

Sleep Disorder and its Treatment: From Nature to Laboratory

Mohit Varshney¹, Supriyo Saha^{1*}, Prinsa², Vikash Jakhmola¹

¹ Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Dehradun-248007, Uttarakhand, India.

² Siddhartha Institute of Pharmacy, Sahastradhara Road, Near IT-Park, Dehradun, Uttarakhand, India

ABSTRACT

Sleep is the natural cellular repair mechanism to improve and restore central neural mechanism, memory, hormonal imbalance, and finally, cell rejuvenation. Sleep disorder is characterized by insomnia, circadian rhythm disorder (CRD), sleep apnea, narcolepsy, parasomnia, and restless leg syndrome (RLS) or periodic limb movement disorder (PLMD). Both oversleeping and less sleeping are associated with sleep disorders (SD). Anxiety, schizophrenia, weight loss/gain, hypothyroidism, and oxidative stress are the most common outcomes of SD. There is also a genetic explanation behind circadian rhythmicity, circadian disorder, narcolepsy-cataplexy syndrome, fatal familial insomnia, and somnambulism. Excessive work pressure, stress, and consumption of caffeine and alcohol collectively push a person toward sleep deprivation. Anxiety, schizophrenia, weight loss/gain, hypothyroidism, and oxidative stress are the most common outcomes of SD. Adenosine, melatonin, dopamine, serotonin, gamma amino butyric acid (GABA), orexin, and histamine regulate SDs by various pathways. Among natural sources, *Centella asiatica*, *Bacopa monnieri*, *Acorus calamus*, *Withania somnifera*, *Nardostachys jatamansi*, *Poria cocos*, *Valeriana officinalis*, *Matricaria chamomilla*, *Lavandula angustifolia*, *Nelumbo nucifera*, *Melissa officinalis*, *Convolvulus pluricaulis*, *Camellia sinensis*, *Ziziphus jujube*, *Datura stramonium*, *Zhizhipus jujube*, *Passiflora incarnata*, and *Moringa oleifera* showed remarkable effects on different forms of SDs through GABA_A, serotonin, and melatonin receptors. Pramipexole, ropinirole, rotigotine, clonazepam, lorazepam, estazolam, zolpidem, lemborexant, daridorexant, and suvorexant showed its activity in the treatment of SDs as a dopamine agonist, inhibitor of GABA_A receptor, dual orexin receptor antagonist, respectively. This article focused on the types of SDs, the effects of SDs on mental health, receptors involved in the sleep cycle, and the impact of natural molecules and synthetic molecules in the management of SDs.

Keywords: Melatonin; Natural sources; Orexin; Sleep disorder; Synthetic molecules.

INTRODUCTION

We are on the edge of technological evolution and high-speed life. Now both the speed of the internet and the loosening of quality lifestyle is in 5G speed. In this fast-moving life, humans compromise the most essential physiological process, sleep (Abad & Guilleminault, 2003). Sleep is the natural cellular repair mechanism to improve and restore central neural mechanism, memory, hormonal imbalance, and finally, cell rejuvenation (Pavlova & Latreille, 2019). Excessive work pressure, stress, and consumption of caffeine and alcohol collectively push a person toward sleep deprivation. Sleep disorder (SD) is characterized by insomnia, CRD, sleep apnea (SA), narcolepsy, parasomnia, restless leg syndrome or periodic limb movement disorder, sleep-disordered breathing, and circadian rhythm sleep-wake disorders. Both oversleeping and less sleeping are associated with SD (Winters et al., 2023). Adults (10-30)% are suffered from insomnia whereas adults (2-9)% suffered from

obstructive sleep apnea. Males have better quality sleep than females (National Sleep Foundation, 2023). Anxiety, schizophrenia, weight loss/gain, hypothyroidism, and oxidative stress are the most common outcomes of SD (Alessi et al., 2008). There is also a genetic explanation behind circadian rhythmicity, circadian disorder, narcolepsy-cataplexy syndrome, fatal familial insomnia, and somnambulism. Mutation in the clock gene associated with SD is observed in drosophila and rodents (Medic et al., 2017). The clock gene interacted with period proteins (Per1 & 2) and cryptochromes (Cry1 & 2). These two proteins negatively controlled the transcription of the Clock-Bmal1 gene. Mutation in the S662G gene of the human Per2 protein is associated with familial advanced sleep phase syndrome (Miller, 2015). Phosphorylation of human Per2 affected by human casein kinase-I and a missense mutation in the enzyme produced advanced sleep phase syndrome-like effects. The genetic background of narcolepsy-cataplexy is shared from one to the next generation with (10-40) % higher rate of occurrence (Taheri & Mignot 2002). HLA-DQB1 is directly related to this type of SD. Mutation in the

*Corresponding author : Supriyo Saha
Email : supriyo9@gmail.com

prion protein D178N codon was responsible for fatal familial insomnia (Taheri & Mignot, 2002). Somnambulism is also connected with HLA O501 and DQB1 expression. Hypertension, obesity, diabetes, hyperthyroidism, hypothyroidism, Parkinson's, free radical generation, osteoarthritis (Ashbrook et al., 2019), schizophrenia, anxiety, depression, and ADHD (Attention-Deficit/Hyperactivity Disorder) are the most common diseases caused by sleep deprivation (Franken, 2013). This manuscript focused on the types of sleep disorders, the etiology of different types of sleep disorders, receptors linked with sleep disorders, plants, and synthetic molecules used in the treatment of sleep disorders.

RECEPTORS INVOLVED IN THE SLEEP CYCLE

Adenosine receptor

Adenosine receptors are G-protein-coupled receptors (GPCR) activated by the neuromodulator adenosine. These receptors are categorized into A1, A2A, A2B, and A3. The categorization is based on factors such as GPCR coupling, affinity towards adenosine, and intracellular signal transduction mechanism. When it interacts with inhibitory A1 receptors and stimulatory A2A receptors, adenosine promotes nonrapid eye movement (NREM) sleep. During awakening, the level of extracellular adenosine is elevated in the basal forebrain, and it decreases during sleep (Dierickx et al., 2017, Lazarus et al., 2017). A2A receptor agonists are well-known as sleep inducers because their activation promotes sleep. This suggests that targeting the A2A receptor can be a potential strategy for treating SDs.

Melatonin receptor

Melatonin is a neurohormone primarily secreted by the pineal gland in the brain, particularly at night. The release of melatonin is regulated by the body's internal circadian clock, with levels increasing in response to darkness and decreasing during daylight hours. Melatonin receptors are a type of G-protein-coupled receptor (GPCR) found in various body regions, including the suprachiasmatic nucleus (SCN) of the hypothalamus. There are two main types of melatonin receptors: MT1 and MT2. Although melatonin is not sedating, it acts on these GPCRs to regulate the sleeping and awake cycle. By binding to its receptors, melatonin helps to synchronize the body's circadian rhythm and promote sleep (Dubocovich, 2007). Activating melatonin receptors in the SCN of the hypothalamus helps regulate the timing and duration of sleep. During the daytime, melatonin levels in the body are

typically lower, while they increase at night, signaling the body to prepare for sleep (Gobbi & Comai, 2019). This natural variation in melatonin levels helps to regulate the sleep-wake cycle and promote healthy circadian rhythms (Figure 1) (Table I).

Dopamine Receptor

Dopamine is the predominant catecholamine neurotransmitter in the brain, and it plays a crucial role in regulating various functions, including emotion, cognition, endocrine regulation, and locomotor activity. The effects of dopamine on sleep can be complex. At high levels, dopamine can cause excitation, leading to difficulties in falling asleep and insomnia. Conversely, dopamine has been associated with sleep disturbances and disorders at low levels. Dopamine exerts its effects by interacting with five dopamine receptors: D1, D2, D3, D4, and D5 (França et al., 2015). These receptors are all G-protein-coupled receptors (GPCRs) and can be further divided into two families: the D1-like family (D1 and D5 receptors) and the D2-like family (D2, D3, and D4 receptors) (Figure 2). The relationship between dopamine and sleep is bidirectional. Dopamine can both positively and negatively impact rest (Dzirasa et al., 2006). It plays a role in promoting wakefulness and regulating sleep-wake cycles. However, disrupted or imbalanced dopamine levels can contribute to SDs. The interaction of dopamine with its receptors can indeed inhibit the effects of norepinephrine, another neurotransmitter. This inhibition can result in decreased production and release of melatonin, leading to insomnia or difficulties initiating sleep (Jie et al., 2022). Overall, dopamine and sleep have a complex relationship, with dopamine influencing sleep processes and sleep controlling dopamine levels. Imbalances in dopamine signaling can significantly impact sleep patterns and contribute to SDs.

Serotonin (5-HT) Receptor

Serotonin is a monoamine neurotransmitter that plays a vital role in cognition, sleep, digestion, mood swings, and memory. Serotonin receptors are situated in the cerebral cortex in a large amount, particularly in the hippocampal region and the ventromedial prefrontal cortex. A low concentration of serotonin is linked with insomnia. Systemic application of flesinoxan or 8-OH-DPAT, both agonists of the 5-HT_{1A} receptor, increases waking and reduces slow-wave sleep and rapid eye movement (REM) sleep in rats. This suggests that the postsynaptic 5-HT_{1A} receptor activation is

Table I. Acute effects of melatonin, non-selective MT1/MT2 receptors agonists, and selective MT2 receptors partial agonists, agonists, and antagonists on sleep/wake stages of rats during the 24-h light/dark cycle.

	Latency to NREM sleep	NREM sleep duration	REM sleep duration	Wake fullness duration
Melatonin	0 D NR	0 Dark phase: D, I Depend on time after administration Light phase: 0	0 Dark phase: D, I Depend on time after administration Light phase: 0	0 Dark phase: I Depend on time after administration Light phase: 0
Non-selective MT1/MT2 receptors agonist UCM793	0	0	0	0
Non-selective MT1/MT2 receptors agonist Agomelatine	NR 0	0 Dark Phase: I light phase: 0	0 Dark Phase: I light phase: 0	0 Dark Phase: D light phase: 0
Non-selective MT1/MT2 receptors agonist Ramelteon	D 0	I Dark phase: transient I 4 h after administration Light phase: 0	0 Dark phase: transient I 4 h after administration Light phase: 0	D Dark phase: transient: I 4 h after administration Light phase: 0
Selective MT2 receptors partial agonists UCM765 and UCM924	D	I	0	D
Selective MT2 receptors agonist IIK7	D	I	0	NR
Selective MT2 receptors Antagonist 4P-PDOT	0	0	0	0

0: No change; I: Increase; D: Decrease; NR: Not reported

vital in promoting wakefulness. Furthermore, pretreatment with the mixed β -adrenoceptor and 5-HT1A/1B receptor antagonist (-) pindolol or the selective 5-HT1A receptor antagonist p-MPPI reverses the effects of 8-OH-DPAT on waking and slow wave sleep. This suggests that blocking the 5-HT1A receptor counteracts the wake-promoting effects of 8-OH-DPAT. The reduction in REM sleep observed after the administration of flesinoxan or 8-OH-DPAT may be attributed to the activation of postsynaptic 5-HT1A receptors on REM-on neurons in the laterodorsal and pedunculopontine

tegmental nuclei (Iwasaki et al., 2018). Direct infusion of 8-OH-DPAT or flesinoxan into the dorsal raphe nucleus increased REM sleep in rats, an effect that was prevented by local injection of the 5-HT1A receptor antagonist WAY 100635. This suggests that the activation of 5-HT1A receptors in the dorsal raphe nucleus is involved in the modulation of REM sleep. Additionally, the inhibition of dorsal raphe nucleus activity following somatodendritic 5-HT1A receptor stimulation suppresses the inhibitory effect of serotonin on mesopontine cholinergic neurons,

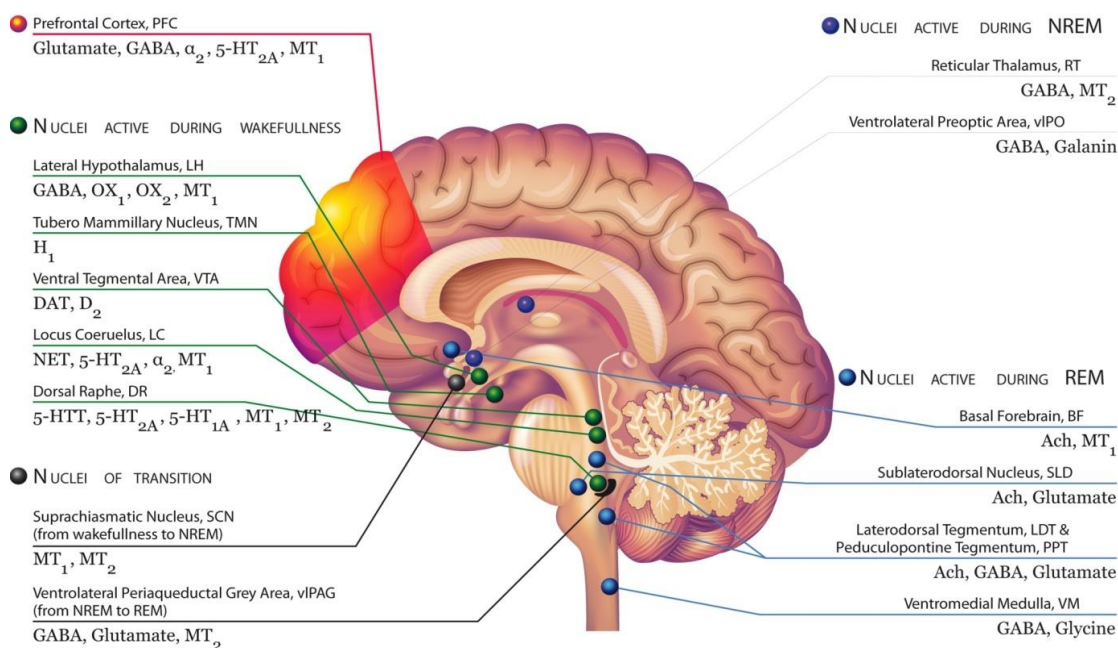


Figure 1. Brain areas involved in the regulation of sleep and wakefulness with their respective receptors, including MT1 and MT2 receptors.

Top left, green: During NREM, the serotonin neurons of the Dorsal Raphe (DR), the dopaminergic neurons of the Ventral tegmental area (VTA), and the noradrenergic neurons of the Locus Coeruleus (LC) decrease their firing activity. These neurons are silent during REM. OX1 and OX2-containing orexinergic neurons of the Lateral Hypothalamus (LH) decrease their firing activity during NREM and REM. The histaminergic H1-containing neurons of the Tubero-mammillary Nucleus (TMN) decrease their firing activity during sleep. During wakefulness, neurons of the arousal system (i.e., monoaminergic neurons, orexinergic neurons) send widespread ascending projections to the cerebral cortex, stimulating cortical desynchronization with high-frequency gamma and low-frequency theta rhythmic activity. Bottom left, black: MT1 and MT2 receptors expressed in suprachiasmatic neurons, which receive inputs directly from the retinohypothalamic tract (RHT), influenced by light and external stimuli may be likely involved in the switch from wakefulness to NREM sleep. The transition from NREM and REM is controlled by the ventrolateral periaqueductal gray area (vIPAG), containing GABA, glutamate receptors, but also melatonin MT2 receptors. Top right, red: During NREM sleep, two nuclei are particularly active: the reticular thalamus (RT), containing melatonin MT2 and GABA receptors, which is responsible for thalamocortical input to the prefrontal cortex (showing synchronized activity during NREM); and the ventrolateral preoptic area (vIPAG), containing GABA and galanin receptors. They inhibit noradrenergic, serotonergic, cholinergic, histaminergic, and hypocretinergic neurons. These nuclei play a role in the "reciprocal inhibitory" model of the sleep-wake switch. Bottom right, blue: The vIPAG is a putative "REM ON" nucleus, switching the brain to the REM sleep mode. During REM, the sublaterodorsal nucleus (SLD), the basal forebrain (BF), the lateral tegmentum/ pedunculopontine tegmentum (LDT/PPT, rich in acetylcholine receptors), and the ventromedial medulla (VM) neurons are particularly active. The BF is active in REM and wakefulness and inhibited during NREM.

increasing REM sleep (Yuan et al., 2006). Microinjection of 8-OH-DPAT or flesinoxan into the laterodorsal tegmental nuclei or the medial pontine reticular formation, regions involved in promoting and inducing REM sleep, selectively inhibits REM sleep in cats and rats. This suggests that the activation of 5-HT1A receptors in these brain regions modulates REM sleep.

Gamma Amino Butyric Acid (GABA)

GABA receptors are three types such as GABA_A, GABA_B, and GABA_C. The GABA_A receptor, a subtype of the GABA receptor, has three binding sites: the barbiturate site, the benzodiazepine site, and the neurosteroid site. Barbiturates stimulate the K1 and L1 sites on the GABA_A receptor, which enhances the binding of GABA to the receptor.

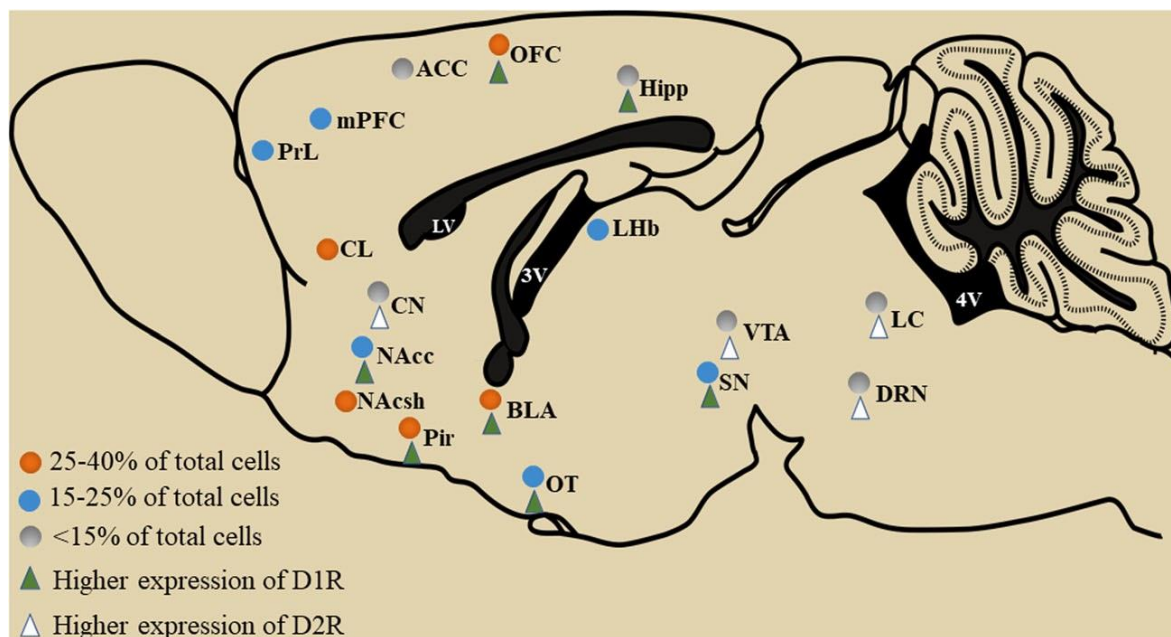


Figure 2. Distribution of dopamine D1 and D2 receptors in rat brain regions.

D1R and D2R: Dopamine 1 and 2 Receptors; BLA: Basolateral amygdale; OT: Oxytocin; VTA: Ventral Tegmental Area; CN: Cranial Nerve; NAcc: Nucleus Accumbens; NAcsh: Nucleus Accumbens Shell; PrL: Prolactin; mPFC: medial Prefrontal Cortex; Hipp: Hippocampus; SN: Substantia Nigra; DRN: Dorsal Raphe Nucleus; LC: Locus Coeruleus; OFC: Orbitofrontal Cortex; LHb: Lateral habenula

At higher doses, barbiturates can directly activate the chloride channel of the receptor without the presence of GABA. This direct activation leads to an increase in inhibitory signaling. The benzodiazepine binding site on the GABA_A receptor is functionally coupled with the GABA binding site, and they interact with each other in an allosteric manner. Benzodiazepine agonists enhance the affinity of GABA for its receptor, resulting in increased inhibitory function. Similarly, GABA or GABA_A receptor agonists, such as muscimol, increase the affinity of benzodiazepine agonists for their receptors. Stimulation of the GABA_A and benzodiazepine binding sites does not directly potentiate sleep. In humans, the stimulation of the benzodiazepine binding site promotes slow-wave sleep, particularly stage II sleep, with enhanced spindle activity while inhibiting REM sleep. In animals, most benzodiazepines increase intermediate stages of sleep and decrease or suppress REM sleep (Lancel, 1999). Injecting benzodiazepines into the dorsal raphe nucleus of the brain raises wakefulness, similar to insomnia induced by lesions in the raphe nucleus in cats. The third generation of sedative-hypnotic compounds includes imidazopyridines (e.g., zolpidem) and cyclopyrrolones (e.g., zopiclone), which bind to the GABA_A receptor complex. Zolpidem, for example, binds to the receptor's K1, L2, and Q2 subunits,

with a preference for the Q2L variant. It induces sleep at lower doses compared to benzodiazepines (Gottesmann, 2002). Zolpidem reduces sleep latency but does not significantly alter the distribution of sleep stages, although it decreases low-frequency EEG bands, enhances the frequency range of spindles, and reduces REM sleep. Neuroactive steroids like allopregnanolone and pregnanolone, active analogs, also bind to the GABA_A receptor complex. They induce an increase in slow-wave sleep, with allopregnanolone decreasing slow-frequency EEG activity and increasing spindle frequencies. Pregnenolone, a steroid precursor, does not significantly alter the distribution of sleep stages but promotes slow cortical waves within the slow-wave sleep stage. GABAB receptor antagonists, when infused in the thalamus, decrease EEG slow waves and deep slow-wave sleep while increasing light slow-wave sleep (Kim et al., 2019). At this level, reducing GABA_A receptor-mediated inhibition enhances GABA_A receptor inhibitory postsynaptic potentials in relay cells. GABA acting on GABA_C receptors, also involved in sleep-wake regulation, can influence sleep stages. For example, TPMPA, a GABA_C receptor antagonist, increases quiet and active waking, decreases total slow-wave sleep primarily by reducing the slow-wave background (with no significant effect on spindles and intermediate

stage), and decreases REM sleep (Brickley et al., 2018).

Orexin Receptor

Orexin receptors belong to the GPCR family, activated by neuropeptide orexin, also known as hypocretins. Orexins, or hypocretins, are neuropeptides crucial in regulating sleep-wake cycles and promoting wakefulness. The neurons that release orexins are most active during the day, suggesting their involvement in promoting alertness and maintaining wakefulness. Orexins stimulate other neurons to release neurotransmitters that promote wakefulness, such as dopamine, serotonin, and norepinephrine (Figure 3). These neurotransmitters help to keep us awake and alert by enhancing arousal and inhibiting sleep-promoting signals. In individuals with type 1 narcolepsy, there is a significant reduction (about 85% to 95%) in the number of orexin-producing neurons. This loss of orexin neurons is believed to be primarily responsible for the symptoms associated with narcolepsy. Common symptoms of narcolepsy include excessive daytime sleepiness, where individuals experience overwhelming and uncontrollable bouts of sleep during the day (Mieda, 2017). Other symptoms include sleep paralysis (temporary inability to move or speak while falling asleep or waking up), hallucinations (vivid and often unsettling sensory experiences during sleep-wake transitions), and cataplexy (sudden loss of muscle tone triggered by emotions). The absence or deficiency of orexin in narcolepsy disrupts the normal regulation of sleep and wakefulness, leading to the characteristic symptoms of the disorder. There are two types of orexin receptors: OX1R and OX2R. Orexin and its receptors play an essential role or the critical modulator in regulating the sleep-wake cycle, feeding, and emotions. These receptors are widely distributed in the brain. Loss of orexin is associated with narcolepsy. Dual orexin receptor antagonists (DORAs) are a relatively new class of prescription sleep aids that target the orexin system in the body. These medications, such as suvorexant, act as antagonists to orexin receptors, blocking the effects of orexins (Pizza et al., 2022). By blocking the effects of orexins, DORAs reduce the drive to stay awake and promote sleep. They help facilitate the initiation and maintenance of sleep by inhibiting the wake-promoting effects of orexins. By modulating the orexin system, DORAs can help individuals with SDs, such as insomnia, by promoting more consolidated and restful sleep. In clinical trials, DORAs are effective in improving sleep onset and maintenance and have been

approved to treat insomnia in some countries. They provide an alternative to other classes of sleep aids, such as benzodiazepines or non-benzodiazepine sedative-hypnotics, which target different neurotransmitter systems (Sun et al., 2021). Single or Dual Orexin Receptor Antagonists offer an alternative approach to promoting and maintaining sleep by targeting the orexin system. The scope of orexin signaling in the brain is much more targeted than that of the whole-brain population of GABA neurons, which may result in a more favorable side-effect profile for some patients. Initial research suggests that Single or Dual Orexin Receptor Antagonists promote Non-REM sleep and REM sleep (Feng et al., 2020).

Histamine

Histamine receptors, particularly the H1 receptors, are widely distributed throughout the brain in regions involved in sleep-wake regulation, such as the basal forebrain, locus coeruleus, raphe nuclei, mesopontine tegmentum, and thalamus. Administration of H1 receptor antagonists, such as pyrilamine and diphenhydramine, through intraperitoneal injection, has decreased wakefulness and promoted NREM sleep. These antagonists block the actions of histamine at the H1 receptors, leading to a sedative effect and facilitating sleep (Thakkar, 2011). Conversely, central administration of H1 receptor agonists, such as 2-thiazolyl ethylamine, has been found to promote wakefulness and reduce both NREM and REM sleep in a dose-dependent manner. When the H1 agonist is administered bilaterally into the pontine tegmentum, it encourages wakefulness and reduces NREM sleep during the first three hours post-injection. The effects of histamine on sleep-wakefulness regulation are further confirmed by the administration of H1 antagonists or agonists into specific brain regions. Bilateral application of an H1 antagonist, like mepyramine, in the pontine tegmentum and tuberomammillary nucleus areas has been shown to reduce wakefulness and promote sleep, supporting the role of histamine and its H1 receptors in promoting wakefulness (Hondo et al., 2010). These findings demonstrate that histamine, acting on H1 receptors in various brain regions, plays a significant role in regulating sleep-wakefulness states. Activation of H1 receptors promotes wakefulness, while their blockade facilitates sleep.

NATURAL SOURCE USED IN THE TREATMENT OF SLEEP DISORDERS

From ancient times, brahmi, jatamansi, ashwagandha, chamomile, and lavender have been used in the management of sleep disorders.

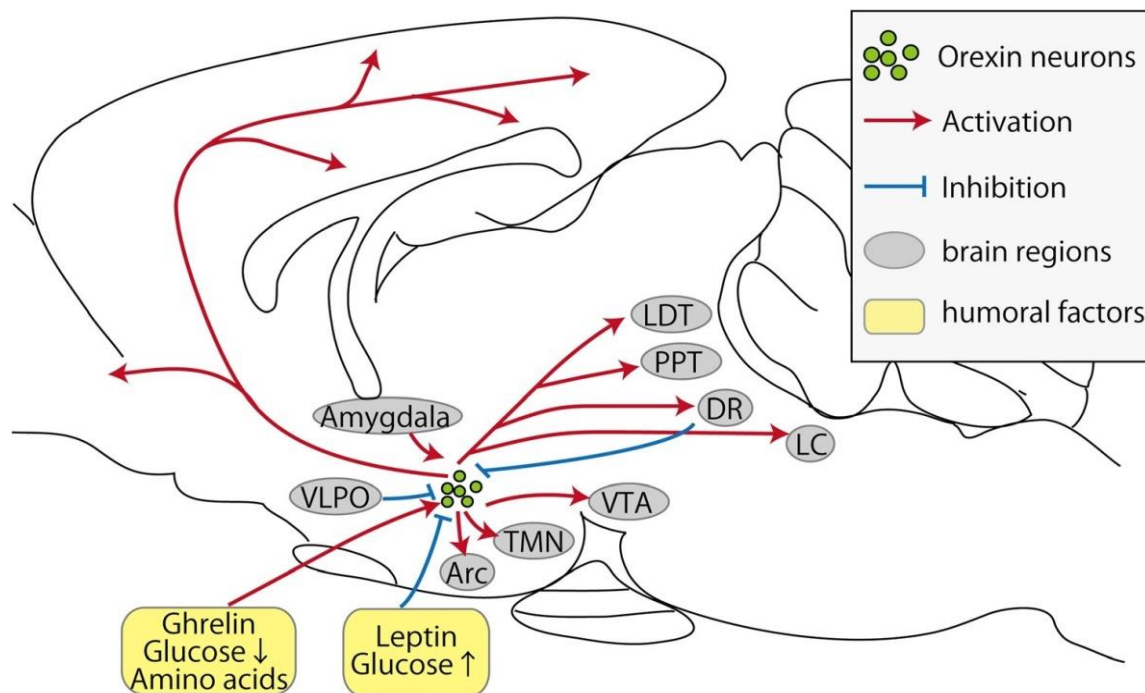


Figure 3. Schematic representation of inputs and outputs of orexin neurons.

Orexin neurons are found only in the lateral hypothalamic area but project throughout the entire central nervous system. Red arrows show excitatory projections, while blue lines show inhibitory projections. Abbreviations: Arc:: arcuate nucleus; DR:: dorsal raphe nucleus; LC:: locus coeruleus; LDT::latero dorsal tegmental nucleus; PPT:: Pedunculopontine tegmental nucleus; TMN:: Tubero Mammillary Nucleus; VTA:: Ventral Tegmental Area; VLPO:: Vento lateral optoc nucleus.

Humans apply brahmi paste on the forehead to calm their minds and bodies and use green tea decoction fused with chamomile, jatamansi, or lavender to distress their minds and boost their immunity.

Brahmi

Brahmi leaves are used in traditional medicine to alleviate restlessness, insomnia, and other neurological disorders. However, the effects of *Bacopa monnieri* on sleep patterns have shown mixed results. According to a study using the Bergen Insomnia Scale, *Bacopa monnieri* did not significantly improve sleep patterns compared to a placebo. However, its use did show improvements in emotions, health, and pain. *Bacopa monnieri* has also been associated with notable reductions in immunoglobulin A and α -amylase levels compared to a placebo. These findings suggest the potential effects of *Bacopa monnieri* on stress and immune functions. On the other hand, *Centella asiatica* has demonstrated anxiolytic effects in various rodent models, including healthy, chronically stressed, and sleep-deprived animals (Lopresti et al., 2021). In sleep-deprived mice, *Centella asiatica* has been found to reduce oxidative stress and alleviate

anxiety symptoms, suggesting a potential protective effect against the negative consequences of sleep deprivation or wakefulness. Moreover, the efficacy of *Centella asiatica* has been found to increase when co-administered with nitric oxide antagonists, while it decreases when administered with nitric oxide agonists. This suggests an interaction between *Centella asiatica* and nitric oxide signaling pathways, possibly contributing to its anxiolytic effects (Gray et al., 2017). Brahmi has some side effects such as slow heart rate, higher secretion of thyroid hormones, and irregular menstruation. Bacoside A and B are the important saponins responsible for the transmission of nerve impulses and indirectly affect sleep disorders (Patel et al., 2018).

Vacha

Vacha, the *Acorus calamus*, can treat various health problems. The root of Vacha contains several phytochemicals such as β -asarone, β carotene, phytic acids, choline, flavones, ethanol, methanol, camphor, eugenol, and phenols. In Traditional Chinese Medicine and Ayurveda, Vacha addresses neurological disorders, including epilepsy, headaches, Alzheimer's disease, and

insomnia. The herb is believed to have calming and sedative effects, which can contribute to its use in promoting sleep and addressing SDs. Studies have shown that the *Acorus calamus*'s rhizome can positively impact body mass index (BMI) and sleep patterns. These findings suggest that Vacha root may have a potential role in improving sleep quality and body weight regulation. In Ayurveda, Vacha root is sometimes used with herbs such as amla, brahmi, and ashwagandha to address SDs. These herbal combinations are believed to enhance the overall efficacy of treatment for sleep-related issues (V. Sharma et al., 2020). Vacha showed some side effects such as irritable bowel, constipation, and diarrhea. Beta asarone of vacha is effective in the treatment of sleep disorders (Liu et al., 2023).

Ashwagandha

Withania somnifera, commonly known as Indian ginseng or ashwagandha, and its potential effects on sleep. Ashwagandha is known for its ability to promote vitality, longevity, and overall well-being. One of the components of ashwagandha, trimethylene glycol, has been suggested to be responsible for its sleep-inducing properties. Ashwagandha is believed to enhance the coordination between the mind and senses, balance hormones, reduce stress, and improve nerve and muscle activity, contributing to better sleep. Traditionally, ashwagandha root powder is taken orally with warm milk as a medium to promote better sleep. In recent studies, a meta-analysis assessed various parameters related to sleep, including the sleep quality Scale, sleep onset latency, total sleep time, wake time after sleep onset, total time in bed, and sleep efficiency. The findings of the meta-analysis indicated that ashwagandha extracts significantly positively impacted overall sleep compared to a placebo. The effects were more pronounced in adults diagnosed with insomnia, mainly when the treatment dose was equal to or greater than 600 mg/day and the treatment duration was similar to or longer than 8 weeks. However, the impact of age on the effectiveness of ashwagandha extract for sleep improvement still needs to be determined due to a lack of sufficient trials specifically examining different age groups (Cheah et al., 2021). Liver damage, liver failure, hallucination, and constipation are the common side effects of ashwagandha. Different concentrations of withanolide of ashwagandha successfully help with sleep disorders (Kalpesh et al., 2020).

Jatamansi

Nardostachys jatamansi is widely used to treat various disorders in different medicinal systems. *Nardostachys jatamansi* possesses several pharmacological activities, including sedative, antidepressant, anti-epileptic, hypolipidemic, hepatoprotective, neuroprotective, anti-ischemic, anti-arrhythmic, and anticonvulsant effects. Jatamansone, nardostachone, and actinidine are among this plant's primary and secondary metabolites. One of the critical mechanisms by which *Nardostachys jatamansi* exerts its effects is by increasing the levels of neurotransmitters like serotonin. This can contribute to its sedative and antidepressant activities. *Nardostachys jatamansi* is also known for its potent antioxidant properties, which help reduce oxidative stress. Lowering oxidative stress can benefit conditions such as neurosis and SDs. Studies have demonstrated that *Nardostachys jatamansi* extract has significant effects on sleep parameters. In albino mice, it has been found to reduce the latency of sleep onset, meaning it shortens the time it takes to fall asleep. Additionally, *Nardostachys jatamansi* has been shown to potentiate the effects of pentobarbital, a sedative. It shortens sleep latency and prolongs total sleeping time, although not as significantly as diazepam, a well-known sedative drug. The effects of *Nardostachys jatamansi* on sleep and the central nervous system (CNS) may be related to its modulation of the GABAergic system. GABA is an inhibitory neurotransmitter that is crucial in regulating sleep and anxiety. Changes in the duration of pentobarbital-induced sleep can be used to investigate the stimulatory or inhibitory effects on the CNS, particularly concerning the GABAergic system (H. Kim et al., 2022). Jatamansone significantly reduced the time taken to start sleep.

Poria cocos

Poria cocos, commonly known as Fu Ling, is a sclerotium fungus that grows on the roots of pine trees. It has a long history of traditional use in various medicinal systems. *Poria cocos* have been traditionally used to treat insomnia and improve sleep quality and structure. *Poria cocos* contains several bioactive compounds as its primary, and secondary metabolites, including parchymic acid, pericollic acid, periodic acid, and 3 β -hydroxylanosta-7,9-diene-24,26-diol. These compounds contribute to the medicinal properties of *Poria cocos*. One of the mechanisms by which *Poria cocos* may exert its effects on sleep is through the modulation of inhibitory neurotransmission via

regulating GABA_A receptors. GABA is the primary inhibitory neurotransmitter in the central nervous system, and activation of GABA_A receptors promotes relaxation, reduces anxiety, and facilitates sleep. By regulating GABA_A receptors, *Poria cocos* may enhance the inhibitory neurotransmission mediated by GABA, leading to improved sleep quality and structure. However, it's important to note that the specific mechanisms and pathways involved in *Poria cocos*' effect on sleep are still being studied, and further research is needed to fully understand its actions. Pachymic acid of *Poria cocos* is responsible for sleep-related disorder (Toolika et al., 2015).

Valerian

Valeriana officinalis, commonly known as valerian root, has been traditionally used for its sedative and sleep-enhancing properties. It is believed to have a calming effect on the nervous system and promote sleep. Valerian root has been found to reduce brain activity in the motor cortex, which may contribute to its relaxation and sedative effects. It is thought to exert its effects by increasing the levels of GABA in the brain. GABA is an inhibitory neurotransmitter that helps reduce nervous system activity and promote relaxation. By elevating GABA levels, valerian root can calm the brain, reducing anxiety and inducing sleep. This is why it has been traditionally used for insomnia and sleep disturbances. One of the chemical constituents of *Valeriana officinalis*, known as valepotriate, has been found to exhibit mild sedative effects and improve sleep quality and sleep latency.

Chamomile

Matricaria chamomilla, commonly known as chamomile, is traditionally used for its calming and sleep-promoting effects. Chamomile contains several active phytochemicals, including apigenin, chamazulene, and bisabolol, contributing to its medicinal properties. Apigenin, one of the primary phytochemicals found in chamomile, has been shown to possess benzodiazepine-like hypnotic activity. It interacts with GABA receptors in the brain, acting as a GABA antagonist. GABA is an inhibitory neurotransmitter that helps reduce neuronal activity and promote relaxation. Chamomile tea is a popular herbal remedy that promotes sleepiness and relieves insomnia. It is believed to have a calming effect on the nervous system and induce relaxation. The antioxidants present in chamomile, including apigenin, may also contribute to its sleep-enhancing properties. In a study involving elderly participants, chamomile extracts significantly improved sleep quality

compared to a control group (Adib-Hajbaghery & Mousavi, 2017). The participants who received chamomile extract showed a notable improvement in sleep quality, as assessed by the Sleep Quality Index.

Lavender

Lavandula angustifolia, commonly known as lavender, is a flowering plant that produces an essential oil with various compounds, including linalyl acetate and linalool (Chen et al., 2022). These compounds have been found to act on GABA pathways in the brain, which promote relaxation and reduce anxiety. Linalyl acetate and linalool in lavender oil have been associated with sedative and stress-relieving activities. They can modulate the activity of GABA receptors, which results in a calming effect on the nervous system. Lavender oil is commonly used as a natural remedy for insomnia. Inhalation of lavender oil or its use in aromatherapy massage has positively impacted sleep quality, particularly in individuals with insomnia (Oh et al., 2011).

Lotus

Nelumbo nucifera, commonly known as lotus, is traditionally used for its medicinal properties. Both the seeds and leaves of *Nelumbo nucifera* contain γ -aminobutyric acid (GABA), a neurotransmitter that reduces neuronal activity and promotes relaxation. Lotus leaf extracts, specifically quercetin-3-glucuronide found in the sections, have been shown to increase sleep time and promote NREM sleep. This is believed to occur through the binding of quercetin-3-glucuronide to the GABA_A-benzodiazepine receptor, which regulates sleep (Nasim et al., 2020). *Nelumbo nucifera* has also been found to increase the concentration of GABA and the expression of GABA_A receptors, further supporting its potential role in promoting sleep.

Lemon balm

Melissa officinalis (lemon balm) extracts, especially rosmarinic acid, improved sleep quality in post-menopausal women. Before the treatment, the mean score of sleep quality in the intervention group was 13.1 ± 48.60 , and after the treatment, it improved to 8.1 ± 58.97 . There was a significant difference in the mean score of sleep quality before and after the intervention. On the other hand, in the control group, the sleep quality score was 12.98 ± 2.50 at the beginning of the study and 11.72 ± 2.45 after the study. This indicates that the control group did not experience a significant improvement in sleep quality (Sharma et al., 2022). These findings suggest that lemon balm extracts

had a positive effect on sleep quality in post-menopausal women.

Shankpushpi

Convolvulus pluricaulis, also known as Shankpushpi, is an ayurvedic medicine used for centuries to treat nervous system ailments. The plant contains several chemical constituents such as shankpushpine, convolvuline, convolidine, convolvine, convolamine, convoline, confoline, and convozine. These compounds contribute to its therapeutic properties. Shankpushpi has been found to possess antioxidant and antiapoptotic properties, which can help protect the nervous system from oxidative stress and cell death. The secondary metabolites present in Shankpushpi interact with various neurosynaptic and serotonergic signaling pathways in the brain. One of the mechanisms by which Shankpushpi exerts its effects is by inducing calmness in the nerves and reducing stress. It does this by lowering the levels of cortisol and adrenaline, which are stress hormones. By regulating these hormones, Shankpushpi promotes a sense of calmness and relaxation. Furthermore, the various compounds found in Shankpushpi have shown therapeutic potential in central nervous system (CNS) disorders (Unno et al., 2017).

Green tea

A unique beverage from *Camellia sinensis* is popular among Asian homes. Due to its medicinal properties, it is known worldwide as the second most consumable drink after water. It contains alkaloids, flavonoids, catechins, polyphenols, amino acids, carbohydrates, aromatic compounds, vitamins, and minerals. It possessed anti-diabetic, antiviral, antibacterial, antioxidant, and neuroprotective effects. L- theanine, an essential amino acid in green tea, is responsible for its calming properties. L- theanine elevates the levels of GABA, serotonin, and dopamine. It triggers the release of alpha waves, enhancing calmness and reducing stress. Consuming green tea at bedtime improves the quality of sleep and fights insomnia (Tuo et al., 2023).

Angelica species

Angelica species, including *Angelica sinensis* (also known as Dong Quai), *Angelica gigas*, *Angelica acutiloba*, *Angelica archangelica*, and *Angelica pubescentis*, have a long history of traditional use in various cultures. These plants have been attributed to a range of medicinal properties. In conventional medicine, Angelica species are often used for their ability to nourish the blood, regulate menstruation, and treat

conditions such as constipation and fever. Additionally, Angelica species have been utilized for their sedative and analgesic effects. *Angelica archangelica* and *Angelica pubescentis* have traditionally been employed to treat stomach and intestinal disturbances, skin diseases, respiratory problems, rheumatoid arthritis, headaches, paralysis, nervousness, and insomnia. Furanocoumarin especially archangelicin, and bergapten has been studied for its effects on SDs and sleep rhythm. Research on the sleep patterns of *Drosophila* flies (a common model organism in scientific studies) showed that *Angelica sinensis* improved SDs by modulating sleep rhythm (Bian et al., 2021).

Ziziphi spinosae Semen

The seeds of *Ziziphus jujuba* var. spinosae, a variety of jujube or Chinese date, have been used in traditional medicine for various purposes, including treating anxiety, depression, insomnia, and neurological disorders such as headaches and vertigo. These seeds possess several pharmacological effects, including anti-inflammatory, anticonvulsant, antiplatelet aggregation, anti-myocardial ischemia, anti-arrhythmic, anti-aging, antioxidant, and blood pressure-lowering properties. Sanjoinine A, jujuboside A, and spinosin are essential secondary metabolites found in the seeds of *Ziziphus jujuba* var. spinosae. These compounds contribute to its therapeutic effects. The sedative and hypnotic effects of *Ziziphus jujuba* var. spinosae are primarily mediated through the GABAergic and serotonergic systems. The GABAergic system plays a crucial role in promoting relaxation and reducing anxiety. By interacting with GABA receptors, *Ziziphus jujuba* var. spinosae can enhance the activity of GABA, leading to sedative and calming effects. The serotonergic system, specifically serotonin receptors, also regulates sleep and mood, and the impact of *Ziziphus jujuba* var. spinosae on these receptors may further enhance its sedative and hypnotic properties (Sobhanifar et al., 2022).

Datura

Datura stramonium, commonly known as jimsonweed, is a highly toxic plant. It contains several tropane alkaloids, including hyoscyne (also known as scopolamine), hyoscyamine, and nicotinamide, as well as other phytochemicals such as sitosterol, triterpenes, daturaolone, and datura diol. While *Datura stramonium* has been used in traditional medicine, particularly in Ayurveda, it is essential to note that its use carries significant risks due to its toxicity. The purification process is

crucial to remove or reduce the concentration of toxic compounds, making it safer for medicinal use. In Ayurveda, *Datura stramonium* has been historically employed to treat various conditions, including insomnia, fever, insanity, lumbago, sciatica, neuralgia, skin diseases, and diarrhea. However, it is crucial to emphasize that the use of *Datura stramonium* for medicinal purposes should only be undertaken under the guidance and supervision of trained healthcare professionals with knowledge and expertise in its appropriate use and dosage. One of the mechanisms of action of *Datura stramonium* is its interaction with opioid receptors, which may contribute to its hypnotic or sleep-inducing activity (Ayala-Guerrero & Medina 2017).

Passion flower

Passiflora incarnata, commonly known as passionflower, is a flowering plant that contains various bioactive compounds. Some of the notable compounds found in *Passiflora incarnata* L flowers include chrysin, vitexin, coumarin, umbelliferone, schaftoside, isoschaftoside, isovitexin-2"-O- β -glucoside, isoorientin-2"-O- β -glucoside, vicenin-2, lucenin-2, isovitexin, and isoorientin. Passion flower has been traditionally used in the treatment of anxiety and insomnia (Patel et al., 2009). Its mechanisms of action involve interactions with the GABA neurotransmitter system. It has been observed to elevate the levels of GABA in the brain, which has calming and relaxing effects. Studies have shown that passion flower extract can decrease wakefulness and the timing of REM sleep (Liu et al., 2022).

Drum stick (Saijan)

Moringa oleifera, also known as drumstick tree or said, is a plant with high nutritional and medicinal value. In an experiment assessing the effects of the ethanolic extract of *Moringa oleifera* on sleep, estazolam (a sedative-hypnotic drug) and kaempferol (a flavonoid compound) were used as reference substances. The experiment results indicated that administering 2g/kg of *Moringa oleifera* ethanolic extract and 2mg/kg of kaempferol significantly affected sedative-hypnotic behavior. Additionally, the levels of GABA and glutamic acid were increased (Schmidt et al., 2006) (Figure 4).

SYNTHETIC MOLECULES USED IN THE TREATMENT OF SLEEP DISORDERS

Pramipexole

Pramipexole is a benzothiazole derivative that acts as a dopamine D2-3 agonist. It has been primarily used to treat Parkinson's disease and

restless legs syndrome (RLS). While it is not explicitly approved for treating REM SD, some evidence suggests its potential efficacy in managing this condition. REM sleep behavior disorder (RBD) is an SD characterized by the absence of normal muscle paralysis during the REM sleep phase, resulting in the acting out of dreams. Pramipexole has been investigated as a potential treatment for RBD due to its ability to modulate dopamine receptors in the brain. Several studies have reported positive outcomes with pramipexole in reducing the frequency and intensity of RBD symptoms, such as dream enactment and sleep-related injuries. It improves sleep quality by reducing the amount of muscle activity during REM sleep. One advantage of using pramipexole for RBD treatment is its relatively low risk of adverse effects compared to other medications commonly used for RBD, such as clonazepam, a benzodiazepine (Petr et al., 2010). However, it is essential to note that pramipexole, like any medication, can have potential side effects. Common side effects of pramipexole include nausea, dizziness, drowsiness, and orthostatic hypotension.

Ropinirole

Ropinirole is an indolone derivative that acts as a dopamine agonist. It has been widely used to treat restless legs syndrome (RLS) and Parkinson's disease. Ropinirole works by stimulating dopamine receptors in the brain, which helps to alleviate symptoms associated with these conditions. In the context of RLS, ropinirole has demonstrated efficacy in reducing the unpleasant sensations and urge to move the legs that typically occur at rest, especially during the evening and night-time. By increasing dopamine activity in the brain, ropinirole helps to regulate movement and reduce RLS symptoms, thus improving sleep quality. Moreover, prolonged-release formulations of ropinirole have shown promising results in modifying sleep quality and minimizing the occurrence of sleep attacks. Prolonged-release formulations are designed to release the medication gradually over an extended period, providing a more steady and controlled release of the active compound (Pierantozzi et al., 2016). Compared to immediate-release formulations of ropinirole, which are rapidly absorbed and metabolized, prolonged-release formulations provide a sustained effect throughout the day and night. This continuous coverage helps maintain stable dopamine levels and effectively manage symptoms, improving sleep quality and reducing sleep attacks.

Rotigotine

or non-benzodiazepine sedative-hypnotics, ramelteon does not exert its effects through direct



Figure 4. Natural sources are effective in the treatment of sleep disorders.

Rotigotine is a dopamine receptor agonist in the class of thiophene-linked tetrahydronaphthalene derivatives. It has been primarily used to treat Parkinson's disease and restless legs syndrome (RLS). By activating dopamine receptors, specifically D1 and D2 receptors, rotigotine helps to regulate dopamine signaling in the brain, which plays a crucial role in movement and other neurological functions. In addition to its primary therapeutic effects on motor symptoms, rotigotine has been reported to impact sleep timing and wakefulness. Sleep disturbances, including disrupted sleep patterns and excessive daytime sleepiness, are common symptoms of Parkinson's disease and RLS. By modulating dopamine receptors, rotigotine promotes more regular sleep-wake cycles and reduces the frequency and intensity of wakeful periods during sleep (Neubauer 2008).

Ramelteon

Ramelteon is a selective melatonin receptor agonist that explicitly targets the MT1 and MT2 receptors. It is approved by the US Food and Drug Administration (FDA) for treating insomnia characterized by difficulty with sleep onset. Unlike other sleep medications, such as benzodiazepines

sedation. Instead, it acts by enhancing sleep through its actions on sleep regulatory mechanisms within the brain's suprachiasmatic nucleus. The suprachiasmatic core regulates the circadian rhythm, crucial in sleep-wake cycles. By binding to the MT1 and MT2 receptors in this area, ramelteon helps to synchronize the sleep-wake cycle and promote sleep onset (Czeisler et al., 2005).

Modafinil

Shift-work SD refers to the disruption of the normal sleep-wake cycle experienced by individuals who work non-traditional hours, such as night shifts. The study's findings indicated that treatment with 200 mg of modafinil reduced extreme sleepiness in patients with shift-work SD, compared to a placebo. Furthermore, there was a modest but statistically significant improvement in performance measures in the treated group. However, it is essential to note that despite the treatment with modafinil, patients still experienced residual sleepiness during the night shift. This suggests a need to develop more effective interventions to address the excessive sleepiness observed in individuals with shift-work SD. The study also highlighted the similarities

between the drowsiness experienced by individuals with shift-work SD. during night work and the daytime somnolence observed in patients with narcolepsy. While modafinil showed some benefits in reducing sleepiness and improving symptoms in shift-work SD, it did not fully restore sleepiness to normal daytime levels (Wichniak et al., 2021).

Trazodone

Trazodone, an antidepressant medication, effectively treats primary and secondary insomnia. Primary insomnia is not attributable to another medical condition, while secondary insomnia is a symptom of another disease. Studies conducted from 1980 to 2000 primarily focused on using trazodone at higher doses ($\geq 100\text{mg/d}$) for treating insomnia in individuals with depression. Trazodone's sedating properties made it helpful in improving sleep quality and treating depression-related sleep disturbances during that time. However, since the 2000s, the utility of trazodone has been expanded to include the treatment of secondary insomnia in individuals without depression. It effectively manages insomnia symptoms associated with conditions such as dementia and in otherwise healthy individuals. The side effects of trazodone are typically dose-dependent, with drowsiness being the most common side effect. This sedative effect can be beneficial in the treatment of insomnia. Other side effects may include dizziness, dry mouth, blurred vision, and low blood pressure (Li & Yang 2020,).

Pitolisant

Pitolisant is a medication that acts as a histamine 3 receptor antagonist/inverse agonist. Blocking or inhibiting these receptors can increase histamine release in the brain, enhancing wakefulness. Clinical studies have demonstrated the efficacy of pitolisant in reducing excessive daytime sleepiness and cataplexy. Excessive daytime sleepiness is a common symptom in conditions such as narcolepsy, and cataplexy refers to sudden muscle weakness or loss of muscle tone often triggered by strong emotions. Compared to a placebo, pitolisant has been shown to significantly decrease excessive daytime sleepiness and reduce the frequency of cataplexy episodes. This indicates its potential as a treatment option for individuals with narcolepsy or other conditions associated with excessive sleepiness (Lin et al., 2023).

Quetiapine

Low-dose quetiapine, an antipsychotic medication, may be effective in improving sleep quality compared to a placebo. The effect sizes

were estimated using mean difference (M.D.), standard mean difference (SMD), and odds ratio (OR) in a random-effects model. The analysis of 21 clinical trials indicated that quetiapine significantly improved sleep quality in various populations, including those with general anxiety disorder, major depressive disorder, and healthy individuals. The dosages of 50 mg, 150 mg, and 300 mg were found to be effective. Furthermore, quetiapine was found to increase total sleep time compared to placebo. However, its effect on sleep time was not significantly different from other psychiatric drugs. It's important to note that using quetiapine for insomnia is considered off-label, meaning it is not explicitly approved by regulatory authorities for this indication. Off-label use should be carefully considered and monitored by healthcare professionals, taking into account the potential benefits and risks associated with the medication (Dokkedal-Silva et al., 2020). Individual factors such as age and sex were correlated with the effect size of sleep quality, suggesting that these variables may influence the response to quetiapine treatment.

Clonazepam

Clonazepam, a medication commonly used to treat various conditions, including anxiety and seizures, has been suggested to treat REM sleep behavior disorder (RBD). RBD is a type of parasomnia that primarily affects older individuals. Patients with sleep bruxism admitted for the study exhibited worsened sleep quality, daytime sleepiness, depressive symptoms, and restless leg syndrome severity (Saletu et al., 2005). Compared to a placebo, administering 1 mg of clonazepam resulted in significant improvements in various sleep parameters. Specifically, clonazepam led to a considerable reduction in the mean bruxism index, which measures the frequency of teeth grinding during sleep. The index decreased from 9.3 to 6.3 teeth-grinding events per hour of sleep. In addition to the improvement in bruxism, clonazepam also had a positive impact on overall sleep patterns. It significantly increased the total sleep period, sleep time, sleep efficiency (the percentage of time spent asleep during the entire sleep period), and stage 2 sleep (a stage of NREM sleep). Clonazepam also reduced the time to fall asleep (sleep latency) and the time spent awake during the total sleep period. Furthermore, clonazepam resulted in a decrease in periodic leg movements during sleep.

Lorazepam

Lorazepam, an anxiolytic drug commonly used to treat anxiety disorders, uses a 2-mg dose.

The evaluation was conducted over a 16-night protocol, with 7 nights dedicated to the drug trial. Initially, and with continued use, lorazepam was found to be moderately effective in inducing and maintaining sleep. This suggests that the drug helped individuals fall asleep and stay asleep during the night. There are some side effects associated with lorazepam use (Kales et al., 1986). Two subjects experienced episodes of memory impairment and confusion. These side effects are known to be associated with benzodiazepine medications like lorazepam. Additionally, as the trial progressed and the drug was used for an extended period, the group means showed increased daytime anxiety and tension.

Estazolam

Estazolam, a medication used for its hypnotic (sleep-inducing) effects, in a group of individuals experiencing insomnia. The study included seven men and eight women with a mean age of 30.3 +/- 8.6 years. These participants complained of insomnia and showed polysomnographic evidence of disturbed sleep, measuring and recording various physiological parameters during sleep. The study was conducted in a laboratory setting throughout four consecutive nights with a placebo, which served as the baseline and screening phase. Following this, five 2-night drug administration periods were separated by 5-day drug washout periods spent at home. The drug administration periods involved using estazolam at four doses (0.25, 0.5, 1.0, and 2.0 mg) and a placebo. The study's results indicated that estazolam had a dose-dependent effect on sleep parameters. Specifically, it significantly increased total sleep time and reduced the time spent awake during sleep (Roehrs et al., 1983). The sleep latency, which refers to the time it takes to fall asleep, was decreased systematically with increasing doses of estazolam.

Triazolam

A study found that both acute (short-term) and chronic (long-term) administration of triazolam were effective in reducing sleep latency, which is the time it takes to fall asleep. Triazolam also increased sleep duration, improved sleep efficiency (the ratio of time spent asleep to time spent in bed), and decreased total wake time. These effects indicate that triazolam facilitated the onset and maintenance of sleep. The study did not find any significant results of triazolam on sleep staging. Sleep staging refers to the categorization of sleep into different stages, such as stages 1, 2, 3 (deep sleep), and REM sleep. Triazolam did not significantly alter deep sleep or REM sleep, and

there was no evidence of REM rebound (an increase in REM sleep following discontinuation of the medication). However, sleep stages 1 and 2 were significantly altered by triazolam treatment in a positive direction. This means that the drug improved the quality of lighter stages of sleep, possibly by decreasing sleep onset and enhancing sleep continuity (Pegram et al., 1980). After discontinuing triazolam treatment, some of the measured sleep parameters shifted toward baseline measures on the first night.

Temazepam

Patients with obstructive sleep apnea (OSA) were administered temazepam (10 mg) to aid in sleep. The study compared the temazepam group (n = 73) to a control group of OSA patients. During the initial 3 hours of the study, no significant differences in sleep-related variables were observed between the temazepam and control groups. This indicates that the administration of temazepam did not result in notable changes in sleep parameters during the early phase of the study. However, when considering the entire study duration, the temazepam group exhibited a reduced total sleep time compared to the control group. This reduction in whole sleep time may be attributed to the sleep difficulties experienced by the patients that led to the administration of temazepam in the first place. Regarding respiratory-related variables, including measures such as the apnea-hypopnea index (AHI), arousal index, oxygen desaturation, apnea index, hypopnea index, and event duration, no significant differences were observed between the temazepam group and the control group (Walsh et al., 2018). This suggests that temazepam did not considerably impact these respiratory parameters, whether assessed during the initial 3 hours of the study or over the entire duration.

Doxepin

U.S. Food and Drug Administration (FDA) granted doxepin, a sedating tricyclic drug, to treat insomnia. The analysis included nine randomized placebo-controlled trials that investigated the effectiveness of doxepin at doses of 3 mg and 6 mg. Out of the nine trials, six focused on doxepin at amounts ranging from 1 mg to 6 mg per day, two studies examined doxepin at higher doses ranging from 25 mg to 300 mg per day, and one study investigated the combination of ramelteon (8 mg) and doxepin (3 mg). The analysis revealed that low-dose doxepin (1-6 mg) had a small to medium effect size compared to placebo for improving sleep maintenance and duration. However, there was no significant effect on sleep initiation,

meaning that low-dose doxepin did not significantly help with falling asleep faster. These effects were observed both immediately after treatment and in the short term. Notably, there was no significant residual effect the next day with low-dose doxepin, suggesting that it did not cause significant daytime drowsiness or impairment (Yeung et al., 2015). The most common side effects associated with low-dose doxepin were headache and somnolence, which refers to a state of drowsiness or sleepiness.

Zopiclone

Zopiclone is a hypnotic medication with sedative and hypnotic properties. It is classified as a non-benzodiazepine (NBZD) hypnotic and is not chemically related to benzodiazepines (BZDs). The mode of action of zopiclone involves its agonistic activity at GABA_A receptors, which are inhibitory in the brain. Zopiclone enhances GABA-driven synaptic inhibition by binding to specific GABA_A receptor subtypes. Unlike other Z-drugs (a class of hypnotics including zolpidem), zopiclone is relatively less selective in binding to GABA receptor subtypes. It exhibits a high affinity for subtypes that contain $\alpha 1$ and $\alpha 2$ subunits (Louzada et al., 2021).

Zolpidem

Zolpidem belongs to the imidazopyridine class of compounds and exerts its effects by enhancing the function of the GABA_A receptor through its interaction with the Omega-1 receptor subtype. One of the advantages of zolpidem is its favorable pharmacokinetic profile. It has a rapid onset of action, allowing patients to use it when they have trouble falling asleep later at night. Significantly, zolpidem is associated with minimal residual cognitive impairment the following morning, an advantage compared to other hypnotic medications. Zolpidem has been shown to improve the total duration of sleep and reduce night-time awakenings, making it effective in addressing sleep difficulties associated with insomnia. In terms of adverse effects, zolpidem has been found to have a good profile (Dang et al., 2011). It is associated with a low potential for addiction or dependence compared to benzodiazepines, an important consideration when selecting sleep medications.

Suvorexant

Suvorexant is an aromatic amide compound that is synthesized by formally condensing the carboxy group of 5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoic acid with the secondary amino group of 5-chloro-2-[(5R)-5-methyl-1,4-diazepan-1-yl]-1,3-

benzoxazole. It is classified as an orexin receptor antagonist primarily used to manage insomnia. As a central nervous system depressant and an orexin receptor antagonist, suvorexant blocks the activity of orexin receptors OX1R and OX2R. Orexin receptors play a crucial role in regulating wakefulness and arousal. By inhibiting these receptors, suvorexant promotes sleep by reducing sleeplessness and decreasing arousal levels. Suvorexant has been approved by regulatory authorities for the treatment of insomnia, providing a novel therapeutic option for individuals experiencing sleep difficulties. Regarding its pharmacological properties, suvorexant functions as an orexin receptor antagonist and a P-Glycoprotein inhibitor. The P-Glycoprotein inhibition may affect the pharmacokinetics of certain medications that are substrates for this transporter protein. Furthermore, suvorexant acts as a cytochrome P450 3A inhibitor, which can influence the metabolism of other drugs metabolized by this enzyme system (Han et al., 2023).

Lemborexant

Lemborexant is a novel medication for insomnia characterized by sleep onset and maintenance difficulties. It belongs to the class of dual orexin receptor antagonists, similar to suvorexant, and targets the brain's orexin system. Recent research in the field of S.D.s has shed light on the underlying mechanisms of insomnia. It is now believed that insomnia is not solely due to a lack of sleep-promoting circuits but rather an inability to inhibit wake-promoting circuits effectively. This shift in understanding has led to the development of medications like lemborexant that focus on countering inappropriate wakefulness rather than simply enhancing sleep drive. Traditionally used pharmacological treatments for insomnia, such as zopiclone, zolpidem, and benzodiazepines, primarily modulate GABA and melatonin receptors to enhance sleep drive. In contrast, lemborexant and other orexin antagonists, like suvorexant, target the orexin receptors and work by inhibiting the wake-promoting effects of orexin in the brain. The mechanism of action of lemborexant is mainly attributed to its activity as an orexin receptor antagonist. By blocking the orexin receptors, lemborexant helps reduce wakefulness and promote sleep. Additionally, lemborexant has been identified as a cytochrome P450 2B6 inducer, which may increase the activity of this specific enzyme involved in drug metabolism. This interaction can affect the metabolism and effectiveness of other medications

metabolized by cytochrome P450 2B6 (Moline et al., 2020).

Daridorexant

Daridorexant, previously known as nemorexant, is a selective dual orexin receptor antagonist used to treat insomnia. Insomnia is an S.D. characterized by difficulties with sleep onset and/or sleep maintenance, leading to impairment of daytime functioning. It is a chronic condition with long-term health effects often associated with co-morbidities like hypertension, diabetes, and depression. Conventional treatments for insomnia typically target receptors such as GABA_A, serotonin, histamine, or melatonin. However, these medications often have undesirable side effects, including next-morning residual sleepiness, motor incoordination, falls, and memory and cognitive impairment. Novel drugs focusing on the orexin signaling pathway regulating wakefulness have gained attention. Orexin receptor antagonists have shown promise in improving sleep and addressing the wake-promoting effects associated with insomnia. Daridorexant was developed through an intensive drug discovery program to enhance potency, maximize the duration of action, and minimize next-morning residual activity. It selectively blocks the binding of orexins, wake-promoting neuropeptides, and endogenous ligands to orexin receptors OX1R and OX2R. In investigational trials, daridorexant has been reported to improve sleep and daytime functioning in patients with insomnia. Phase 3 clinical trials demonstrated dose-dependent improvements in objective latency to persistent rest, accurate wake time after sleep onset, subjective total sleep time, and subjective daytime functioning compared to placebo (Nie & Blair, 2023). Overall, daridorexant was well tolerated by the participants.

Almorexant

Almorexant increased REM and NREM sleep in a dose-dependent manner. REM sleep is associated with dreaming and cognitive processes, while NREM sleep is characterized by deep sleep stages. Orexin 1 and 2 are two subtypes of orexin receptors. Orexin 1 and 2 receptors did not respond to almorexant or orexin A, indicating that these receptors are necessary for the effects of both compounds. This suggested that the orexin 2 receptor is essential for locomotion and sleep regulation mediated by almorexant. Cataplexy is a sudden loss of muscle tone triggered by strong emotions and is a characteristic symptom of narcolepsy. Almorexant did not induce cataplexy in normal mice. Almorexant does not cause cataplexy under normal conditions. In vitro experiments

revealed that under non-equilibrium conditions, almorexant acted as a dual antagonist (blocking both orexin 1 and 2 receptors), while under equilibrium conditions, it became selective for the orexin 2 receptor (Mang et al., 2012). All the structures are put in Figure 5.

DISCUSSION

In this modern era, physical health comes first. We always neglect mental health. Mental health depends upon a healthy brain. A healthy brain depends upon quality sleep. Sleep is the most important physiological phenomenon that nourishes our body, maintains hormonal balance, improves memory, and minimizes the occurrence of various complications like psychosis, Alzheimer's, mania, anxiety, and anger management. More sleep, less sleep, sleep apnea, narcolepsy, teeth grinding, REM sleep disorder, and NREM sleep disorder are the most common types of sleep disorders. Adenosine, melatonin, dopamine, serotonin (5-HT), GABA, and orexin receptors are linked with the sleep cycle. There are numerous plants available in nature to treat various forms of sleep disorders. In ancient India people with sleep disorders used brahmi, ashwagandha, jatamansi, shankpushpi, and datura extract to treat the condition. In Chinese medicine, vacha extract, chamomile tea extract, and green tea extract are used to calm a person and promote sleep. There are some other plants explored by scientists to mitigate the spectrum of sleep disorders such as passion flower (Krishnakamala in India), *Ziziphus jujube*, *Poria cocos*, *Melissa officinalis* (lemon balm), and drum stick. Most of the plants work via modulation of GABA_A receptor-mediated chloride ion channel followed by melatonin and serotonin receptors. Green tea decoction mixed with chamomile, lavender, and ashwagandha is effective in the management of sleep disorders. In case of synthetic molecules, pramipexole, ropinirole, and rotigotine showed their activity against REM sleep disorder, insomnia, and restless syndrome via dopamine agonistic activity. The anti-insomniac activity of ramelteon showed its activity through melatonin (1 and 2) receptors. The antidepressant agent trazodone showed its activity in the treatment of insomnia. Pitolisant and quetiapine showed histamine antagonistic activity in the treatment of insomnia. Benzodiazepine derivatives lorazepam, clonazepam, estazolam, triazolam and non-benzodiazepine derivatives zolpidem, zopiclone showed anti-sleep disorder activities through GABA_A-benzodiazepine mechanisms. Suvorexant, daridorexant, and lemborexant showed anti-sleep disorder activities such as insomnia, REM sleep disorder, and NREM sleep

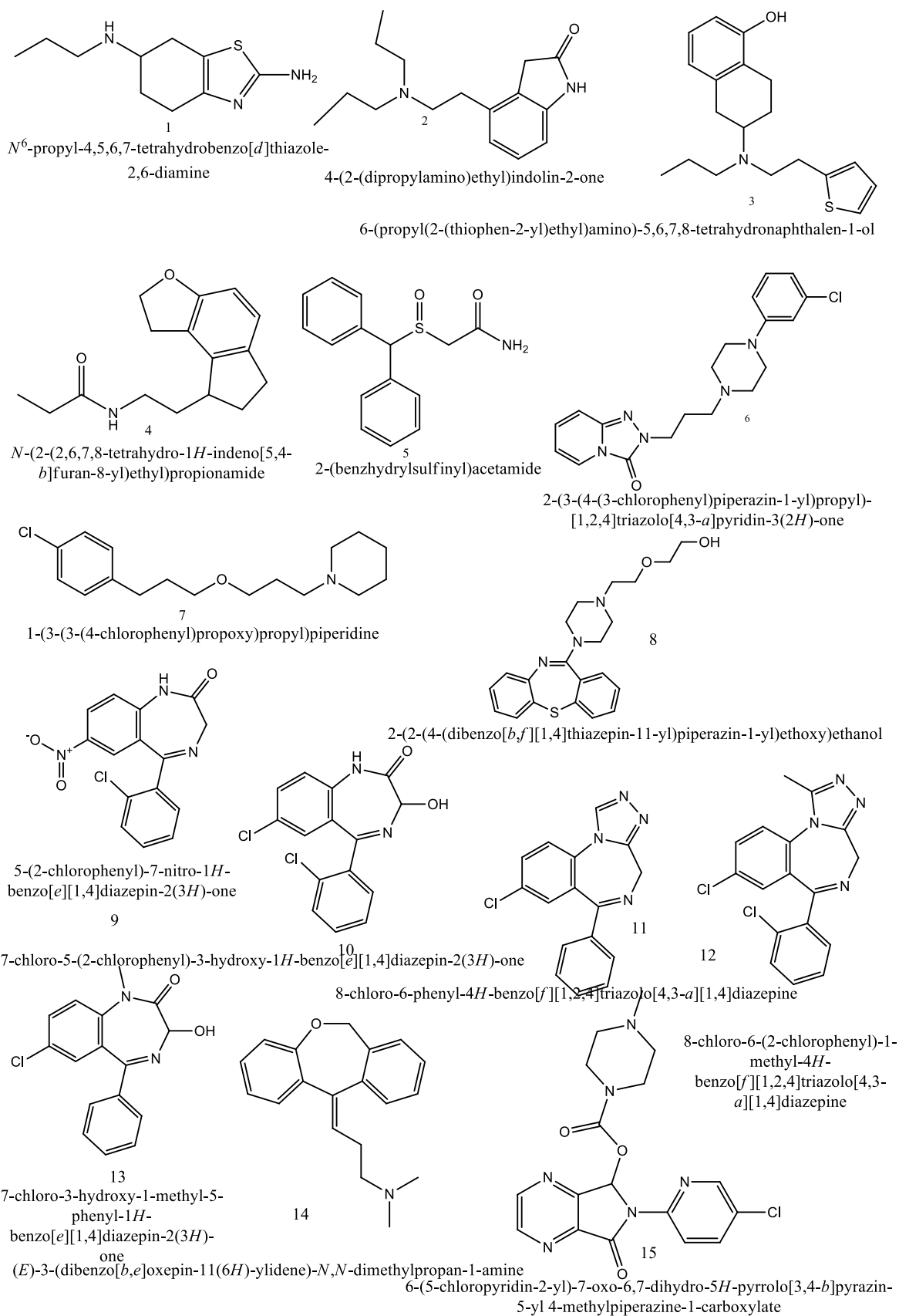


Figure 5. Synthetic molecules active against sleep disorders.

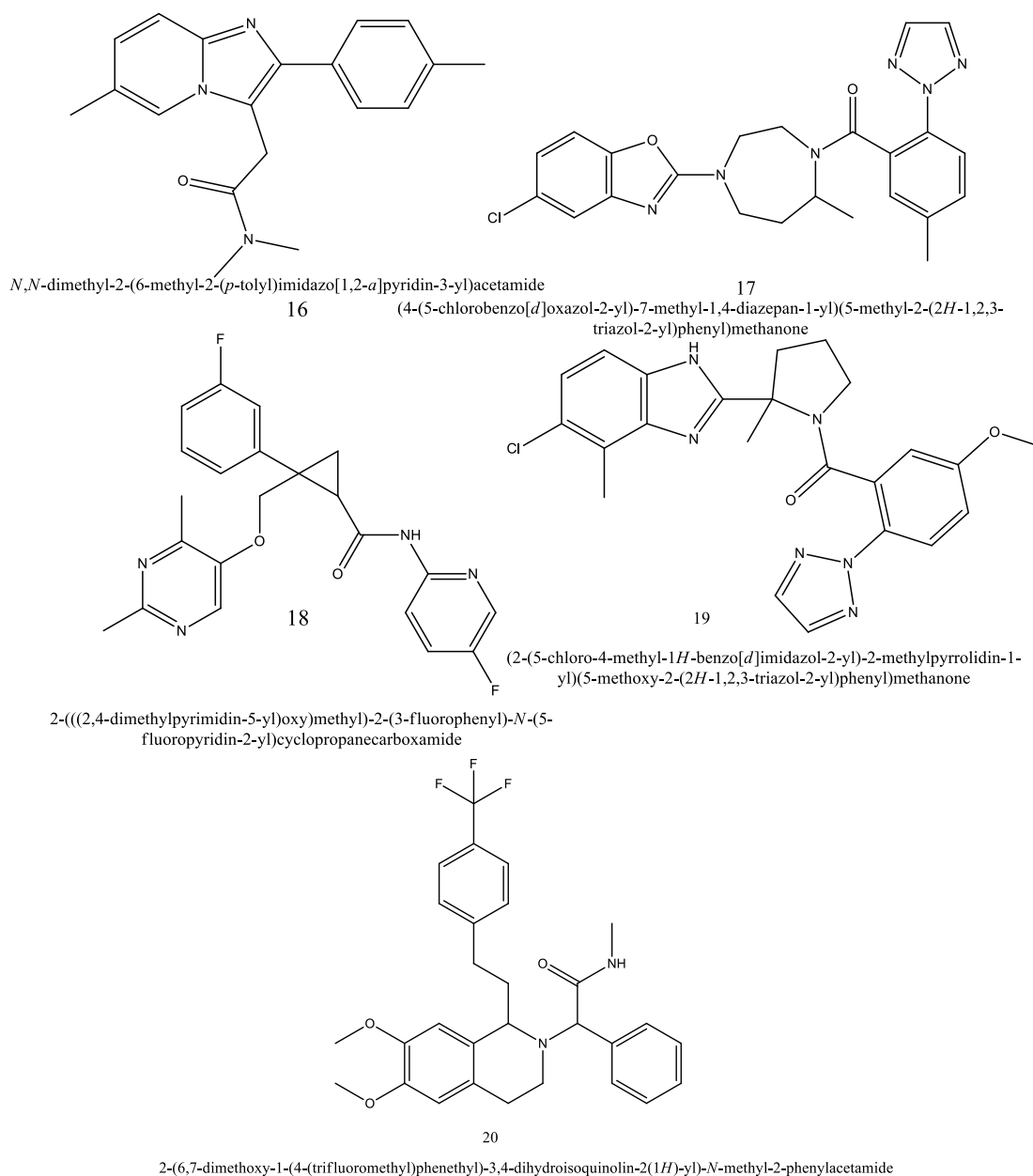


Figure 5 (continued). Synthetic molecules active against sleep disorders.

disorder using single/dual orexin receptor antagonism process. Most of the natural molecules or plant-based extracts showed activity against various types of sleep disorders using GABA_A and melatonin receptors. In recent times, orexin has emerged as a new target for sleep disorders. The development and approval of suvorexant, and daridorexant open a new dimension for the development of new-generation synthetic molecules effective against sleep disorders. Dual orexin receptor antagonists effectively worked as anti-sleep disorder agents without causing any addiction or dependency.

CONCLUSION AND FUTURE ASPECT

This manuscript highlighted the severity and types of sleep disorders, receptors associated with sleep disorders, natural and synthetic molecules effective against sleep disorders with possible mechanisms. Sleep disorder is a much-neglected condition because most human beings think it is not such a big concern. Sleep disorder itself is a big problem and its associated diseases like psychosis, Alzheimer's, and depression are the most progressive neuronal disorders. Through this manuscript, we tried to attract concern about this condition along with highlighting the availability of

natural and synthetic molecules to treat the condition. If we cultivate these natural molecules along with the discovery of new natural sources as well as the development of newer generation synthetic molecules with higher efficacies and lower addiction profiles to treat sleep disorders then it will be a gift of nature amalgamated with the scientific mind to the mankind.

ACKNOWLEDGEMENT

Author Contributions: P and SS conceptualized the study; MV and TS did bench work; TP, VJ and SS did literature search and initial manuscript writing; MV, TS, TP, VJ, P, SS did final editing and approved for final publication.

CONFLICT OF INTEREST

There is no conflict of interest no funding sources.

ETHICAL APPROVAL

Not Applicable

REFERENCES

- Abad, V. C., & Guilleminault, C. (2003). Diagnosis and treatment of sleep disorders: a brief review for clinicians. *Dialogues in Clinical Neuroscience*, 5(4), 371–388. <https://doi.org/10.31887/dcns.2003.5.4/vabad>
- Adib-Hajbaghery, M., & Mousavi, S. N. (2017). The effects of chamomile extract on sleep quality among elderly people: A clinical trial. *Complementary Therapies in Medicine*, 35, 109–114. <https://doi.org/10.1016/j.ctim.2017.09.010>
- Alessi, C.A., Martin, J.L., Webber, A.P., Alam, T., Littner, M.R., Harker, J.O., & Josephson, K.R. (2008). More daytime sleeping predicts less functional recovery among older people undergoing inpatient post-acute rehabilitation. *Sleep*, 31(9), 1291–300. PMID: 18788654
- Ashbrook, L. H., Krystal, A. D., Fu, Y., & Ptáček, L. J. (2019). Genetics of the human circadian clock and sleep homeostat. *Neuropsychopharmacology*, 45(1), 45–54. <https://doi.org/10.1038/s41386-019-0476-7>
- Ayala-Guerrero, F., & Medina, G. M. (2017). Effect of a medicinal plant (*Passiflora incarnata* L) on sleep. *Sleep Science*, 10(03), 96–100. <https://doi.org/10.5935/1984-0063.20170018>
- Bian, Z., Zhang, W., Tang, J., Fei, Q., Hu, M., Chen, X., Su, L., Fei, C., Ji, D., Mao, C., Tong, H., Yuan, X., & Lu, T. (2021). Mechanisms Underlying the action of *Ziziphi spinosae* semen in the treatment of insomnia: a study involving network pharmacology and experimental validation. *Frontiers in Pharmacology*, 12. <https://doi.org/10.3389/fphar.2021.752211>
- Brickley, S. G., Franks, N. P., & Wisden, W. (2018). Modulation of GABA A receptor function and sleep. *Current Opinion in Physiology*, 2, 51–57. <https://doi.org/10.1016/j.cophys.2017.12.011>
- Cheah, K. L., Norhayati, M. N., Yaacob, L. H., & Rahman, R. A. (2021). Effect of Ashwagandha (*Withania somnifera*) extract on sleep: A systematic review and meta-analysis. *PLOS ONE*, 16(9), e0257843. <https://doi.org/10.1371/journal.pone.0257843>
- Chen, T., Hiyama, A., Muramatsu, M., & Hinotsu, A. (2022). The effect of lavender on sleep quality in individuals without insomnia. *Holistic Nursing Practice*, 36(4), 223–231. <https://doi.org/10.1097/hnp.0000000000000528>
- Czeisler, C. A., Walsh, J. K., Roth, T., Hughes, R. J., Wright, K. P., Kingsbury, L., Arora, S., Schwartz, J., Niebler, G., & Dinges, D. F. (2005). Modafinil for Excessive Sleepiness Associated with Shift-Work Sleep Disorder. *The New England Journal of Medicine*, 353(5), 476–486. <https://doi.org/10.1056/nejmoa041292>
- Dang, A., Garg, A., & Rataboli, P. V. (2011). Role of Zolpidem in the management of insomnia. *CNS Neuroscience & Therapeutics*, 17(5), 387–397. <https://doi.org/10.1111/j.1755-5949.2010.00158.x>
- Dierickx, P., Van Laake, L. W., & Geijsen, N. (2017). Circadian clocks: from stem cells to tissue homeostasis and regeneration. *EMBO Reports*, 19(1), 18–28. <https://doi.org/10.15252/embr.201745130>
- Dokkedal-Silva, V., Kim, L. J., Morelhão, P. K., Galduróz, J. C. F., Tufik, S., & Andersen, M. L. (2020). Use of clonazepam in REM sleep behavior disorder: association with fall-related injuries and alternative treatments. *Journal of Clinical Sleep Medicine*, 16(4), 655–656. <https://doi.org/10.5664/jcsm.8308>
- Dubocovich, M. L. (2007). Melatonin receptors: Role on sleep and circadian rhythm regulation. *Sleep Medicine*, 8, 34–42.

- <https://doi.org/10.1016/j.sleep.2007.10.007>
- Dzirasa, K., Ribeiro, S., Costa, R. M., Santos, L. M., Lin, S., Grosmark, A., Sotnikova, T. D., Gainetdinov, R. R., Caron, M. G., & Nicolelis, M. a. L. (2006). Dopaminergic control of Sleep-Wake states. *The Journal of Neuroscience*, 26(41), 10577–10589. <https://doi.org/10.1523/jneurosci.1767-06.2006>
- Feng, H., Wen, S., Qiao, Q., Pang, Y., Wang, S., Li, H., Cai, J., Zhang, K., Chen, J., Hu, Z., Luo, F., Wang, G., Yang, N., & Zhang, J. (2020). Orexin signaling modulates synchronized excitation in the sublaterodorsal tegmental nucleus to stabilize REM sleep. *Nature Communications*, 11(1). <https://doi.org/10.1038/s41467-020-17401-3>
- França, A. S. C., Lobão-Soares, B., Muratori, L., Nascimento, G. J. F. D., Winne, J., Pereira, C. M., Jerônimo, S. M. B., & Ribeiro, S. (2015). D2 dopamine receptor regulation of learning, sleep and plasticity. *European Neuropsychopharmacology*, 25(4), 493–504. <https://doi.org/10.1016/j.euroneuro.2015.01.011>
- Franken, P. (2013). A role for clock genes in sleep homeostasis. *Current Opinion in Neurobiology*, 23(5), 864–872. <https://doi.org/10.1016/j.conb.2013.05.002>
- Gobbi, G., & Comai, S. (2019). Differential function of melatonin MT1 and MT2 receptors in REM and NREM sleep. *Frontiers in Endocrinology*, 10. <https://doi.org/10.3389/fendo.2019.00087>
- Gottesmann, C. (2002). GABA mechanisms and sleep. *Neuroscience*, 111(2), 231–239. [https://doi.org/10.1016/s0306-4522\(02\)00034-9](https://doi.org/10.1016/s0306-4522(02)00034-9)
- Gray, N. E., Magaña, A. A., Lak, P., Wright, K. M., Quinn, J. F., Stevens, J. F., Maier, C. S., & Soumyanath, A. (2017). Centella asiatica: phytochemistry and mechanisms of neuroprotection and cognitive enhancement. *Phytochemistry Reviews*, 17(1), 161–194. <https://doi.org/10.1007/s11101-017-9528-y>
- Han, A. H., Burroughs, C. R., Falgoust, E. P., Hasoon, J., Hunt, G., Kakazu, J., Lee, T., Kaye, A. M., Kaye, A. D., & Ganti, L. (2023). Suvorexant, a novel dual orexin receptor antagonist, for the management of insomnia. *Health Psychology Research*, 10(5). <https://doi.org/10.52965/001c.67898>
- Hondo, M., Nagai, K., Ohno, K., Kisanuki, Y., Willie, J. T., Watanabe, T., Yanagisawa, M., & Sakurai, T. (2010). Histamine-1 receptor is not required as a downstream effector of orexin-2 receptor in maintenance of basal sleep/wake states. *Acta Physiologica*, 198(3), 287–294. <https://doi.org/10.1111/j.1748-1716.2009.02032.x>
- Iwasaki, K., Komiya, H., Kakizaki, M., Miyoshi, C., Abe, M., Sakimura, K., Funato, H., & Yanagisawa, M. (2018). Ablation of central serotonergic neurons decreased REM sleep and attenuated arousal response. *Frontiers in Neuroscience*, 12. <https://doi.org/10.3389/fnins.2018.00535>
- Jie, Z., Li, J., Liu, C., Gui, H., Yuan, C., & Zhang, Y. (2022). The role of intracerebral dopamine D1 and D2 receptors in sleep-wake cycles and general anesthesia. *Ibrain*, 8(1), 48–54. <https://doi.org/10.1002/ibra.12024>
- Kales, A., Bixler, E. O., Soldatos, C. R., Jacoby, J. A., & Kales, J. D. (1986). Lorazepam: Effects on sleep and withdrawal phenomena. *Pharmacology*, 32(3), 121–130. <https://doi.org/10.1159/000138160>
- Kalpesh, P., Mukeshkumar, N., Nishteswar, K. (2020). Central nervous system depressant activity of *Jatamansi* (*Nardostachys jatamansi* DC.) rhizome. *Ayu*. 41(4), 250–254. <https://doi.org/10.4103/ayu.AYU25120>
- Kim, H., Park, I., Park, K., Park, S., Kim, Y. I., & Park, B. (2022). The Positive Effects of Poria cocos Extract on Quality of Sleep in Insomnia Rat Models. *International Journal of Environmental Research and Public Health*, 19(11), 6629. <https://doi.org/10.3390/ijerph19116629>
- Kim, S., Jo, K., Hong, K. T., Han, S. H., & Suh, H. J. (2019). GABA and l-theanine mixture decreases sleep latency and improves NREM sleep. *Pharmaceutical Biology*, 57(1), 64–72. <https://doi.org/10.1080/13880209.2018.1557698>
- Lancel, M. (1999). Role of GABA receptors in the regulation of sleep: initial sleep responses to peripherally administered modulators and agonists. *SLEEP*, 22(1), 33–42. <https://doi.org/10.1093/sleep/22.1.33>
- Lazarus, M., Chen, J., Huang, Z., Urade, Y., & Fredholm, B. B. (2017). Adenosine and sleep. In *Handbook of experimental pharmacology* (pp. 359–381).

- https://doi.org/10.1007/164_2017_36
- Li, S., & Yang, J. (2020). Pitolisant for treating patients with narcolepsy. *Expert Review of Clinical Pharmacology*, 13(2), 79–84. <https://doi.org/10.1080/17512433.2020.1714435>
- Lin, C., Chiang, C., Tseng, M., Tam, K., & Loh, E. (2023). Effects of quetiapine on sleep: A systematic review and meta-analysis of clinical trials. *European Neuropsychopharmacology*, 67, 22–36. <https://doi.org/10.1016/j.euroneuro.2022.11.008>
- Liu, H., Zhou, R., Yin, L., Si, N., Yang, C., Huang, C., Wang, R., & Chen, X. (2023). β -asarone prolongs sleep via regulating the level of glutamate in the PVN. *Biochemical and Biophysical Research Communications*, 665, 71–77. <https://doi.org/10.1016/j.bbrc.2023.05.010>
- Liu, W., Wu, B., Shang, J. K., Wang, X., Zhao, Y., & Huang, A. (2022). Moringa oleifera seed ethanol extract and its active component kaempferol potentiate pentobarbital-induced sleeping behaviours in mice via a GABAergic mechanism. *Pharmaceutical Biology*, 60(1), 810–824. <https://doi.org/10.1080/13880209.2022.2056207>
- Lopresti, A. L., Smith, S. J., Ali, S., Metse, A., Kalns, J., & Drummond, P. D. (2021). Effects of a Bacopa monnieri extract (Bacognize®) on stress, fatigue, quality of life and sleep in adults with self-reported poor sleep: A randomised, double-blind, placebo-controlled study. *Journal of Functional Foods*, 85, 104671. <https://doi.org/10.1016/j.jff.2021.104671>
- Louzada, L. L., Machado, F. V., De Tôledo Nóbrega, O., & Camargos, E. F. (2021). Zopiclone to treat insomnia in older adults: A systematic review. *European Neuropsychopharmacology*, 50, 75–92. <https://doi.org/10.1016/j.euroneuro.2021.04.013>
- Mang, G. M., Dürst, T., Bürki, H., Imobersteg, S., Abramowski, D., Schuepbach, E., Hoyer, D., Fendt, M., & Gee, C. E. (2012). The dual Orexin receptor antagonist Almorexant induces sleep and decreases Orexin-Induced locomotion by blocking orexin 2 receptors. *SLEEP*, 35(12), 1625–1635. <https://doi.org/10.5665/sleep.2232>
- Medic, G., Wille, M., & Hemels, M. (2017). Short- and long-term health consequences of sleep disruption. *Nature and Science of Sleep*, Volume 9, 151–161. <https://doi.org/10.2147/nss.s134864>
- Mieda, M. (2017). The roles of orexins in sleep/wake regulation. *Neuroscience Research*, 118, 56–65. <https://doi.org/10.1016/j.neures.2017.03.015>
- Miller, M. A. (2015). The role of sleep and sleep disorders in the development, diagnosis, and management of neurocognitive disorders. *Frontiers in Neurology*, 6. <https://doi.org/10.3389/fneur.2015.00224>
- Moline, M., Thein, S., Bsharat, M., Rabbee, N., Kemethofer-Waliczky, M., Filippov, G., Naoki, K., & Dhadha, S. (2020). Safety and efficacy of lemborexant in patients with Irregular Sleep-Wake Rhythm Disorder and Alzheimer’s Disease dementia: results from a phase 2 randomized clinical trial. *The Journal of Prevention of Alzheimer’s Disease*, 1–12. <https://doi.org/10.14283/jpad.2020.69>
- Nasim, K., Haniyeh, A., Farahnaz, H., Mahdis, N., Shekofe, T., Abolfazl, M.B. (2020). Evaluation of Extract Efficacy of Lemon Balm on Sleep Quality Score in Postmenopausal Women: A Double-Blinded Randomized Clinical Trial. *Der. Pharmacia. Lettre*. 12(9), 22-29.
- National Sleep Foundation. (2021, 12, 3). *Sleep by the Numbers*. <https://www.thensf.org/sleep-facts-and-statistics/>
- Neubauer, D. N. (2008). A review of ramelteon in the treatment of sleep disorders. *Neuropsychiatric Disease and Treatment*, 69. <https://doi.org/10.2147/ndt.s483>
- Nie, T., & Blair, H. A. (2023). Daridorexant in insomnia Disorder: A Profile of its Use. *CNS Drugs*, 37(3), 267–274. <https://doi.org/10.1007/s40263-023-00987-9>
- Oh, S., Yu, J., Kim, H., Oh, K., & Eun, J. (2011). Effects of white lotus extracts on sleeping, chloride influx, and oxidation. *Food Science and Biotechnology*, 20(4), 949–954. <https://doi.org/10.1007/s10068-011-0131-5>
- Panara, K., Nariya, M., Karra, N. (2020). Central nervous system depressant activity of Jatamansi (Nardostachys jatamansi DC.) rhizome. *Ayu*. 41(4), 250-254. doi: 10.4103/ayu.AYU_251_20.
- Patel, D., Shankar, S., Preeti, B., Basu, S., Deshmukh, G., Datir, R. (2018). Brahmi (Bacopa monnieri) as functional food ingredient in food processing industry. *J. Pharmacognosy. Phytochemistry*, 7(3), 189-194.

- Patel, S., Verma, N.K., Karunakaran, G. (2009). *Passiflora Incarnata* Linn: A Review on Morphology, Phytochemistry and Pharmacological Aspects. *Phcog Rev.* 3, 5, 175-181.
- Pavlova, M., & Latreille, V. (2019). Sleep disorders. *The American Journal of Medicine*, 132(3), 292-299. <https://doi.org/10.1016/j.amjmed.2018.09.021>
- Pegram, V., Hyde, P., & Linton, P. (1980). Chronic use of triazolam: The effects on the sleep patterns of insomniacs. *Journal of International Medical Research*, 8(3), 224-231. <https://doi.org/10.1177/030006058000800308>
- Petr, D., Jitka, B., Evzen, R., Veronika, M., Antonin, S., Robert, J., Jan, R., & Karel, S. (2010). Effects of Ropinirole Prolonged-Release on Sleep Disturbances and Daytime Sleepiness in Parkinson Disease. *Clinical Neuropharmacology*. 33, 186-190.
- Pierantozzi, M., Placidi, F., Liguori, C., Albanese, M., Imbriani, P., Marciani, M. G., Mercuri, N. B., Stanzione, P., & Stefani, A. (2016). Rotigotine may improve sleep architecture in Parkinson's disease: a double-blind, randomized, placebo-controlled polysomnographic study. *Sleep Medicine*, 21, 140-144. <https://doi.org/10.1016/j.sleep.2016.01.016>
- Pizza, F., Barateau, L., Dauvilliers, Y., & Plazzi, G. (2022). The orexin story, sleep and sleep disturbances. *Journal of Sleep Research*, 31(4). <https://doi.org/10.1111/jsr.13665>
- Roehrs, T., Zorick, F., Lord, N., Koshorek, G.L., & Roth, T. (1983). Dose-related effects of estazolam on sleep of patients with insomnia. *J. Clin. Psychopharmacol*, 3(3), 152-6. PMID: 6135720.
- Saletu, A., Parapatics, S., Saletu, B., Anderer, P., Prause, W., Putz, H., Adelbauer, J., & Saletu-Zyhlarz, G. (2005). On the Pharmacotherapy of Sleep Bruxism: Placebo-Controlled Polysomnographic and Psychometric Studies with Clonazepam. *Neuropsychobiology*, 51(4), 214-225. <https://doi.org/10.1159/000085917>
- Schmidt, M. H., Koshal, V. B., & Schmidt, H. S. (2006). Use of pramipexole in REM sleep behavior disorder: Results from a case series. *Sleep Medicine*, 7(5), 418-423. <https://doi.org/10.1016/j.sleep.2006.03.018>
- Sharma, R., Singla, R. K., Banerjee, S., Sinha, B., Shen, B., & Sharma, R. (2022). Role of Shankpushpi (*Convolvulus pluricaulis*) in neurological disorders: An umbrella review covering evidence from ethnopharmacology to clinical studies. *Neuroscience & Biobehavioral Reviews*, 140, 104795. <https://doi.org/10.1016/j.neubiorev.2022.104795>
- Sharma, V., Sharma, R., Gautam, D. N. S., Kuča, K., Nepovimová, E., & Martins, N. (2020). Role of Vacha (*Acorus calamus* Linn.) in Neurological and Metabolic Disorders: Evidence from Ethnopharmacology, Phytochemistry, Pharmacology and Clinical Study. *Journal of Clinical Medicine*, 9(4), 1176. <https://doi.org/10.3390/jcm9041176>
- Sobhanifar, M., Rashidi, R., Rajabian, A., Forouzanfar, F., Hasanpour, M., Iranshahi, M., Rakhshandeh, H., & Hosseini, A. (2022). The possible mechanism of Datura stramonium on pentobarbital-induced sleep in mice. *International Journal of Neuroscience*, 133(8), 879-887. <https://doi.org/10.1080/00207454.2021.1998045>
- Sun, Y., Tisdale, R. K., & Kilduff, T. S. (2021). Hypocretin/Orexin receptor pharmacology and sleep phases. In *Frontiers of neurology and neuroscience* (pp. 22-37). <https://doi.org/10.1159/000514963>
- Taheri, S., & Mignot, E. (2002). The genetics of sleep disorders. *Lancet Neurology*, 1(4), 242-250. [https://doi.org/10.1016/s1474-4422\(02\)00103-5](https://doi.org/10.1016/s1474-4422(02)00103-5)
- Thakkar, M. (2011). Histamine in the regulation of wakefulness. *Sleep Medicine Reviews*, 15(1), 65-74. <https://doi.org/10.1016/j.smrv.2010.06.004>
- Toolika, E., Bhat, N. P., & Shetty, S. K. (2015). A comparative clinical study on the effect of Tagara (*Valeriana wallichii* DC.) and Jatamansi (*Nardostachys jatamansi* DC.) in the management of Anidra (primary insomnia). *Ayu*, 36(1), 46. <https://doi.org/10.4103/0974-8520.169008>
- Tuo, W., Wang, S., Shi, Y., Cao, W., Liu, Y., Su, Y., Xiu, M., & He, J. (2023). Angelica sinensis polysaccharide extends lifespan and ameliorates aging-related diseases via insulin and TOR signaling pathways, and antioxidant ability in *Drosophila*. *International Journal of Biological*

- Macromolecules*, 241, 124639. <https://doi.org/10.1016/j.ijbiomac.2023.124639>
- Unno, K., Noda, S., Kawasaki, Y., Yamada, H., Morita, A., Iguchi, K., & Nakamura, Y. (2017). Reduced Stress and Improved Sleep Quality Caused by Green Tea Are Associated with a Reduced Caffeine Content. *Nutrients*, 9(7), 777. <https://doi.org/10.3390/nu9070777>
- Walsh, J. H., Visser, C., Maddison, K. J., Bharat, C., Hillman, D. R., & Eastwood, P. R. (2018). The effect of temazepam on assessment of severity of obstructive sleep apnea by polysomnography. *Sleep and Breathing*, 23(1), 49–56. <https://doi.org/10.1007/s11325-018-1653-3>
- Wichniak, A., Wierzbicka, A., & Jarema, M. (2021). Treatment of insomnia – effect of trazodone and hypnotics on sleep. *Psychiatria Polska*, 55(4), 743–755. <https://doi.org/10.12740/pp/125650>
- Winters, B., Serpas, D. G., Fullmer, N., Hughes, K., Kincaid, J., Rosario, E. R., & Schnakers, C. (2023). Sleep quality should be assessed in inpatient rehabilitation settings: a preliminary study. *Brain Sciences*, 13(5), 718. <https://doi.org/10.3390/brainsci13050718>
- Yeung, W., Chung, K. F., Yung, K., & Ng, T. H. (2015). Doxepin for insomnia: A systematic review of randomized placebo-controlled trials. *Sleep Medicine Reviews*, 19, 75–83. <https://doi.org/10.1016/j.smrv.2014.06.001>
- Yuan, Q., Joiner, W. J., & Sehgal, A. (2006). A Sleep-Promoting role for the drosophila serotonin receptor 1A. *Current Biology*, 16(11), 1051–1062. <https://doi.org/10.1016/j.cub.2006.04.032>