

CHAPTER 8

PHYTOTHERAPEUTIC APPLICATIONS FOR INSOMNIA

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BACKGROUND

Insomnia, a severe sleep problem, is a growing health hazard. It poses a major threat to mental health, heart function and the immune system. Anxiety and depression are the two main problems affected by insomnia. Mechanisms underlying the association between insomnia, anxiety, and depression are being investigated. Poor sleep quality and depression are prevalent during pregnancy and may negatively impact maternal-fetal outcomes. Sleep problems in infants and young children are common and often underdiagnosed. Insomnia complaints in children and adolescents should be taken into account. The American College of Physicians developed a guideline on the management of insomnia in adults. Insomnia is also common in the elderly. Nonpharmacological treatment options have favorable and enduring benefits compared to pharmacological therapy. In the first line, improving sleep-hygiene parameters and considering cognitive-behavioral therapy are the nonpharmacological interventions. Then come pharmacological agents in combination with behavioral modifications.¹⁻⁸

Chronic insomnia impairs the quality of life. It can rob the individuals of their families, jobs and even their sanity. There are prescribed medicines used for the treatment of insomnia. They are effective but, at the same time, exhibit significant adverse effects. Thus, patients are in need for an alternative treatment to cure this problem. So far, some herbs have been studied for their potential sedative and hypnotic activities. They are expected to improve sleep. Most of them exert their actions on the central nervous system with a major influence on the inhibitory gamma-aminobutyric acid (GABA), which promotes relaxation and reduce anxiety or serotonin neurological systems.⁹⁻¹⁴

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efficiency. Its procyanidin content increases tryptophan availability, reduces inflammation and may partially improve insomnia. Milk fermented with a strain of *Lactobacillus brevis* with GABA-producing capacity may improve sleep.⁸¹⁻⁸⁴

Data on phytotherapeutic applications for insomnia are still not sufficient. Natural remedies are considered much safer than pharmacological agents; however, further studies are needed to evaluate their risk and the safety concerns for many supplements. Potential integrative approaches without serious side effects are being investigated. The need for a good understanding of the safety and the efficiency of medicinal plants for the treatment of insomnia stimulates further investigations to manage this commonly observed health problem.

Studies, which will be performed, should cover safe dosages, as well as doses confined to herbs suggested to be used during insomnia treatment. Standard measures designed for the quality/quantity of sleep should also be considered. They are also expected to focus on active constituents in the herbs and their potential adverse effects. The matter concerning their interactions with prescribed drugs, as well as with other herbs is a great problem to be largely investigated.

REFERENCES

1. Lin YF, Liu ZD, Ma W, Shen WD. Hazards of insomnia and the effects of acupuncture treatment on insomnia. *J Integr Med.* 2016; 14(3):174-86.
2. Blake MJ, Trinder JA, Allen NB. Mechanisms underlying the association between insomnia, anxiety, and depression in adolescence: Implications for behavioral sleep interventions. *Clin Psychol Rev.* 2018; 63:25-40.
3. Pauley AM, Moore GA, Mama SK, Molenaar P, Downs DS. Associations between prenatal sleep and psychological health: A systematic review. *J Clin Sleep Med.* [Online ahead of print, 2020 Jan 31]
4. Owens JA, Moore M. Insomnia in infants and young children. *Pediatr Ann.* 2017; 46(9):e321-e326.
5. Nunes ML, Bruni O. Insomnia in childhood and adolescence: clinical aspects, diagnosis, and therapeutic approach. *J Pediatr (Rio J).* 2015;91(6 Suppl 1):S26-35.
6. Qaseem A, Kansagara D, Forcica MA, Cooke M, Denberg TD; Clinical guidelines committee of the American College of Physicians. Management of chronic insomnia disorder in adults: A clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2016;165(2):125-33.
7. Patel D, Steinberg J, Patel P. Insomnia in the elderly: A review. *J Clin Sleep Med.* 2018;14(6):1017-1024.
8. Bragg S, Benich JJ, Christian N, Visserman J, Freedy J. Updates in insomnia diagnosis and treatment. *Int J Psychiatry Med.* 2019; 54(4-5):275-289.
9. National Sleep Foundation. *Insomnia.* 2019.
10. Singh A, Zhao K. Treatment of insomnia with traditional Chinese herbal medicine. *Int Rev Neurobiol.* 2017; 135(5): 97-115.
11. Leach MJ, Page AT. Herbal medicine for insomnia: A systematic review and meta-analysis. *Sleep Med Rev.* 2015; 24: 1-12.
12. Liu L, Liu C, Wang Y, Wang P, Li Y, Li B. Herbal medicine for anxiety, depression and insomnia. *Curr Neuropharmacol.* 2015; 13(4): 481-493
13. Romero K, Goparaju B, Russo K, Westover MB, Bianchi MT. Alternative remedies for insomnia: a proposed method for personalized therapeutic trials. *Nat Sci Sleep.* 2017; 9: 97-108.

14. Palmieri G, Contaldi P, Fogliame G. Evaluation of effectiveness and safety of a herbal compound in primary insomnia symptoms and sleep disturbances not related to medical or psychiatric causes. *Nat Sci Sleep*. 2017; 9: 163–169.
15. Neubauer DN, Pandi-Perumal SR, Spence DW, Buttoo K, Monti JM. Pharmacotherapy of insomnia. *J Cent Nervous Sys Dis*. 2018; 10: 1–7.
16. Herring WJ, Roth T, Krystal AD, Michelson D. Orexin receptor antagonists for the treatment of insomnia and potential treatment of other neuropsychiatric indications. *J Sleep Res*. 2019;28:e12782.
17. Seol J, Fujii Y, Park I, Suzuki Y, Kawana F, Yajima K, et al. Distinct effects of orexin receptor antagonist and GABA(A) agonist on sleep and physical/cognitive functions after forced awakening. *Proc Natl Acad Sci U S A*. 2019;116(48):24353–24358.
18. Jiang B, He D, Gao Z. Efficacy and placebo response of multimodal treatments for primary insomnia: A network meta-analysis. *Clin Neuropharmacol*. 2019;42(6):197–202.
19. Hoyer D, Allen A, Jacobson LH. Hypnotics with novel modes of action. *Br J Clin Pharmacol*. 2019 Nov 22. [Epub ahead of print]
20. Roehrs T, Roth T. Insomnia pharmacotherapy. *Neurotherapeutics: J Am Soc Exp NeuroTherapeutics*. 2012; 9: 728–738.
21. Savage K, Stough FJC, Sarris J. GABA-modulating phytomedicines for anxiety: A systematic review of preclinical and clinical evidence. *Phytother Res*. 2018;32:3–18.
22. Doherty R, Madigan S, Warrington G, Ellis J. Sleep and nutrition interactions: Implications for athletes. *Nutrients* 2019, 11, 822.
23. Afaghi A, O'Connor H, Chow CM. High-glycemic-index carbohydrate meals shorten sleep onset. *Am J Clin Nutr* 2007; 85: 426–430.
24. Meng X, Li Y, Li S et al. Dietary sources and bioactivities of melatonin. *Nutrients*. 2017; 9(367):1–64.
25. Esposito S, Laino D, D'Alonzo R et al. Pediatric sleep disturbances and treatment with melatonin. *J Transl Med*. 2019; 17(77):1–8.
26. Pereira N, Naufel MF, Ribeiro EB, Tufik S, Hachul H. Influence of dietary sources of melatonin on sleep quality: A review. *J Food Sci*. 2020;85(1):5–13.
27. Trabelsi K, Ammar A, Zlitni S, Boukhris O, Khacharem A, El-Abed K, et al. Practical recommendations to improve sleep during Ramadan observance in healthy practitioners of physical activity. *Tunis Med*. 2019;97(10):1077–1086.
28. Bravaccio C, Terrone G, Rizzo R, Gulisano M, Tosi M, Curatolo P, et al. Use of nutritional supplements based on melatonin, tryptophan and vitamin B6 in children with primary chronic headache, with or without sleep disorders: a pilot study. *Minerva Pediatr*. 2019 Oct 11. [Epub ahead of print]
29. Pin Arboledas G, Soto Insuga V, Jurado Luque MJ et al. Insomnia in children and adolescents. A consensus document. *An Pediatr (Barc)*. 2017;86(165):e1–e11.
30. Abad VC, Guilleminault C. Insomnia in elderly patients: Recommendations for pharmacological management. *Drugs Aging*. 2018; 35:791–817.
31. Kwon CY, Lee B, Chung SY, Kim JW, Kim SH. Oriental herbal medicine for insomnia in the elderly with hypertension. A systematic review protocol. *Medicine*. 2018; 97(36):1–5.
32. Silvani A. Sleep disorders, nocturnal blood pressure, and cardiovascular risk: A translational perspective. *Autonomic Neurosci: Basic Clin*. 2019; 218:31–42.
33. Akram M, Daniyal M, Munir N, Mohiuddin E, Sultana S. Medicinal plants combating against insomnia: A green anti-insomnia approach. *J Nerv Ment Dis*. 2019;207(11):927–935.
34. Mun S, Lee S, Park K, Lee SJ, Koh BH, Baek Y. Effect of traditional East Asian medicinal herbal tea (HT002) on insomnia: A randomized controlled pilot study. *Integr Med Res*. 2019; 8(1): 15–20.
35. Baek Y, Kim H, Mun S, Lee S. Three-component herbal tea alleviates prolonged fatigue and improves sleep quality: A randomized controlled pilot study. *Explore*. 2018; 14(6): 420–423.

36. Candelario M, Cuellar E, Reyes-Ruiz JM et al. Direct evidence for GABAergic activity of *Withania somnifera* on mammalian ionotropic GABAA and GABA_p receptors. *J Ethnopharmacol.* 2015;171:264-272.
37. Kaushik MK, Kaul SC, Wadhwa R, Yanagisawa M, Urade Y. Triethylene glycol, an active component of *Ashwagandha* (*Withania somnifera*) leaves, is responsible for sleep induction. *PLoS ONE* 2017;12(2): e0172508.
38. Langade D, Kanchi S, Salve J, Debnath K, Ambegaokar D. Efficacy and safety of *Ashwagandha* (*Withania somnifera*) root extract in insomnia and anxiety: A double-blind, randomized, placebo-controlled study. *Cureus.* 2019;11(9):e5797.
39. Koulivand PH, Ghadiri MK, Gorji A. Lavender and the nervous system. *Evidence-Based Compl Altern Med.* 2013; 2013(681304): 1-10.
40. Seifritz E, Schläfke S, Holsboer-Trachsler E. Beneficial effects of Silexan on sleep are mediated by its anxiolytic effect. *J Psychiatr Res.* 2019;115:69-74.
41. Velasco-Rodríguez R, Pérez-Hernández MG, Maturano-Melgoza JA, Hilerio-López ÁG, Monroy-Rojas A, Arana-Gómez B, et al. The effect of aromatherapy with lavender (*Lavandula angustifolia*) on serum melatonin levels. *Complement Ther Med.* 2019;47:102208.
42. Chien L-W, Cheng SL, Liu CF. The effect of lavender aromatherapy on autonomic nervous system in midlifewomen with insomnia. *Evidence-Based Compl Altern Med.* 2012; 2012(740813):1-8.
43. Nasiri Lari Z, Hajimonfarednejad M, Riasatian M, Abolhassanzadeh Z, Iraj A, Vojoud M, et al. Efficacy of inhaled *Lavandula angustifolia* Mill. Essential oil on sleep quality, quality of life and metabolic control in patients with diabetes mellitus type II and insomnia. *J Ethnopharmacol.* 2020;251:112560.
44. Miraj S, Azizi N, Kiani S. A review of chemical components and pharmacological effects of *Melissa officinalis* L. *Der Pharmacia Lettre.* 2016; 8(6):229-237.
45. Miraj S, Azizi N, Kiani S. A review of chemical components and pharmacological effects of *Melissa officinalis* L. *J Evidence-Based Compl Altern Med.* 2017; 22(3): 385-394.
46. Cases J, Ibarra A, Feuille`re N, Roller M, Sukkar SG. Pilot trial of *Melissa officinalis* L. leaf extract in the treatment of volunteers suffering from mild-to-moderate anxiety disorders and sleep disturbances. *Mediterr J Nutr Metab.* 2011; 4:211–218.
47. Ranjbar M, Firoozabadi A, Salehi A et al. Effects of herbal combination (*Melissa officinalis* L. and *Nepeta menthoides* Boiss. & Buhse) on insomnia severity, anxiety and depression in insomniacs: Randomized placebo controlled trial. *Integr Med Res.* 2018; 7(4):328–332.
48. Meolie AL, Rosen C, Kristo D et al. Oral nonprescription treatment for insomnia: an evaluation of products with limited evidence. *J Clin Sleep Med.* 2005;1(2):173-187.
49. Lemoine P, Bablon JC, Da Silva C. A combination of melatonin, vitamin B6 and medicinal plants in the treatment of mild-to-moderate insomnia: A prospective pilot study. *Complement Ther Med.* 2019;45:104-108.
50. Khodadadi S. Herbal medication to cure insomnia. *J Prev Epidemiol.* 2016;1(1):e02.
51. Srivastava JK, Shankar E, Gupta S. Chamomile: A herbal medicine of the past with bright future. *Mol Med Report.* 2010;3:895-901.
52. Hieu TH, Dibas M, Surya Dila KA et al. Therapeutic efficacy and safety of chamomile for state anxiety, generalized anxiety disorder, insomnia, and sleep quality: A systematic review and meta-analysis of randomized trials and quasi-randomized trials. *Phytother Res.* 2019; 33(6): 1604-1615.
53. Zick SM, Wright BD, Sen A, Arnedt JT. Preliminary examination of the efficacy and safety of a standardized chamomile extract for chronic primary insomnia: A randomized placebo controlled pilot study. *BMC Compl Altern Med.* 2011; 11(78): 1-8.
54. Miraj S, Alesaeidi S. A systematic review study of therapeutic effects of *Matricaria recuita* chamomile (chamomile). *Ephysician.* 2016; 8(9): 3024-3031.
55. Chang SM, Chen CH. Effects of an intervention with drinking chamomile tea on sleep quality and depression in sleep disturbed postnatal women: a randomized controlled trial. *J Adv Nurs.* 2016; 72(2): 306-315.

56. Adib-Hajbaghery M, Mousavi SN. The effects of chamomile extract on sleep quality among elderly people: A clinical trial. *Complement Ther Med.* 2017;35:109-114.
57. Sang S, Chu Y. Whole grain oats, more than just a fiber: Role of unique phytochemicals. *Mol Nutr Food Res.* 2017;61(7):1600715.
58. Hudson C, Hudson SP, Hecht T, MacKenzie J. Protein source tryptophan versus pharmaceutical grade tryptophan as an efficacious treatment for chronic insomnia. *Nutr Neurosci.* 2005;8(2):121-7.
59. Wurtman JJ. Chasing away insomnia with a bowl of oatmeal. *Psychology Today.* Sussex Publishers, Posted Nov 11, 2014.
60. Rowe A, Zhang LY, Ramzan I. Toxicokinetics of kava. *Adv Pharmacol Sci.* 2011; 2011(326724):1- 6.
61. Zhou P, Gross S, Liu JH, et al. Flavokawain B, the hepatotoxic constituent from kava root, induces GSH-sensitive oxidative stress through modulation of IKK/NF-kappaB and MAPK signaling pathways. *FASEB J.* 2010;24(12):4722-4732.
62. Wang P, Zhu J, Shehu AI, Lu J, Chen J, Zhong XB, Ma X. Enzymes and pathways of kavain bioactivation and biotransformation. *Chem Res Toxicol.* 2019; 32(7):1335-1342.
63. Kim GH, Lim K, Yang HS et al. Improvement in neurogenesis and memory function by administration of *Passiflora incarnata* L. extract applied to sleep disorder in rodent models. *J Chem Neuroanat.* 2019; 98:27-40.
64. Guerrero FA, Medina GM. Effect of a medicinal plant (*Passiflora incarnata* L.) on sleep. *Sleep Sci.* 2017;10(3):96-100.
65. Traub M. Passionflower: An overview of the research and clinical indications. *Gaia Herbs. Professional Solutions.* 1-13, 2012.
66. Kim GH, Kim Y, Yoon S, Kim SJ, Yi SS. Sleep-inducing effect of *Passiflora incarnata* L. extract by single and repeated oral administration in rodent animals. *Food Sci Nutr.* 2019;8(1):557-566.
67. Lee J, Jung HY, Lee SI, Choi JH, Kim SG. Effects of *Passiflora incarnata* Linnaeus on polysomnographic sleep parameters in subjects with insomnia disorder: a double-blind randomized placebo-controlled study. *Int Clin Psychopharmacol.* 2020;35(1):29-35.
68. Panossian A., Wikman G. Pharmacology of *Schisandra chinensis* Bail.: An overview of Russian research and uses in medicine. *J. Ethnopharmacol.* 2008;118:183-212.
69. Nowak A, Zakłós-Szyda M, Błasiak J, Nowak A, Zhang Z, Zhang B. Potential of *Schisandra chinensis* (Turcz.) Baill. in human health and nutrition: A review of current knowledge and therapeutic perspectives. *Nutrients.* 2019;11(2):333.
70. Yan T, He B, Wan S et al. Antidepressant-like effects and cognitive enhancement of *Schisandra chinensis* in chronic unpredictable mild stress mice and its related mechanism. *Nature. Sci Rep.* 2017; 7(6903): 1-15.
71. Rybníkář M, Šmejkal K, Žemlička M. *Schisandra chinensis* and its phytotherapeutical applications. *Čes. slov. Farm.* 2019; 68, 95-118
72. Hu Z, Zhao P, Xu H. Hyperoside exhibits anticancer activity in nonsmall cell lung cancer cells with T790M mutations by upregulating FoxO1 via CCAT1. *Oncol Rep.* 2020;43(2):617-624.
73. Lazzara S, Carrubba A, Napoli E. Variability of Hypericins and Hyperforin in *Hypericum* Species from the Sicilian Flora. *Chem Biodivers.* 2020;17(1):e1900596.
74. Kligler B, Teets R, MD, Quick M. Complementary/Integrative Therapies That Work: A Review of the Evidence. *Am Fam Physician.* 2016;94(5):369-374.
75. Butterweck V. Mechanism of action of St John's Wort in depression: What is known? *CNS Drugs* 2003; 17(8):539-562.
76. Taavoni S, Ekbatani N, Kashaniyan M, Haghani H. Effect of valerian on sleep quality in postmenopausal women: a randomized placebo-controlled clinical trial. *Menopause.* 2011;18(9):951-955.
77. Evidence-Based Medicine Consult. The mechanism of action for Valerian (*Valeriana officinalis*) in the treatment of insomnia., 2015.
78. Bent S, Padula A, Moore D, Patterson M, Mehling W. Valerian for sleep: A systematic review and meta-analysis. *Am J Med.* 2006;119(12): 1005-1012.

79. Nunes A, Sousa M. Use of valerian in anxiety and sleep disorders: What is the best evidence? *Acta Med Port.* 2011; 24(Suppl 4): 961-966.
80. Dumur J, Csajka C, Pavec O, Messaoudi S, Cretignier T, Gaspar F, et al. Which alternative to benzodiazepines, Z-pills and other hypnotics for aged people? Melatonin, valerian, or clome-thiazole. *Rev Med Suisse.* 2018;14(626):2018-2023.
81. Ghafarzadeh J, Sadeghniaat-Haghighi K, Sadeghpour O, Akbarpour S, Amini-Behbahani. Investigating the prevalence of sleep disorder and the impact of sweet almond on the quality of sleep in students of Tehran, Iran. *Iran J Public Health.* 2019;48(6):1149-1154.
82. Feyzabadi Z, Rezaeitalab F, Badiie S, Taghipour A, Moharari F, Soltanifar A, et al. Efficacy of violet oil, a traditional Iranian formula, in patients with chronic insomnia: A randomized, double-blind, placebo-controlled study. *J Ethnopharmacol.* 2018 Mar 25;214:22-28.
83. Losso JN, Finley JW, Karki N, Liu AG, Prudente A, Tipton R, Yu Y, Greenway FL. Pilot study of the tart cherry juice for the treatment of insomnia and investigation of mechanisms. *Am J Ther.* 2018; 25(2):e194-e201.
84. Yu L, Han X, Cen S, Duan H, Feng S, Xue Y, et al. Beneficial effect of GABA-rich fermented milk on insomnia involving regulation of gut microbiota. *Microbiol Res.* 2020 Jan 7;233:126409.