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ORIGINAL PAPERS

CIRCADIAN RHYTHMS AND SLEEP DISORDERS THE ROLE OF PHYTONUTRITHERAPY IN RESTORING PHYZIOLOGICAL BALANCE

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Abstract. *Sleep disorders are increasingly prevalent in modern society, often resulting from disrupted circadian rhythms and lifestyle-related factors. Circadian rhythms, the body's internal biological clock, play a critical role in regulating the sleep–wake cycle and overall physiological homeostasis. Phytonutritherapy, which involves the therapeutic use of bioactive compounds from plants with nutritional value, offers a promising complementary approach to managing sleep disturbances. This article explores the interplay between circadian regulation and sleep quality, highlighting the mechanisms through which specific phytonutrients—such as flavonoids, melatonin-like compounds, and essential oils—may influence chronobiological balance. Emphasis is placed on plant-based interventions including valerian root, chamomile, passionflower, and lavender, analyzing current scientific evidence regarding their efficacy and safety. By supporting the realignment of circadian rhythms and enhancing sleep quality, phytonutritherapy may serve as a valuable tool in the integrative management of sleep disorders.*

Keywords: circadian rythms, sleep disorders, phytonutritherapy, biological clock, physiological balance

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Introduction

Circadian rhythms are natural cycles in our body that affect everything from gene activity to how different organs work together. These rhythms follow a roughly 24-hour pattern and continue even without any signals from the environment [1]. In the brain, the circadian system helps regulate important functions like sleep, body temperature, eating habits, and social behavior. It plays

a key role in keeping our internal body systems in sync with each other and with the outside world.

This internal clock affects many areas of health, including how we process food, think, fight off illness, and even how certain cancers may develop in the brain. The sleep-wake cycle is one of the most visible and well-known signs of the circadian system working properly [2]. Based on brainwave activity (EEG), eye movements, and muscle tone (EMG), sleep is split into two main phases: REM (rapid eye movement) and NREM (non-rapid eye movement) sleep.

When our circadian rhythms are thrown off, it can seriously impact our health, affecting sleep, attention, thinking, mood, movement, and metabolism [3]. These disruptions have also been linked to a number of health issues, including neurodegenerative diseases [2].

Sleep disorders often involve problems with how the brain processes rewards and motivation. People with these disorders tend to experience less pleasure and have less drive to go after things that usually bring joy. In mammals, everything from heart activity to sleep patterns and brain function runs on an internal clock that follows a 24-hour rhythm in sync with the day-night cycle. Researchers have found that genes, brain activity, and levels of certain brain chemicals like neurotransmitters follow daily rhythms in brain areas linked to mood and reward, in both humans and animals [4].

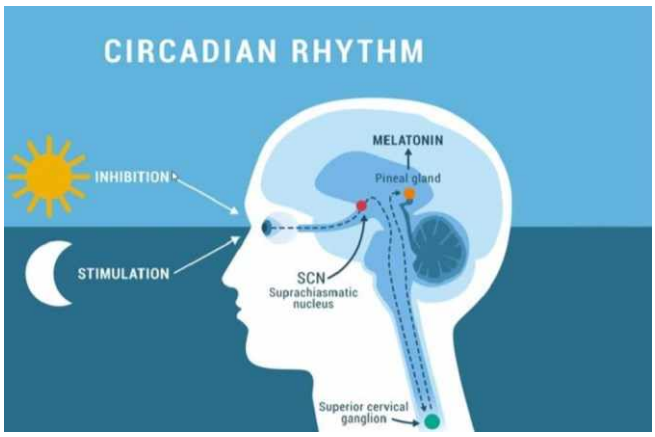

Image 1: Light Therapy Device for Circadian Rhythm Disorders. Image adapted from Circadian Rhythm Sleep-wake Cycle How Exposure Stock Vector

People with depression often have disruptions in these daily rhythms [5][6][7]. More and more studies show that mood disorders and the body's natural rhythms are closely connected. One reason depression is on the rise globally could be modern lifestyles—think too much artificial light, working night shifts, and

frequent travel across time zones—which can throw off our internal clocks and sleep cycles [8].

Dopamine is one of several brain chemicals, like glutamate, serotonin (5-HT), orexin, noradrenaline, and GABA, that follow a daily rhythm [9][10]. Problems in how the brain uses dopamine have been linked to conditions like schizophrenia, addiction, and more recently, depression—pointing to a possible connection between disrupted dopamine activity and circadian rhythm issues in mood disorders.

Sleep problems are also pretty common nowadays and can seriously affect quality of life. These sleep issues often show up in conditions where dopamine activity is impaired. For instance, up to 90% of people with Parkinson's disease experience some form of sleep disturbance. In more advanced stages of Parkinson's, a condition called akathisia—linked to problems in dopamine pathways in the brain—often brings major sleep disruptions [11]. REM sleep behavior disorder (RBD), another sleep problem, might be tied to damage in a part of the brainstem called the pedunculopontine tegmental nucleus, which connects to dopamine-producing areas like the VTA [12].

Image 2: Brain Structures in Dopamine Pathways Linked to Sleep. Image adapted from https://dobiohacking.com/what-is-circadian-rhythm-how-to-fix-the-sleep-cycle/

All of this points to a strong connection between how dopamine works in the brain and how we sleep. In this review, we'll look at how dopamine pathways relate to mood disorders triggered by stress, the body's internal clock, and sleep/wake cycles.

Mechanisms Behind Circadian Rhythms and Sleep-Wake Activity

Circadian Rhythms

Main Brain Pathways in the Circadian System

Circadian rhythms control a wide range of physical and behavioral processes and are found throughout the body, both in the brain and in other organs. At the center of this system is the suprachiasmatic nucleus (SCN), a cluster of thousands of neurons that generate and maintain their own synchronized 24-hour cycles of electrical activity. The SCN is key to setting and coordinating the body's overall rhythms.

In humans, circadian regulation starts with how we process light. Special light-sensitive cells in the retina, called intrinsically photosensitive retinal ganglion cells (ipRGCs), pick up light and send that information directly to the SCN. Once the SCN gets this light input, it uses it to adjust and sync the body's internal clock, sending out signals to other areas of the brain to help keep everything aligned with the day-night cycle [5].

The SCN sends signals mainly to different parts of the hypothalamus, which help regulate specific circadian rhythms. These brain regions include the paraventricular nucleus (PVN), dorsomedial hypothalamic nucleus, subparaventricular zone, and the medial preoptic nucleus (MPN) [6].

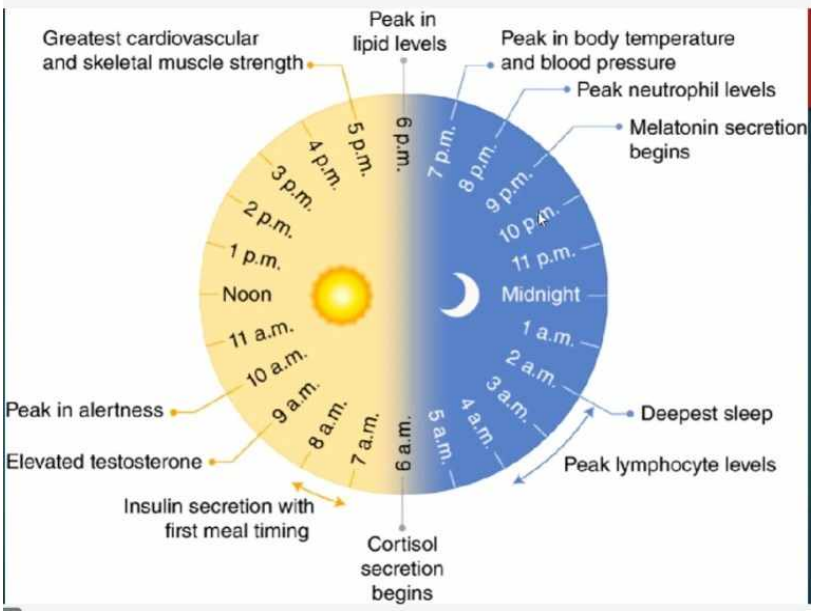

Image 3: Circadian Clock. Image adapted from: https://www.sciencedirect.com/science/article/pii/S0010482522008083

Overview of the Circadian Clock System

On a larger scale, circadian rhythms are defined by three main features: amplitude, phase, and period. On a cellular level, problems with circadian rhythms often come down to changes in the period, typically caused by defects in the core molecular loop known as the transcription-translation feedback loop (TTFL) [7]. The TTFL is mostly controlled by the interaction between two key proteins—BMAL1 (brain and muscle ARNT-like 1) and CLOCK (circadian locomotor output cycles kaput). These two form a heterodimer that drives the cycle. Other important proteins in this loop include PER (Period) and CRY (Cryptochrome).

There's also a secondary loop that helps regulate this system, involving proteins called REV-ERBα/β (which suppress gene expression) and RORα/β (which promote it). Together, they help maintain the proper expression of BMAL1 [8][9]. This entire feedback cycle takes about 24 hours to complete [10][11].

Studies using models of Parkinson's (PD) and Alzheimer's (AD) diseases—across species like mice, rats, fruit flies (Drosophila), and zebrafish—have shown disruptions in circadian rhythms, sleep cycles, and expression of clock-related genes. Tables 2 and 3 in the original text summarize findings from both neurotoxin-induced and genetically modified models.

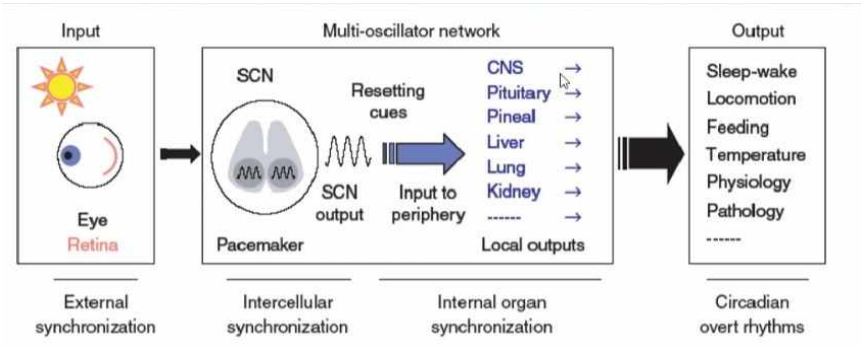

Image 4: Chronotherapy Conceptual Timeline in mental Care. Image adapted from: https://slideplayer.com/slide/13520239/

Sleep-Wake Activity

The sleep-wake cycle is tightly controlled by the body's circadian rhythm. Disruptions to this cycle have been observed in various PD and AD animal models. Researchers have measured these disturbances using tools like running wheels, infrared sensors, piezoelectric systems, and brain activity readings (EEG and EMG).

Some genetic mutations seem to play a role in these sleep issues. For example: fruit flies with pink1 or parkin mutations show broken and fragmented sleep [12]. Mice with a heterozygous mutation in the GBA1 gene (D409V/WT) experience more NREM sleep but less REM sleep [13]. Mice with a transgenic α-synuclein BAC model show REM sleep without muscle paralysis, a hallmark of REM sleep behavior disorder (RBD).

Sleep changes in these models have been thoroughly reviewed by researchers like Fifel and Medeiros [14][15].

Sleep-wake cycles might also be tied to how the brain manages protein waste. Some studies suggest sleep helps the brain's glymphatic system clear out misfolded proteins. Poor sleep, on the other hand, can lead to a buildup of harmful proteins like beta-amyloid (Aβ) in the cerebrospinal fluid [16][17].

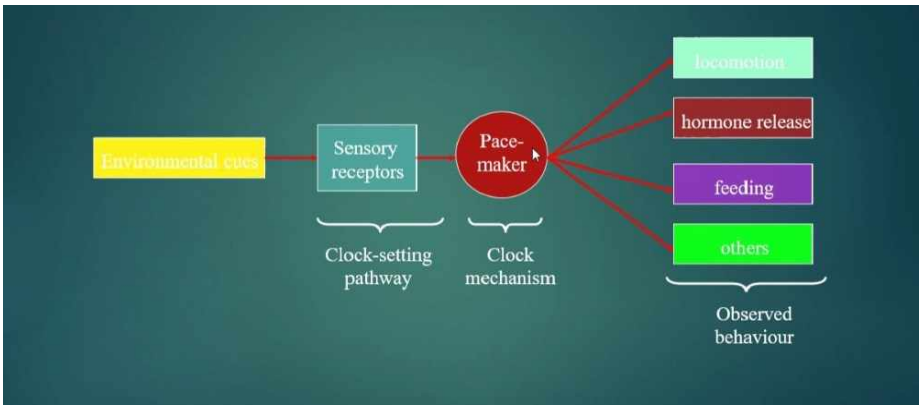

Figure 5: General functioning of biological clocks. Image adapted from: https://slideplayer.com/slide/4415081/

Pharmacological Approaches

Melatonin and Melatonin Receptor Agonists

Melatonin helps regulate the body's circadian rhythm and promotes sleep, which is why it's often used to treat sleep issues and possibly slow down neurodegenerative disease progression. Several clinical studies have found melatonin to be effective for treating insomnia, REM sleep behavior disorder (RBD), and disrupted rest-activity cycles in conditions like Parkinson's and Alzheimer's [18]. However, the results have been mixed. Some studies show that melatonin improves how patients feel about their sleep and increases total sleep time in people with Parkinson's [19], but its effect on excessive daytime sleepiness (EDS) isn't clear.

Still, melatonin is usually the first choice for treating RBD because it's safer than clonazepam and helps reduce injury risk [20]. In Alzheimer's patients, a

recent review found that melatonin helps people fall asleep faster and sleep longer [21]. Extended-release melatonin [22] and melatonin receptor agonists [23] have also shown to improve sleep quality in both Parkinson's and Alzheimer's patients. While melatonin levels are lower in people with Huntington's disease (HD) [24], we don't have enough solid research yet to say how effective melatonin is for them. A recent study in fruit flies with HD showed that melatonin helped restore clock gene activity, suggesting it could have potential [25].

Hypnotics

Hypnotics—including benzodiazepines, non-benzodiazepines, sedative antipsychotics, and sedating antidepressants—are commonly used to treat insomnia, even in people with neurodegenerative conditions.

Clonazepam, a long-acting benzodiazepine, is considered the first-line drug for treating RBD [26]. Studies show it helps with RBD symptoms in Parkinson's patients [27]. A six-week trial with eszopiclone showed it reduced nighttime awakenings and improved how Parkinson's patients felt about their sleep [28]. Similar benefits have been seen in Alzheimer's patients [29]. However, the evidence for clonazepam is mostly based on case reports and observational data [30], so more solid clinical trials are needed.

Sedating antidepressants like trazodone and doxepin have also been shown to help with nighttime sleep in Alzheimer's patients [31] and insomnia in people with Parkinson's [32]. But hypnotics can have downsides, especially for older adults. These include memory problems, worse daytime sleepiness, and even breathing issues during sleep [33]. Doctors should carefully weigh the pros and cons before prescribing them to people with neurodegenerative diseases.

Chronotherapy: Blending Medications with Daily Rhythms

Chronotherapy is a treatment strategy that takes a person's circadian rhythm into account when planning care. The idea is to time medications or combine drug treatments with non-drug strategies (like light exposure or activity schedules) to get the best results with fewer side effects. While it was originally used in conditions like high blood pressure and cancer, recent research shows it may also help in neurodegenerative diseases [34][35][36].

For example, combining bright light therapy (BLT) with melatonin has been shown to improve sleep, reduce nighttime agitation, and boost overall rest for patients with dementia, with benefits lasting as long as 3.5 years [35]. One study found that exposing Alzheimer's patients to an hour of morning light (2500 lux) for 10 weeks—along with a 5 mg melatonin dose in the evening—increased their daytime alertness and helped regulate their activity rhythms better than light therapy alone [36]. Another study found that walking, light therapy, and sleep

education (both individually and in combination) helped improve sleep in Alzheimer's patients [34].

Neuroprotection and New Treatments

Animal research is revealing some exciting possibilities for protecting the brain and even promoting healing. For example, repetitive transcranial magnetic stimulation (rTMS) has shown potential to protect neurons by preventing cell death and helping regulate key brain chemicals and growth factors [37].

Light therapy has also shown some benefits. In Alzheimer's mouse models, it lowers oxidative stress [38], helps clear harmful beta-amyloid (Aβ) through the brain's lymphatic system [39], and in Parkinson's models, it prevents dopamine cell loss and boosts levels of a key enzyme, tyrosine hydroxylase [40].

Another key player in the sleep-wake cycle is the neuropeptide orexin, which helps keep us awake and alert. Suvorexant, a drug that blocks orexin receptors, is already approved for treating insomnia in older adults. Animal studies have shown that it may also reduce amyloid-β plaques, improve brain flexibility (synaptic plasticity), and restore proper circadian protein activity in Alzheimer's mouse models [41].

Researchers are also developing small molecules to fix problems in the circadian system. For example: CKI-7, a casein kinase 1 δ/ε inhibitor, has been shown to lower Aβ production, suggesting a neuroprotective role [42][43]. Rev-erbα, a protein that plays a big part in the body's internal clock and energy use, can be targeted with drugs. Mice lacking this protein show disrupted sleep-wake cycles [44]. Compounds like GSK4112 (an agonist) and SR8278 (an antagonist) could potentially help restore normal rhythms [42].

Traditional Chinese medicine (TCM) is another area of interest. Certain herbs and extracts have antioxidant and anti-inflammatory effects that may benefit patients with neurodegenerative conditions [45][46]. Clinical studies have found that acupuncture [47] and herbal formulas like Yang-Xue-Qing-Nao granules [48] can improve sleep in Parkinson's patients. Moving forward, researchers need to improve quality control in TCM studies and explore how the active ingredients actually work.

Phytonutritional Strategies

Phytonutritional strategies refer to the use of plant-derived compounds to support health and prevent disease, including disorders related to circadian rhythm and sleep. These natural interventions often include antioxidants, anti-inflammatory agents, and phytochemicals that help regulate biological pathways tied to the sleep-wake cycle. For example, compounds found in turmeric (curcumin), green tea (L-theanine and catechins), ginseng, and valerian root have

been shown to modulate neurotransmitter activity, reduce oxidative stress, and influence melatonin production. There is actually a variety of these compounds, including quercetin [50] or even nicotine [49]. Additionally, dietary patterns rich in flavonoids, polyphenols, and essential fatty acids may positively affect circadian gene expression. By incorporating these natural substances into treatment protocols, researchers are exploring how phytonutritional therapies can complement pharmacological and behavioral interventions in restoring circadian alignment, improving sleep quality, and enhancing neuroprotection.

Conclusions

Circadian rhythms are fundamental to the regulation of sleep, mood, and overall health. Disruptions in these biological rhythms are intricately connected to sleep disorders and neurodegenerative diseases such as Parkinson's and Alzheimer's. This review underscores the multifactorial nature of circadian misalignment and its far-reaching impact on brain function, motivation, and emotional regulation. Promising therapeutic approaches—from melatonin and light therapy to pharmacological and phytonutritional strategies—offer hope in managing and potentially preventing circadian-related disorders. The future of treatment lies in chronotherapy and personalized care that respects each individual's internal biological timing. Continued research is essential to unlock the full potential of these therapies in restoring circadian balance and improving quality of life.

R E F E R E N C E S

[1] Czeisler, C. A., & Gooley, J. J. (2007). Sleep and circadian rhythms in humans. Cold Spring Harbor Symposia on Quantitative Biology, 72, 579–597.
[2] Hastings, M. H., Maywood, E. S., & Brancaccio, M. (2018). Generation of circadian rhythms in the suprachiasmatic nucleus. Nature Reviews Neuroscience, 19(8), 453–469.
[3] Bass, J., & Takahashi, J. S. (2010). Circadian integration of metabolism and energetics. Science, 330(6009), 1349–1354.
[4] Sidor, M. M., & McClung, C. A. (2014). Timing of neurobiological events: Circadian rhythms and mood disorders. Current Opinion in Neurobiology, 29, 58–65.
[5] McClung, C. A. (2013). How might circadian rhythms control mood? Let me count the ways.... Biological Psychiatry, 74(4), 242–249.
[6] Wirz-Justice, A., & Van den Hoofdakker, R. H. (1999). Sleep deprivation in depression: What do we know, where do we go? Biological Psychiatry, 46(4), 445–453.
[7] Wirz-Justice, A. (2006). Biological rhythm disturbances in mood disorders. International Clinical Psychopharmacology, 21(Suppl 1), S11–S15.
[8] Arey, R. N., Enwright, J. F., & Matuszewich, L. (2014). Environmental disruption of circadian rhythms: New avenues in mood disorder research. Frontiers in Behavioral Neuroscience, 8, 208.

[9] Inutsuka, A., & Yamanaka, A. (2013). The physiological role of orexin/hypocretin neurons in the regulation of sleep/wakefulness and neuroendocrine functions. Frontiers in Endocrinology, 4, 18.
[10] Castañeda, T. R., de Prado, B. M., Prieto, D., & Mora, F. (2004). Circadian rhythms of neurotransmitter levels and oxidative stress markers in the brain: Their relation with aging. Neurochemical Research, 29(2), 351–360.
[11] Comella, C. L., & Goetz, C. G. (1994). Akathisia in Parkinson's disease. Movement Disorders, 9(6), 545–548.
[12] Lima, M. M. S. (2013). Sleep disturbances in Parkinson's disease: The contribution of dopamine in REM sleep regulation. Sleep Medicine Reviews, 17(5), 367–375.
[13] Fifel, K., & Videnovic, A. (2020). Light and chronotherapy in Alzheimer's and Parkinson's diseases. Neurobiology of Sleep and Circadian Rhythms, 9, 100064.
[14] Medeiros, C. A. M., & Carvalhedo de Bruin, P. F. (2014). Sleep disorders in Alzheimer's disease: A review. Arquivos de Neuro-Psiquiatria, 72(3), 219–226.
[15] Xie, L., Kang, H., Xu, Q., Chen, M. J., Liao, Y., Thiyagarajan, M., ... & Nedergaard, M. (2013). Sleep drives metabolite clearance from the adult brain. Science, 342(6156), 373–377.
[16] Kang, J. E., Lim, M. M., Bateman, R. J., Lee, J. J., Smyth, L. P., Cirrito, J. R., ... & Holtzman, D. M. (2009). Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. Science, 326(5955), 1005–1007.
[17] Cardinali, D. P., Srinivasan, V., Brzezinski, A., & Brown, G. M. (2012). Melatonin and its analogs in insomnia and depression. Journal of Pineal Research, 52(4), 365–375.
[18] Wade, A. G., Ford, I., Crawford, G., McMahon, A. D., Nir, T., Laudon, M., & Zisapel, N. (2007). Efficacy of prolonged release melatonin in insomnia patients aged 55–80 years: Quality of sleep and next-day alertness outcomes. Current Medical Research and Opinion, 23(10), 2597–2605.
[19] Boeve, B. F., Silber, M. H., & Ferman, T. J. (2004). Melatonin for treatment of REM sleep behavior disorder in neurologic disorders: Results in 14 patients. Sleep Medicine, 5(1), 31–35.
[20] Jean-Louis, G., von Gizycki, H., Zizi, F., & Nunes, J. (1998). Mood states and sleepiness in college students: Influences of age, time of day, and caffeine consumption. Physiology & Behavior, 65(4–5), 877–883.
[21] McCurry, S. M., Logsdon, R. G., Teri, L., & Vitiello, M. V. (2007). Sleep disturbances in caregivers of persons with dementia: Contributing factors and treatment implications. Sleep Medicine Reviews, 11(2), 143–153.
[22] Musiek, E. S., & Holtzman, D. M. (2016). Mechanisms linking circadian clocks, sleep, and neurodegeneration. Science, 354(6315), 1004–1008.
[23] Swaab, D. F., Fliers, E., & Partiman, T. S. (1985). The suprachiasmatic nucleus of the human brain in relation to sex, age and senile dementia. Brain Research, 342(1), 37–44.
[24] Turek, F. W. (2007). From circadian rhythms to clock genes in depression. International Clinical Psychopharmacology, 22(Suppl 2), S1–S8.
[25] Benedetti, F., Dallaspezia, S., Fulgosi, M. C., Barbini, B., Colombo, C., & Smeraldi, E. (2007). Actimetric evidence that CLOCK 3111 T/C SNP influences sleep and activity patterns in bipolar depression. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 144B(5), 631–635.
[26] Schenck, C. H., Bundlie, S. R., Ettinger, M. G., & Mahowald, M. W. (1986). Chronic behavioral disorders of human REM sleep: A new category of parasomnia. Sleep, 9(2), 293–308. https://doi.org/10.1093/sleep/9.2.293
[27] Iranzo, A., Santamaria, J., & Tolosa, E. (2009). The clinical and pathophysiological relevance of REM sleep behavior disorder in neurodegenerative diseases. Sleep Medicine Reviews, 13(6), 385–401. https://doi.org/10.1016/j.smrv.2008.11.003

[28] Adler, C. H., & Thorpy, M. J. (2005). Sleep issues in Parkinson's disease. Neurology, 64(12 Suppl 3), S12–S20. https://doi.org/10.1212/WNL.64.12_suppl_3.S12
[29] Petit, D., Gagnon, J. F., Fantini, M. L., Rompré, S., Panisset, M., & Montplaisir, J. (2004). Sleep and quantitative EEG in neurodegenerative disorders. Journal of Psychosomatic Research, 56(5), 487–496. https://doi.org/10.1016/j.jpsychores.2004.02.005
[30] De Cock, V. C., Vidailhet, M., Leu, S., Texeira, A., Apartis, E., Elbaz, A., & Arnulf, I. (2008). Restoration of normal motor control in Parkinson's disease during REM sleep. Brain, 130(2), 450–456. https://doi.org/10.1093/brain/awl359
[31] Maust, D. T., Kales, H. C., & Langa, K. M. (2016). Antipsychotics, other psychotropics, and the risk of death in patients with dementia. JAMA Psychiatry, 73(5), 438–445. https://doi.org/10.1001/jamapsychiatry.2015.4499
[32] LeWitt, P. A., & Standaert, D. G. (2007). Treatment of Parkinson disease with dopamine agonists: A clinical review. JAMA, 297(2), 169–180. https://doi.org/10.1001/jama.297.2.169
[33] Glass, J., Lanctôt, K. L., Herrmann, N., Sproule, B. A., & Busto, U. E. (2005). Sedative hypnotics in older people with insomnia: Meta-analysis of risks and benefits. BMJ, 331(7526), 1169. https://doi.org/10.1136/bmj.38623.768588.47
[34] McCurry, S. M., Pike, K. C., Vitiello, M. V., Logsdon, R. G., Larson, E. B., & Teri, L. (2011). Increasing walking and bright light exposure to improve sleep in community-dwelling persons with Alzheimer's disease: Results of a randomized, controlled trial. Journal of the American Geriatrics Society, 59(8), 1393–1402. https://doi.org/10.1111/j.1532-5415.2011.03488.x
[35] Dowling, G. A., Burr, R. L., Van Someren, E. J. W., Hubbard, E. M., Luxenberg, J. S., & Mastick, J. (2008). Melatonin and bright-light treatment for rest-activity disruption in institutionalized patients with Alzheimer's disease. Journal of the American Geriatrics Society, 56(2), 239–246. https://doi.org/10.1111/j.1532-5415.2007.01543.x
[36] Riemersma-van der Lek, R. F., Swaab, D. F., Twisk, J., Hol, E. M., Hoogendijk, W. J. G., & Van Someren, E. J. W. (2008). Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: A randomized controlled trial. JAMA, 299(22), 2642–2655. https://doi.org/10.1001/jama.299.22.2642
[37] Wang, X., Mei, Q., Chen, Y., Zhang, Y., & Lin, Y. (2011). Repetitive transcranial magnetic stimulation protects dopaminergic neurons from apoptosis via regulation of Bcl-2 and Bax. Brain Research, 1368, 1–9. https://doi.org/10.1016/j.brainres.2010.10.095
[38] Zhang, Y., Yang, X., He, X., Wang, Y., Yu, W., Ye, Q., & Liu, C. (2016). Photobiomodulation therapy ameliorates β-amyloid pathology and cognitive impairment in Alzheimer's disease mouse model. Aging and Disease, 7(6), 735–748. https://doi.org/10.14336/AD.2016.0614
[39] Iliff, J. J., Wang, M., Liao, Y., Plogg, B. A., Peng, W., Gundersen, G. A., ... & Nedergaard, M. (2012). A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. Science Translational Medicine, 4(147), 147ra111. https://doi.org/10.1126/scitranslmed.3003748
[40] Wu, M. F., John, J., Boehmer, L. N., & Siegel, J. M. (2006). Activity of dorsal raphe cells across the sleep–waking cycle and during cataplexy in narcoleptic dogs. Journal of Physiology, 575(2), 447–466. https://doi.org/10.1113/jphysiol.2006.114827
[41] Herring, W. J., Snyder, E., Budd, K., Hutzelmann, J., Snavely, D., & Liu, K. (2012). Orexin receptor antagonism for treatment of insomnia: A randomized clinical trial of suvorexant. Neurology, 79(23), 2265–2274. https://doi.org/10.1212/WNL.0b013e31827689ae
[42] Ohnishi, N., Tahara, Y., Kuriki, D., Haraguchi, A., & Shibata, S. (2014). Warm water bath stimulates phase-shifts of circadian locomotor rhythm in mice via thermoregulatory signaling. PLoS ONE, 9(12), e113162. https://doi.org/10.1371/journal.pone.0113162

[43] Meng, Q. J., Maywood, E. S., Bechtold, D. A., Lu, W. Q., Li, J., Gibbs, J. E., ... & Loudon, A. S. I. (2010). Entrainment of disrupted circadian behavior through inhibition of casein kinase 1 (CK1) enzymes. Proceedings of the National Academy of Sciences, 107(34), 15240–15245. https://doi.org/10.1073/pnas.1005101107

[44] Delezie, J., Dumont, S., Dardente, H., Oudart, H., Gréchez-Cassiau, A., Klosen, P., ... & Pévet, P. (2012). The nuclear receptor REV-ERBα is required for the daily balance of carbohydrate and lipid metabolism. FASEB Journal, 26(8), 3321–3335. https://doi.org/10.1096/fj.11-197244

[45] Wang, S., Li, Y., Fan, J., Zhang, X., & Yu, M. (2013). Traditional Chinese medicine for the treatment of Alzheimer's disease: A review. Frontiers in Pharmacology, 4, 73. https://doi.org/10.3389/fphar.2013.00073

[46] Lu, J. H., Tan, J. Q., & Durairajan, S. S. K. (2012). Herbal medicine in the treatment of Alzheimer's disease. Current Alzheimer Research, 9(4), 437–446. https://doi.org/10.2174/156720512800107615

[47] Wang, Y., Yin, L., & Wang, L. (2011). Acupuncture treatment for insomnia in Parkinson's disease: A randomized controlled trial. Journal of Traditional Chinese Medicine, 31(1), 22–25. https://doi.org/10.1016/S0254-6272(11)60005-9

[48] Chen, L., Wei, W., & Wang, L. (2015). Clinical observation on 60 cases of Parkinson's disease treated with Yang-Xue-Qing-Nao granules. Chinese Journal of Integrative Medicine, 21(3), 205–210. https://doi.org/10.1007/s11655-015-2078-6

[49] Ciobica A, Padurariu M, Hritcu L. The effects of short-term nicotine administration on behavioral and oxidative stress deficiencies induced in a rat model of Parkinson's disease. Psychiatr Danub. 2012 Jun;24(2):194-205. PMID: 22706419.

[50] Rarinca V, Nicoara MN, Ureche D, Ciobica A. Exploitation of Quercetin's Antioxidative Properties in Potential Alternative Therapeutic Options for Neurodegenerative Diseases. Antioxidants (Basel). 2023 Jul 13;12(7):1418. doi: 10.3390/antiox12071418