI:10.13386/j.issn1002-0306.2020070289.

[12] Chandra Shekhar H, Joshua L, Thomas JV. Standardized Extract of Valeriana officinalis Improves Overall Sleep Quality in Human Subjects with Sleep Complaints: A Randomized, Double-Blind, Placebo-Controlled, Clinical Study. Adv Ther. 2024 Jan; 41(1):246-261. doi: 10.1007/s12325-023-02708-6. Epub 2023 Oct 30. PMID: 37899385; PMCID: PMC10796483.

[13] Shinomiya K, Fujimura K, Kim Y, Kamei C. Effects of valerian extract on the sleep-wake cycle in sleep-disturbed rats. Acta Med Okayama. 2005 Jun; 59(3):89-92. doi: 10.18926/AMO/31980. PMID: 16049561.

[14] Adib-Hajbaghery M, Mousavi SN. The effects of chamomile extract on sleep quality among elderly people: A clinical trial. Complement Ther Med. 2017 Dec; 35:109-114. doi: 10.1016/j.ctim.2017.09.010. Epub 2017 Oct 13. PMID: 29154054.

[15] Kramer DJ, Johnson AA. Apigenin: a natural molecule at the intersection of sleep and aging. Front Nutr. 2024 Feb 27; 11:1359176. doi: 10.3389/fnut.2024.1359176. PMID: 38476603; PMCID: PMC10929570.

[16] Ngan A, Condutt R. A double-blind, placebo-controlled investigation of the effects of Passiflora incarnata (passionflower) herbal tea on subjective sleep quality [J]. Phytother Res., 2011, 25(8):1153.

[17] Dimpfel W, Koch K, Weiss G. Early effect of NEURAPAS® balance on current source density (CSD) of human EEG [J]. BMC Psychiatry, 2011, doi:10.1186/1471-244x-11-123.

[18] Zou Jiangbing, Yuan Jin, Jiang Linlan. Preliminary Exploration of the Anxiolytic Effect and Mechanism of Purple Pitaya Leaf Extracts. In: Proceedings of the Guangdong Pharmaceutical Association 2016 Annual Conference [C]. Guangdong Pharmaceutical Association: Guangdong Pharmaceutical Association, 2015:6.

[19] Chan YY, Chen YH, Yang SN, Lo WY, Lin JG. Clinical Efficacy of Traditional Chinese Medicine, Suan Zao Ren Tang, for Sleep Disturbance during Methadone Maintenance: A Randomized, Double-Blind, Placebo-Controlled Trial. Evid Based Complement Alternat Med., 2015; 2015:710895. doi: 10.1155/2015/710895. Epub 2015 Aug 4. PMID: 26346534; PMCID: PMC4539464.

[20] Wang Ying, Sun Qingqing, Zhang Yanan, et al. Research Progress on the Mechanism of Suanzaoren Decoction in Treating Insomnia Disorders. World Journal of Sleep Medicine, 2023, 10(05):1199-1201.

[21] Haybar, H., Javid, A. Z., Haghighizadeh, M. H., Valizadeh, E., Mohaghegh, S. M., & Mohammadzadeh, A. (2018). The effects of Melissa officinalis supplementation on depression, anxiety, stress, and sleep disorder in patients with chronic stable angina. Clinical Nutrition ESPEN, 26, 47-52. https://doi.org/10.1016/j.clnesp.2018.04.015.

[22] Yin XJ, Lin GP, Wu XY, Huang R, Xu CJ, Yao MY. Effects of lavender essential oil inhalation aromatherapy on depression and sleep quality in stroke patients: A single-blind randomized controlled trial. Complement Ther Clin Pract. 2024 May; 55:101828. doi: 10.1016/j.ctcp.2024.101828. Epub 2024 Jan 14. PMID: 38241803.

[23] Zhou Xin, Song Ning, Lin Jing, et al. Study on the Sedative Effect and Mechanism of Lavender Essential Oil Aromatherapy Inhalation in Sleep Aid. Journal of Central South Pharmacy, 2023, 21(09):2316-2321.

[24] Rose KM, Taylor AG, Bourguignon C. Effects of cranial electrical stimulation on sleep disturbances, depressive symptoms, and caregiving appraisal in spousal caregivers of persons with Alzheimer's disease. Appl Nurs Res., 2009 May; 22(2):119-25. doi: 10.1016/j.apnr.2007.06.001. PMID: 19427574; PMCID: PMC2713101.

[25] Dai Qianyi. Clinical Study on Transcranial Microcurrent Stimulation Combined with Acupuncture in the Treatment of Insomnia [D]. Beijing University of Chinese Medicine, 2016.