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REVIEW

Integrative sleep management: from molecular pathways to conventional and herbal treatments

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Abstract

Sleep is regarded as one of the most crucial factors in keeping a healthy lifestyle. To function normally, a person needs at least 6–8 h of sleep per day. Sleep influences not only our mood but also the efficiency with which we complete tasks. Sleep disorders exhibit diverse etiologies across different conditions and populations, with genetic and environmental factors playing a significant role in their development. Many issues emerge as a result of inadequate sleep. Unhealthy food and lifestyle choices have increased our susceptibility to sleep disorders. A well-balanced diet rich in essential vitamins and minerals can have a profound impact on sleep patterns, enhancing both the duration and quality of rest. The primary categories of sleep disorders include insomnia, sleep apnea (SA), narcolepsy, parasomnias, circadian rhythm disorders, and restless legs syndrome (RLS). The drugs used to treat sleep disorders are primarily habit-forming and have a history of withdrawal effects. This insufficiency in medication has prompted the hunt for newer, better options. Nutraceuticals are well-suited to the treatment of such illnesses. Its non-toxic, non-habit-forming properties, and practical efficiency have made it an outstanding choice. This review provides nutraceuticals used in sleep disorders. A comprehensive literature search was conducted utilizing several databases, including Google Scholar, Elsevier, Springer Nature, Wiley, PubMed, and EKB. Nutraceuticals are products that employ food or dietary components to treat or prevent disease. In the therapy of sleep disorders, nutraceuticals such as *Artemisia annua*, valerian, rosemary, jujube, Passionflower, lemon balm, ashwagandha, kava-kava, lavender, and chamomile have been shown to have remarkable benefits. These remedies exert their effects through multiple mechanisms, both directly by modulating neurotransmitter and hormonal pathways within sleep circuits, and indirectly by enhancing sleep quality through the alleviation of stress, inflammation, and oxidative stress. Clinical studies were piloted to validate the efficacy of natural sleep aids. Future research should focus on elucidating the precise mechanisms through which natural products influence sleep.

Keywords Insomnia · Nutraceuticals · Sleep disorders · Risk factors

Introduction

Sleep is an important part of human health since it affects cognitive function, emotional management, physical health, and quality of life (Buysse 2014). However, sleep disorders, particularly insomnia, have become more common in modern culture. About 50–70 million persons in the USA suffer from sleep disorders, with insomnia being the most frequent (Roth 2007a). Insomnia is characterized by difficulties getting asleep, sustaining sleep, or receiving restorative sleep, resulting in daily impairments such as exhaustion, mood disorders, and poor performance (Morin et al. 2015). Conventional treatments for insomnia frequently entail pharmacological treatment, such as benzodiazepines or benzodiazepine receptor agonists (Riemann et al. 2017). Although these drugs may be beneficial in the short-term, they are associated with a variety of side effects, including dependence, tolerance, and severe responses (Kripke 2018). Furthermore, long-term use of these drugs can result in rebound insomnia and withdrawal symptoms after termination (Lader 2011).

Herbal/natural products are one of the most popular forms of complementary and alternative medicine (CAM) (Ni et al. 2002). With the advent of self-managed health care, many people are turning to natural remedies (herbs, vitamins, and mineral supplements) as health promoting strategies or

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solutions to health problems (Chang 2000). They are widely available, can be purchased at supermarkets, pharmacies, and health food stores, and can be consumed without supervision, leading to the perception that these items are necessarily safe and free of health hazards (Ernst 2006). Some herbs and nutritional supplements that have been touted as sleep aids include Valerian root, St. John's Wort, kava, passionflower, and melatonin (Ramakrishnan 2007). These supplements frequently include substances with sedative, anxiolytic, or sleep-promoting characteristics, like flavonoids, terpenes, and amino acids (Shi et al. 2014). The objective of this review was to trace the use of natural products as sleep aids with documentation of their roles in the management of sleep disorders. Additionally, this review encompassed a broad analysis of sleep disorders, including their types, causes, epidemiology, risk factors, pathogenesis, as well as both pharmacological and non-pharmacological therapeutic approaches.

Search strategy

A search using Google Scholar, Elsevier, Springer Nature, Wiley, PubMed, and EKB was conducted. The following Mesh items were used "sleep disorders," "Types of sleep disorders," "natural products," "causes," "pathogenesis," "symptoms," "risk factors," "epidemiology," and "conventional treatments."

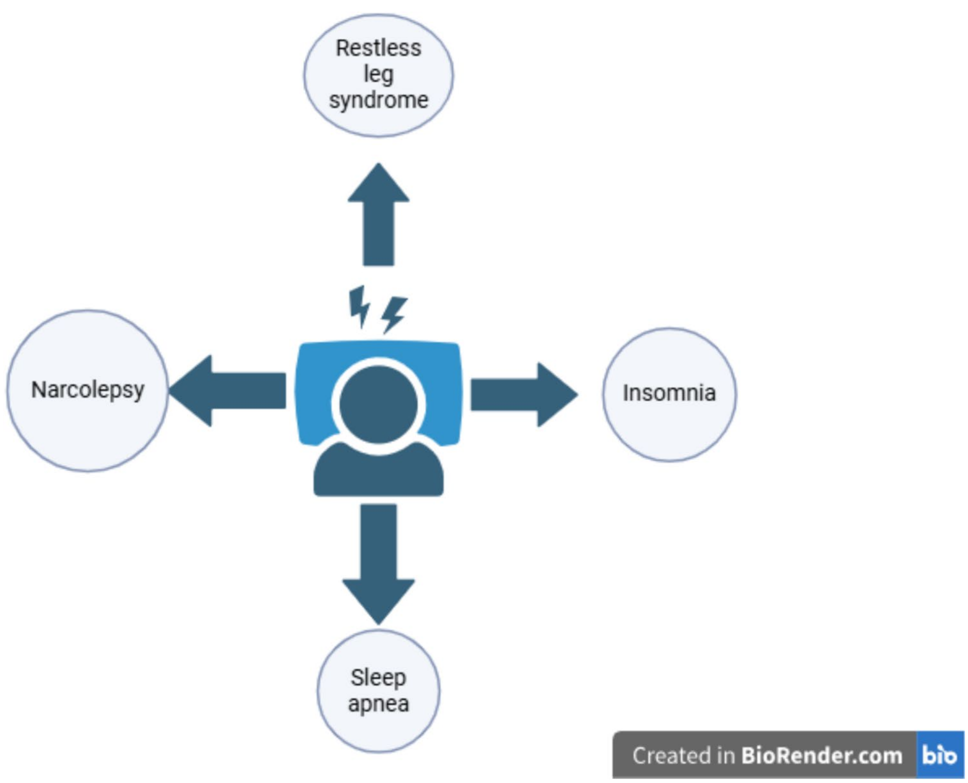
Types of sleep disorders

Sleep disorders are a broad spectrum of conditions that can significantly affect health, safety, and quality of life. Insomnia, sleep apnea (SA), narcolepsy, parasomnias, circadian rhythm disorder, and restless leg syndrome (RLS) are some of the primary types of sleep disorders (Fig. 1).

Insomnia

Insomnia disorder encompasses a plethora of symptoms during night and day that greatly influences wellbeing and quality of life. Some of the night complaints are prolonged onset of sleep, persistent difficulty in maintaining sleep and early morning wakefulness. Common daytimes problems are tiredness, compromised cognitive functions, anxiousness, diminished attention, and a depressed mood (Riemann et al. 2022). Insomnia can be classified into two subtypes: symptoms lasting for less than 3 months and are usually due to a sudden event or stress are classified as acute insomnia, while symptoms extending for more than 3 months is classified as chronic insomnia. Managing chronic insomnia is much harder due to distress evolving from the lack of sleep which can possibly deteriorate sleep over time (Strickland 2022). Zeng et al. concluded in a meta-analysis that insomnia is more prevalent in females than males (Zeng et al. 2020).

Fig. 1 Types of sleep disorders. "Created with BioRender.com."



Sleep apnea

A diminished airflow inspiration lasting for at least 10 is apnea while hypopnea is a lesser decline of airflow lasting 10 s or longer. Both apnea or hypopnea are categorized as obstructive or central (Javaheri et al. 2017).

Central sleep apnea (CSA)	Obstructive sleep apnea (OSA)
Happens when a temporary decrease in generation of beathing rhythm	Happens when there is a complete blockage of the upper airway (tongue falling backward)

Snoring, choking sensation, difficulty in maintaining sleep, and non-restorative sleep are all symptoms that patients with OSA associate with. Obesity, family history of OSA, and small oropharyngeal airway are suggestive indicators for the disease. Gas exchange impairment causes hypercapnia, decreased oxygen saturation, and disrupted sleep, all lead to the repercussions of OSA, such as cardiovascular, metabolic, and neurocognitive effects. It has been noted that OSA is more prevalent in males than females (Jordan et al. 2014; Abbasi et al. 2021).

Restless leg syndrome

RLS is a sensory motor disorder associated with sleep; its pathophysiology is yet to be clear. RLS is marked by a strong need to move that need is intensified with rest and alleviates with movement (Manconi et al. 2012).

Symptoms can range in frequency (occurring once per year to daily) and severity (from mild symptoms to severe effects on sleep and quality of life). Depression and suicide have been noted with very severe cases (Para et al. 2019). RLS is more prevalent in females than males with 30–50% higher occurrence in females. RLS was noted to be more prevalent in pregnant females with a chance of occurrence of one in five pregnant females (Manconi et al. 2012).

Narcolepsy

Narcolepsy is a chronic disorder that usually commence at adolescence, and is mainly marked by excessive daytime sleepiness and, in a significant number of patients, cataplexy which is a sudden loss of muscle tone despite wakefulness that is triggered by strong emotion. Patients with narcolepsy often encounter many obstacles in maintaining employment, accessing education, reduced quality of life, and socioeconomic problems. Earlier, according to the presence or absence of cataplexy, narcolepsy was classified into two type types: narcolepsy type 1 and narcolepsy type 2 (Kornum et al. 2017).

In the 2014 edition of the International Classification of Sleep Disorders, narcolepsy has been redivided into narcolepsy type I (NT1) and narcolepsy type II (NT2), based on the absence or presence of orexins. Orexins are neuropeptides which contribute to the regulation of sleep and wakefulness. Orexins were considered a significant marker for cataplexy associated narcolepsy. Low level of orexins were in the cerebrospinal fluid of patient with NT1 and associated with cataplexy, on the other hand, NT2 had normal level of orexins and do not have cataplexy (Sateia 2014). It was noted that narcolepsy was more prevalent in men than women (1.6–1.8 males per 1 female) (Silber et al. 2002).

Epidemiology

Sleep disorders are prevalent across different populations and commonly associated with various health conditions. In a cross-sectional study carried out by McArdle et al. on young adults, it was observed that, generally, at least one sleep disorder was found in 41% of females. Regarding the percentage in males, it was found to be 42.3% (McArdle et al. 2020). In specific, insomnia is the most common sleep disorder. Insomnia, which is characterized by difficulty in initiating sleep, continuing sleep, or poor sleep, was estimated to affect 13.9% of the population with a higher prevalence in females compared to males (Mai and Buysse 2008; Morin et al. 2020).

Another type of sleep disorder is the SA which is divided into OSA and CSA. In USA, the prevalence of mild OSA among adults aged 30 to 70 years was estimated as 14% for men and 5% for women, and the estimated prevalence of moderate to severe OSA was approximately 13% for males versus 6% for females (US Preventive Services Task Force et al. 2022). CSA is less prevalent compared to OSA (Ishikawa and Oks 2021). Additionally, CSA is rare in women compared to men, where an overall prevalence of CSA is 0.3% in females against 7.8% in males (Badr et al. 2019).

Regarding the prevalence of RLS in the general population, it is postulated to be around 10% (Phillips et al. 2000). However, this percentage can vary considerably in different age groups. In younger adults with an age range from 18 to 29, the prevalence is approximately 3%, while in geriatric population (> 80 years), the percentage is around 19% (Phillips et al. 2000).

On the other hand, narcolepsy, which is characterized by excessive day-time sleepiness, is considered a rare sleep disorder (Chavda et al. 2022; Manfredi et al. 1987). Narcolepsy has two types depending on the presence or the absence of cataplexy. NT1, which is associated with cataplexy, has a prevalence of 12.6/100,000 individuals, whereas NT2, that lacks cataplexy, has a prevalence of 25.1 per 100,000 individuals (Ohayon et al. 2023).

Interestingly, sleep disorders are usually comorbid with other medical conditions. As an example, patients suffering from episodic migraine have a higher risk of insomnia and RLS (Vgontzas et al. 2023). Likewise, patients with epilepsy exhibited higher prevalence of RLS (20.6% against 6.1% in controls) (Khachatryan et al. 2020). Moreover, sleep disorders are commonly encountered in various neurological disorders, including amyotrophic lateral sclerosis, multiple system atrophy, and Parkinson's disease (Taximaimaiti et al. 2021; Anghel et al. 2023). Furthermore, sleep disorders are usually observed in patients having chronic obstructive pulmonary disease (COPD) and cardiovascular diseases (Vanfleteren et al. 2020; Wang et al. 2021).

Pathogenesis

Sleep disorders have various etiologies across different conditions and populations. Indeed, genetics and environmental conditions play a significant role in most sleep disorders (Palagini et al. 2023; Bidaki et al. 2012). Regarding insomnia, there is an interplay between biochemical, neuroendocrine, immune, and psychosocial factors (Kang et al. 2022). On the biochemical level, it was observed that people with insomnia have a higher metabolic rate compared to normal individuals. This was assessed via measuring the oxygen consumption (Bonnet and Arand 1998). Additionally, the neuroendocrine causes of hyperarousal were highlighted in a previous study. Interestingly, patients suffering from insomnia exhibited an activation in the stress response system. This claim was proved by measuring urinary cortisol concentrations, where people with insomnia showed a higher level of urinary cortisol compared to normal subjects. This finding confirms the involvement of the hypothalamic–pituitary–adrenal (HPA) axis in the pathology of insomnia (Vgontzas et al. 2001; Vgontzas et al. 1997). Furthermore, immunity dysfunction was related to insomnia. A greater ratio between the inflammatory cytokines to the anti-inflammatory cytokines was witnessed in insomnia patients (Akkaoui et al. 2023). Moreover, psychological stress, indeed, leads to a hyperarousal state (Harvey 2002).

Concerning the pathogenesis of SA, OSA is mainly due to frequent collapse in the upper airway leading to hypercapnia, hypoxia, and sleeping disturbances (Lv et al. 2023). This collapse is caused by several reasons, like obesity, alteration in the upper airway function, or pharyngeal neuropathy (Lv et al. 2023). In fact, adenoid and/or tonsil hypertrophy are the most common causes of OSA in children, while obesity is the most prevalent cause in older children and adolescents (Mussi et al. 2023). On the other hand, CSA is an abnormal ventilatory drive, causing interruption or reduction in breathing without effort during sleep (Ishikawa and Oks 2021). Breathing interruption may be idiopathic, or due to heart failure, high altitudes, drug-induced, brainstem and spinal cord lesions, congenital, or because of neuromuscular or skeletal disorders (Hernandez and Patil 2016).

Furthermore, the pathogenesis of RLS mainly involves a neural contribution. It is hypothesized that dopamine (DA) deficiency is accused for the RLS. This postulation arose since the dopaminergic drugs and dopamine agonists were found to be effective in treating the condition (Lv et al. 2021). Noteworthy, unlike Parkinson's disease, DA deficiency in RLS is not in the substantia nigra (Lv et al. 2021). Fascinatingly, brain iron deficiency is linked to dopaminergic abnormality (Nanayakkara et al. 2023). In addition, electrophysiological findings indicate the interplay of various generators, causing an increase in the nervous system excitability and alterations in inhibition within somatosensory and nociceptive pathways (Antelmi et al. 2024).

Regarding the pathogenesis of narcolepsy, NT1 is a result of losing hypocretin (orexin)-producing neurons in the hypothalamus, causing a disruption in the sleep–wake cycles (Liblau et al. 2024; Franceschini et al. 2021). Hypocretin is a wake-promoting peptide. The loss of the hypocretin-producing neurons is intensely associated linked to an autoimmune process, where NT1 is correlated to MHC class II allele, *HLA-DQB1 *06:02*, and T cell receptor genes (Liblau et al. 2024; Ollila et al. 2023). Furthermore, heightened T cell reactivity against hypocretin has been described in NT1 patients (Kornum 2020). Interestingly, corticotropin-releasing hormone (CRH)-positive neurons in the paraventricular nucleus of NT1 post-mortem brains have witnessed a considerable decline by 88%; however, other hypothalamic cell groups remained unaffected (Shan et al. 2022). Moreover, H1 N1 influenza A infection and immunization with Pandemrix® were identified as environmental risk factors triggering NT1 development (Ollila et al. 2023). On the other hand, NT2 pathogenesis is not yet fully established (Miyagawa and Tokunaga 2019).

Causes

Sleep disorders are multifactorial (Fig. 2). It can be caused by genetic factors, environmental triggers, or neurological influences (Caylak 2009). Sleep disorders could be an outcome of a certain medical condition. For example, vasomotor symptoms associated with menopause can cause sleep disturbances (Lee et al. 2019). In addition, chronic diseases such as asthma, chronic obstructive pulmonary disease, and rheumatoid arthritis can impose a negative influence on the quality of sleep (Smolensky et al. 2011). Furthermore, obesity, and some drugs can cause respiratory disturbances, thus, increasing the possibility of sleep-related breathing disorders (Romero-Corral et al. 2010). Moreover, leg cramps and RLS were commonly reported in pregnant women (Hensley 2009). Finally, daily life stressors execute a psychological pressure

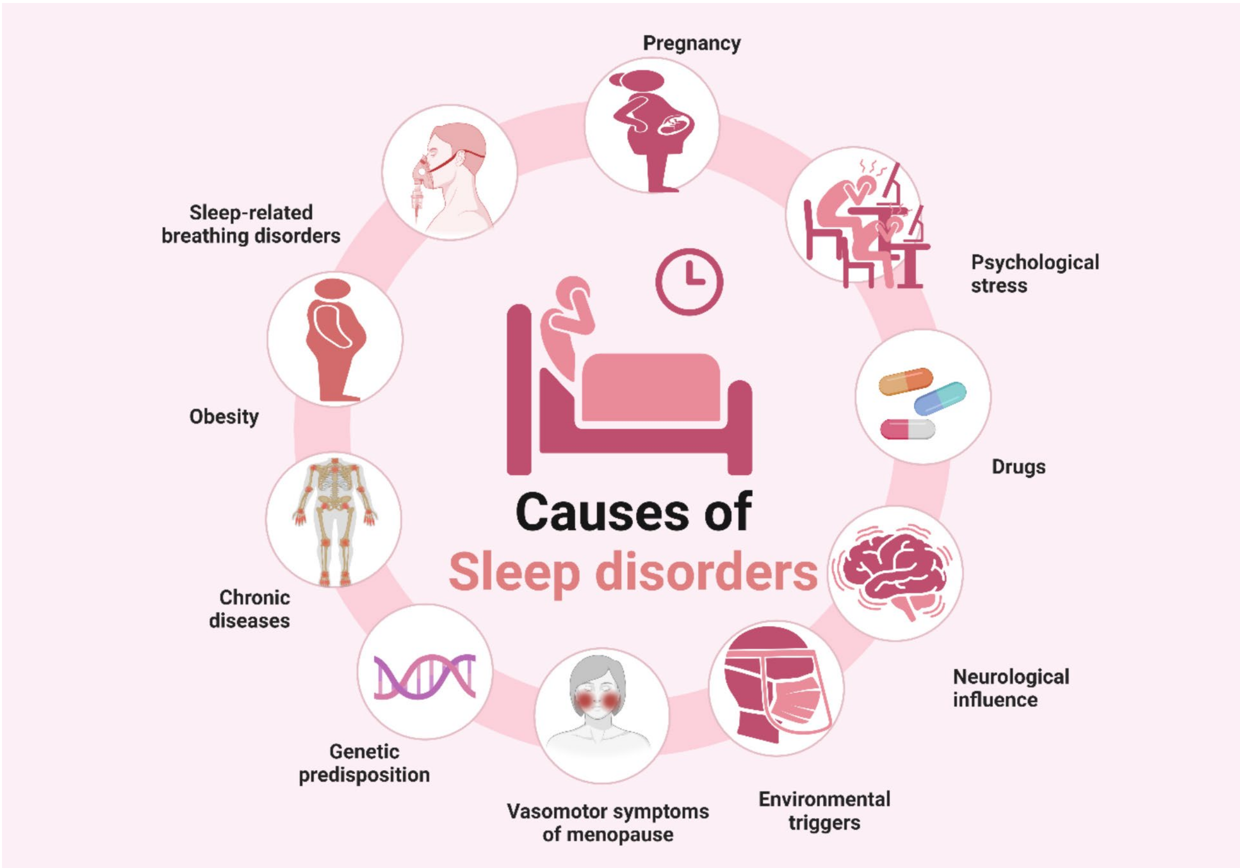


Fig. 2 Causes of sleep disorders. "Created with BioRender.com"

which can indeed have a negative impact on sleep quality, depth, and efficiency (Yoo et al. 2023).

Symptoms

Symptoms of sleep disorders vary according to the type of disorder (Fig. 3). Patients suffering from insomnia experience symptoms of difficulty in falling asleep and/or maintaining sleep (Roth 2007b). In SA, patients may show signs of loud snoring, dry mouth upon waking up, and morning headaches (Spalka et al. 2020). Regarding patients with RLS, they report the symptoms as electric current along their legs leading to a paroxysmal leg movement (Byrne et al. 2006). On the other hand, symptoms of narcolepsy revolve around four main symptoms: excessive daytime sleepiness, sleep paralysis, disturbed nighttime sleep, hallucinations, with or without cataplexy (Chavda et al. 2022). Noteworthy, NT1 is the type of narcolepsy associated with cataplexy while NT2 is not accompanied by cataplexy (Ohayon et al. 2023).

Risk factors

Risk factors contributing to sleep disorders are numerous. According to prospective study, gender is a risk factor, where females are more prone to sleep disturbances than males; however, the exact reason is not known (Smagula et al. 2016). Additionally, depressed mood promotes sleep disorders. Fairly, the relation between depression and sleeplessness is bidirectional, since sleep disturbances results in a depressed mode as well (Smagula et al. 2016). Moreover, physical illness (like hypertension and dyslipidemia) and psychiatric comorbidities (like anxiety) are considered robust risk factors for sleep disorders (Hwang et al. 2022). In addition, chronic stress was found to alter the melatonin-related pathways in animal models, thus triggering sleep disorders (Xia et al. 2023). Furthermore, obesity is considered a potent risk factor for SA (Brzecka et al. 2020). Noteworthy, aging solely is not considered a predictor for sleep disorder; however, it increases the risk of development of other risk factors (Smagula et al. 2016).

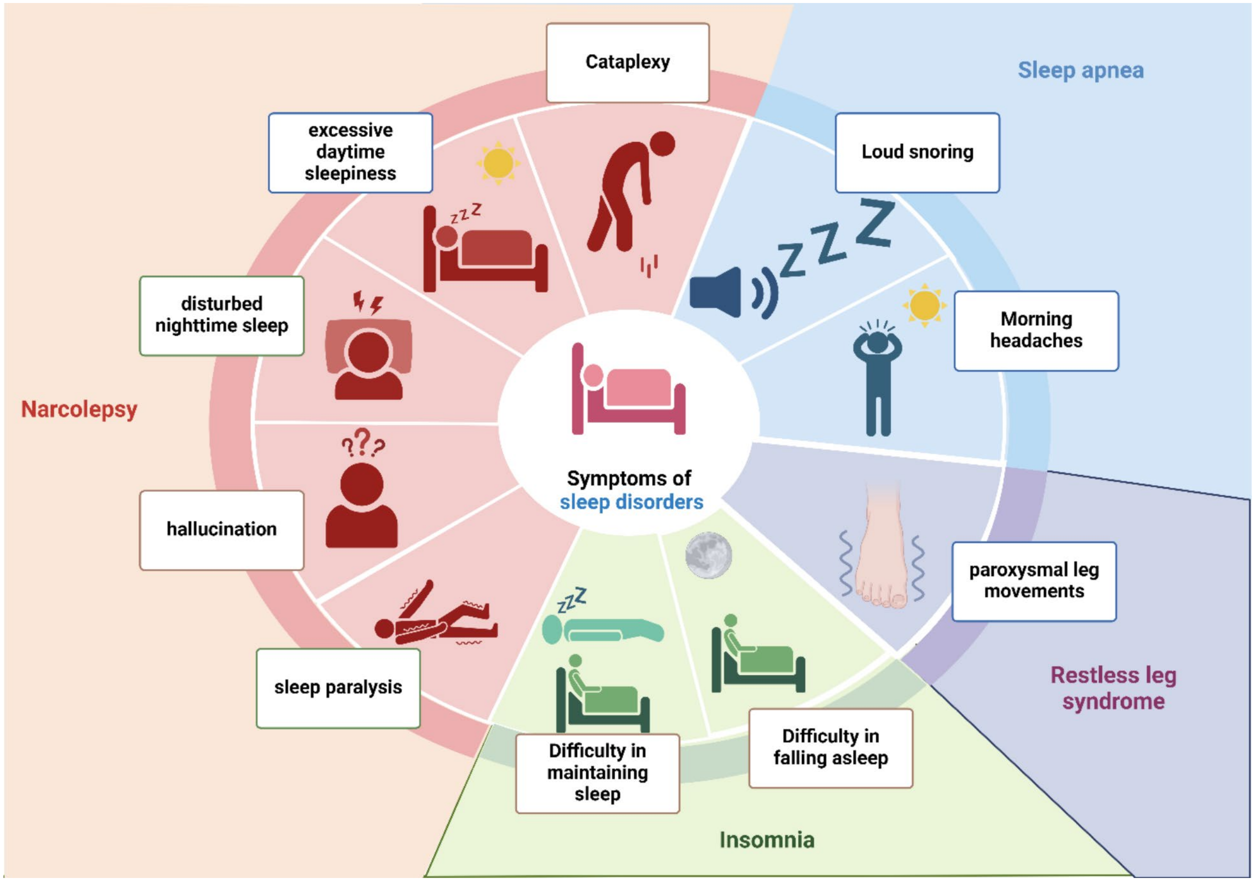


Fig. 3 Symptoms of sleep disorders. "Created with BioRender.com"

Impact on health

Indeed, any disorder affecting sleep quality will have a negative impact on both physical and mental well-being. Consequences on adolescents are critical as sleep disorders affect their overall health, behavior, mood, and academic performance during a crucial stage of their physical and emotional development (Kansagra 2020). In adults, the outcomes of sleep disorders are related to brain health. Patients exhibited a wide range of CNS disorders ranging from stroke to subclinical cerebrovascular disease and cognitive decline, including the development of Alzheimer's disease and related dementias (Gottesman et al. 2024).

Moreover, in cancer patients, sleep disorders are widely prevalent, affecting 30–50% of patients. Unfortunately, these disorders can drastically impact on the patients' quality of life as it is linked to the pain, anxiety, and depression associated with the disease (Strik et al. 2021). Furthermore, there is a substantial bidirectional relationship between cardiovascular diseases (CVDs) and sleep disorders. It is proven that inflammation, sympathetic activation, and endothelial dysfunction play serious roles in sleep disorders, all of which are predisposing factors for CVDs (Wang et al. 2021). Additionally, the influence of sleep disorders extends to pregnancy. Commonly, pregnant women suffer from RLS leading to a negative impact on the sleep quality of pregnant women (Gupta et al. 2016). This can affect maternal and fetal health, thus, possibly contributing to conditions such as preeclampsia and gestational diabetes (Kember et al. 2023).

Sleep as a complex physiological process: neurobiology and molecular physiology

Sleep cycle and endocrine interactions

Sleep is a multifaceted natural phenomenon in most animal kingdoms (Andrillon and Oudiette 2023). It is generally characterized by unconsciousness and reduced responsiveness in which individuals preserve and replenish their energy, maintaining normal physiological and mental activities (Eugene and Masiak 2015). However, it could be easily distinguished from other unconsciousness conditions (coma, seizures, or anesthesia) because sleep is habitually reversed to wakefulness (Joiner 2018). This sleep–wake cycle is maintained by a complex interplay of circadian and homeostatic processes involving various neural circuits and molecular mechanisms, and its disturbance provokes sleep disorders (Eban-Rothschild et al. 2018). Noteworthy, sleep and endocrine system are closely connected as they both regulate each other (Smith and Mong 2019). This section will provide insights into the sleep cycle, sleep-endocrine axis, and the molecular physiology of sleep that could be therapeutically manipulated to manage various sleep disorders.

Brain electrical activity is waving during sleep, classifying sleep into the rapid eye movement (REM) stage and non-REM (NREM) stage (Vyazovskiy et al. 2011). Further investigation classified NREM into three sub-stages in which brain activities and sleep deepness are dissimilar (Patel et al. 2024). Surprisingly, Patel et al. underscored that sleep disorders occur in different sleep cycles; subsequently, diagnosis and intervention will vary among them (Patel et al. 2024). On one hand, REM sleep disorder, insomnia, and narcolepsy could be coupled to the REM phase (Bramich et al. 2023; Feige et al. 2018; Thorpy et al. 2024). On the other hand, somnambulism, sleep terrors, and sleep-related eating disorders are considered NREM parasomnias (Castelnovo et al. 2018). Moreover, SA could be linked to both REM and NREM phases (Alzoubaidi and Mokhlesi 2016).

The suprachiasmatic nucleus (SCN), located in the hypothalamus, receives photic signals from the photoreceptors located in the retina, allowing the SCN to regulate the biological day and night cycle and behave as an internal clock (Welsh et al. 2010). Sleep and hormonal secretion are tightly interconnected; hormonal dysregulation provokes sleep disorders, and the latter could also aggravate hormonal abnormalities (Morgan and Tsai 2015). For instance, melatonin, the central sleeping hormone released at night, is controlled by SCN. Melatonin enhances sleep quality by acting on specific receptors to provoke sedation by suppressing SCN firing (Doghramji 2007). Moreover, melatonin also reduces the levels of the awakening hormone cortisol (Castano et al. 2019). Subsequently, insomnia may lead to stress and metabolic disturbance by upregulating cortisol (Hirotsu et al. 2015). Additionally, growth hormone amends wakefulness and is secreted mainly during deep sleep (Cauter and Plat 1996). Furthermore, prolactin and female gonadal hormone secretion increase during sleep (Liu and Park 1988). Figure 4 illustrates the retinohypothalamic tract that regulates sleep besides sleep stages.

Sleep–wake cycle receptors

Melatonin, regulated by the SCN, is considered the master regulator of sleep that links internal physiological activities to the surrounding environmental changes (Doghramji

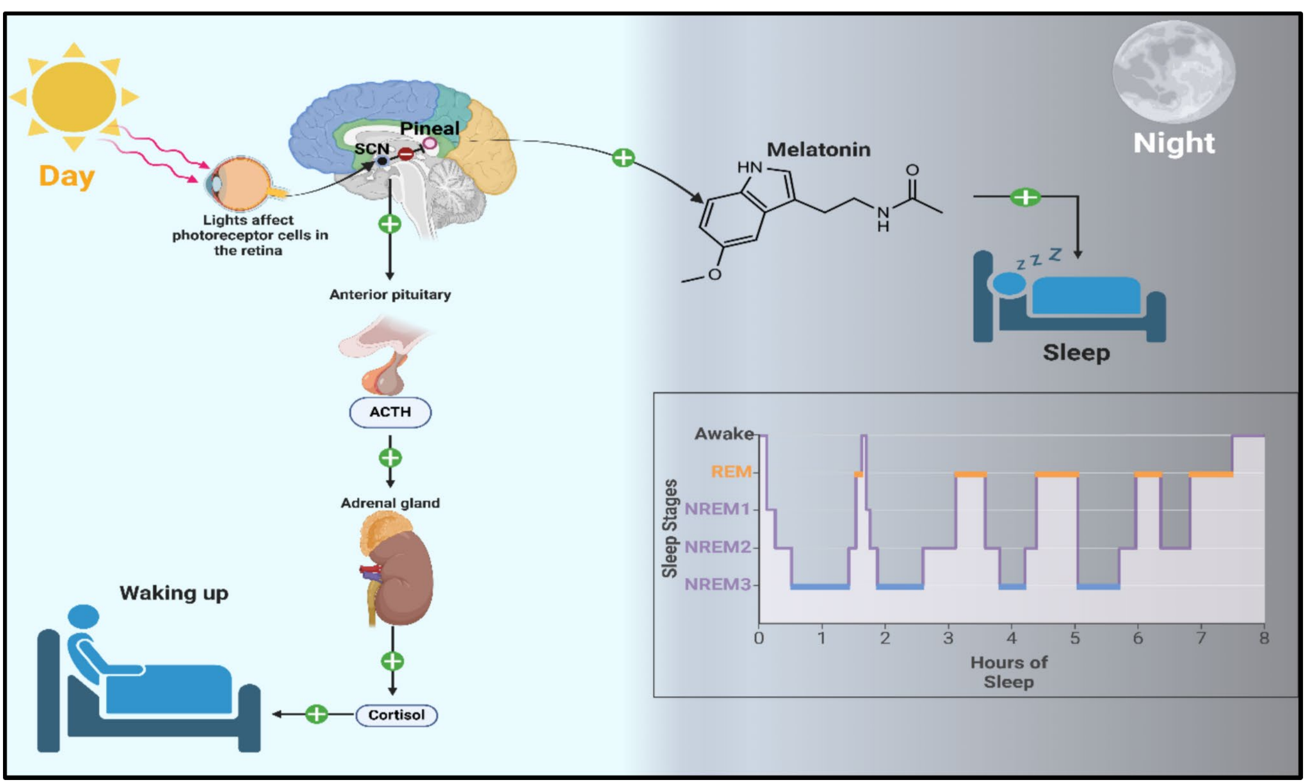


Fig. 4 Illustration of retinohypothalamic tract and sleep stages “Created with BioRender.com.” SCN: Suprachiasmatic nucleus; REM: rapid eye movement; NREM: non-rapid eye movement

2007). Concisely, melatonin binds to three active sites, where the first two (MT_1 and MT_2) are considered G_i-protein coupled receptors localized in the SCN, while MT_3 is a reductase enzyme (Dubocovich 2007). Gobbi et al. reported that MT_1 is involved mainly in REM regulation, while MT_2 regulates NREM sleep (Gobbi and Comai 2019). In both cases, melatonin improves sleep quality by controlling the circadian rhythm and reducing body temperature, which increases sleepiness (Costello et al. 2014). Besides sleep adjustment, melatonin has various properties, including metabolic regulation, hormonal regulation, neuroprotection, antioxidant, and anti-aging (Arendt and Aulinas 2000). Remarkably, melatonin is biosynthesized from serotonin (Zhao et al. 2019), another sleep modulator (Portas et al. 2000). Serotonin's impact on sleep is complex and controversial as it can stimulate sleep and alertness, depending on the site of action and the receptor type (Monti and Jantos 2008).

Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in mammals, located in several brain regions (Smart and Stephenson 2019). It acts by activating an ion-linked $GABA_A$ receptor, promoting a rapid chloride influx, and inhibiting waking neurons (Allen et al. 2024). Interestingly, most drugs acting on $GABA_A$ receptors are allosteric modulators, meaning they enhance the sedative influence of GABA but do not act by themselves (Wisden et al. 2019). GABA also binds to a $G_{i/o}$ protein-coupled receptor, known as $GABA_B$ receptor, that regulates potassium flux and induces a slow synaptic inhibition (Padgett and Slesinger 2010). Besides $GABA_A$ and $GABA_B$ receptors, $GABA_C$ provides a sustained chloride influx (Gottesmann 2002). Interestingly, GABA is biosynthesized from glutamate, a negative sleep regulator (Kaczmarski et al. 2023).

Adenosine is usually produced from the metabolism of adenosine triphosphate, a crucial energy molecule, and exerts a plethora of physiological functions, including sleep regulation (Sheth et al. 2014). Adenosine's influence on sleep is regulated, at least in part, by A_1 and $A_{2\,A}$ receptors (Bjorness and Greene 2009). Concisely, the A_1 receptor is a G_i-protein coupled receptor, and its central activation amends arousing induced by cholinergic in the basal forebrain region, promoting sleep (Thakkar et al. 2003). Conversely, $A_{2\,A}$ receptors are G_s in nature, and their activation stimulates sleep neurons and modulates histaminergic and cholinergic neurons (Bjorness and Greene 2009). These outcomes are supported by the wakefulness induced by the pharmacological antagonism of adenosine receptors by caffeine or by genetic modification in adenosine receptor knock-out genotypes (Reichert et al. 2022).

A series of wakefulness receptors also control the sleep–wake cycle. For instance, as previously mentioned, glutamate is a significant wakefulness neurotransmitter (Kaczmarski et al. 2023). Glutamate binds to a plethora of receptors that provoke wakefulness, including AMPA (Yin et al. 2019), NMDA (Manfridi et al. 1999), and kainate receptors (Yin et al. 2019). Moreover, glutamate can regulate sleep and wakefulness (Shi and Yu 2013). Conversely, NMDA receptor activation by glycine can promote sleep (Kawai et al. 2015). Besides glutamate, histamine's activation of the central H1 receptor promotes wakefulness, explaining the sedative effect of the H1 antagonist (Thakkar 2011). Noteworthy, H3 receptors are presynaptic receptors that negatively regulate histamine release, pointing to H3 agonists as a promising vigilance drug (Parmentier et al. 2007). Moreover, noradrenaline and its precursor, dopamine, control alertness through their central receptors (Ranjbar-Slamloo and Fazlali 2019). To elaborate, noradrenaline released in locus coeruleus enhances arousal via alpha and beta receptors (Berridge et al. 2012). Furthermore, D1 and D2 receptors activated by dopamine inhibit sleepiness (Zhang et al. 2022). Additionally, orexin (OX) receptors (OX1 and OX2) are crucial for arousal, underscoring the possible loss of OX-generating neurons as a pathophysiological event in narcolepsy (Scammell and Winrow 2011). Figure 5 summarizes receptors involved in the sleep–wake cycle.

The chemical structure of all ligands is drawn except orexin since it is a protein in nature with a complex chemical structure; hence, an amino acid chain is used to present orexin.

Therapy of sleep disorders

Non-drug therapies and lifestyle changes in the management of sleep disorders

Sleep disorders, including insomnia, OSA, and RLS, are widespread health concerns that significantly impact individuals' quality of life (Kim, et al. 2024). These conditions are linked to various comorbidities, such as cardiovascular disease, obesity, and mental health disorders (Laaboub et al. 2022; Duraccio et al. 2022; Palagini et al. 2022). While pharmacological treatments are commonly used, there is growing interest in non-drug therapies and lifestyle modifications. The current findings examine the effectiveness of these interventions, focusing on behavioral therapies, sleep hygiene, physical activity, dietary changes, and other complementary approaches (Briguglio et al. 2020; Wilson et al. 2022, 2023).

Cognitive Behavioral Therapy for Insomnia (CBT-I)

Cognitive Behavioral Therapy for Insomnia (CBT-I) is a first-line, non-pharmacological treatment for chronic

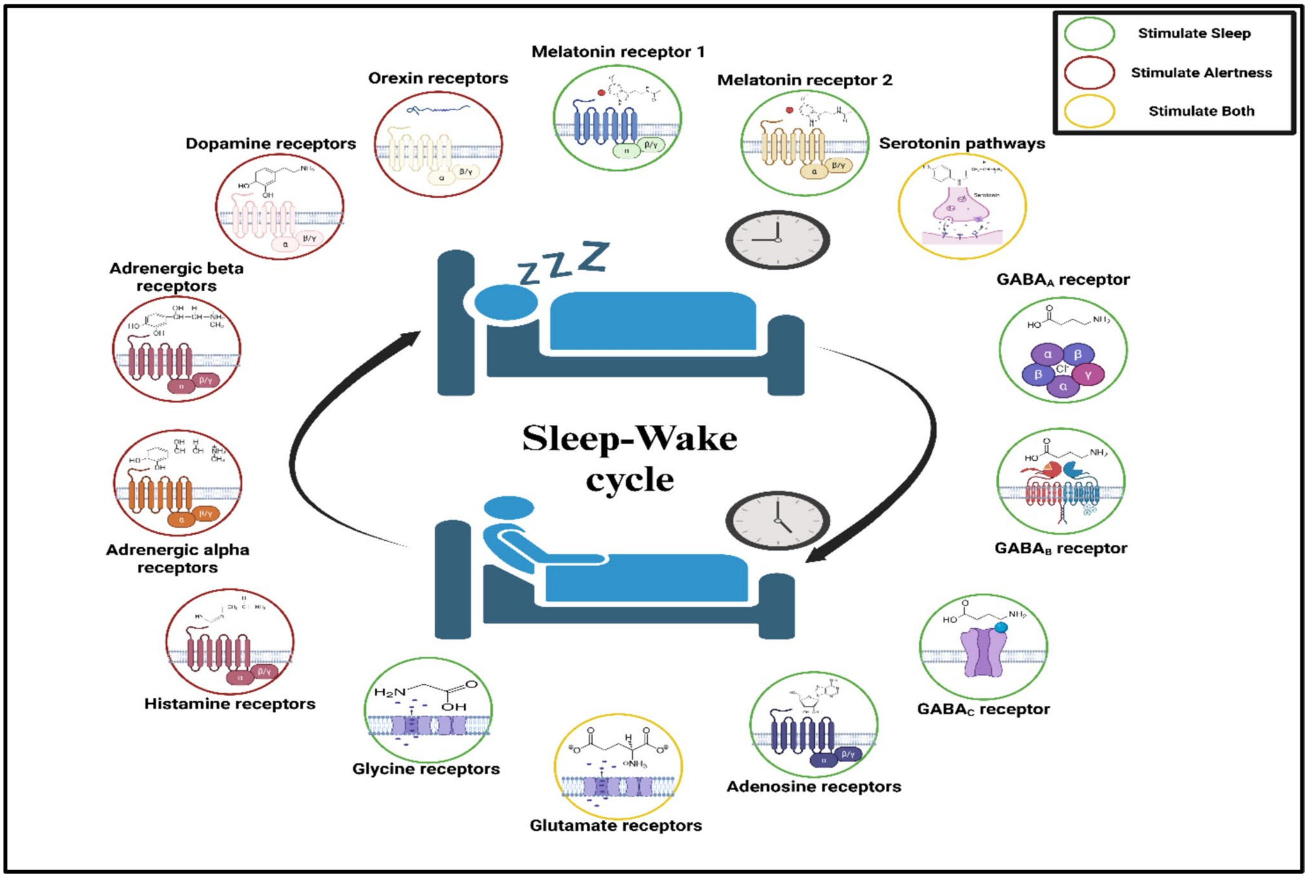


Fig. 5 Influence of specific receptors involved in the sleep–wake cycle with a sketch of its ligand "Created with BioRender.com." GABA: gamma-aminobutyric acid

insomnia. This structured program targets negative thoughts and behaviors contributing to sleep disturbances (Soong et al. 2021). Key techniques include as follows:

Cognitive restructuring Identifying and correcting irrational thoughts related to sleep, such as excessive fear of sleeplessness or overestimating the impact of poor sleep. Patients learn to replace negative thoughts with rational perspectives that reduce stress and anxiety surrounding sleep (Redeker et al. 2020; Sweetman et al. 2021).

Stimulus control Strengthening the association between bed and sleep by limiting bedroom activities to sleep and intimacy. This method discourages behaviors like working, eating, or watching television in bed, ensuring that the mind associates the bed with restful sleep (Iao et al. 2022; Jansson-Fröjmark et al. 2024).

Sleep restriction Enhancing sleep efficiency by initially restricting time in bed to the actual sleep duration, then gradually increasing it. This process helps patients consolidate sleep and improve their ability to fall and stay asleep over time (Maurer et al. 2020; Maurer et al. 2021).

Relaxation training Utilizing methods such as progressive muscle relaxation, deep breathing, and meditation to decrease physiological arousal before bedtime. These practices help to counteract stress-induced insomnia and create a calm pre-sleep routine (Liu et al. 2020; Toussaint et al. 2021).

Research has consistently demonstrated that CBT-I leads to sustained improvements in sleep quality and duration, often proving more effective and with fewer side effects than pharmacological treatments. The adaptability of CBT-I across diverse patient populations enhances its widespread acceptance and efficacy. Digital platforms and mobile applications now offer accessible CBT-I programs, broadening its reach and making effective sleep management more attainable for the general population (Climent-Sanz et al. 2022; Lu et al. 2023; Ntikoudi et al. 2024).

Sleep hygiene education

Sleep hygiene encompasses behavioral and environmental practices that optimize sleep. These include as follows:

Regular sleep schedule Maintaining consistent sleep and wake times, including weekends, to regulate circadian rhythms and reinforce the body's natural sleep–wake cycle. Irregular sleep patterns disrupt biological clocks, making it harder to maintain consistent sleep quality (Walker et al. 2020; Basit et al. 2025).

Optimal sleep environment Creating a quiet, dark, and cool bedroom with blackout curtains, white noise machines, or earplugs to minimize disturbances. Research suggests that cooler room temperatures, typically between 60 and 67 °F (16–19 °C), facilitate deeper sleep (Strøm-Tejsen et al. 2016; Raj et al. 1214).

Limiting stimulants Avoiding caffeine, nicotine, and heavy meals near bedtime to prevent disruptions in the sleep cycle. Late-night consumption of alcohol, although initially sedating, can lead to fragmented sleep and frequent nighttime awakenings (Spadola et al. 2019).

Avoiding screen exposure before bed Reducing exposure to blue light from electronic devices (phones, tablets, and computers) at least 1 h before sleep to support natural melatonin production. Blue light suppresses melatonin release, making it harder for the body to transition into sleep mode (Tähkämö et al. 2019; Shechter et al. 2020).

Educational programs emphasizing sleep hygiene have been shown to improve sleep quality and duration, especially when integrated with other behavioral therapies. Schools, workplaces, and public health campaigns are increasingly recognizing the importance of sleep education, promoting better sleep habits across all age groups (Redeker et al. 2019; Gaskin et al. 2024). The literature is packed with myriad evidence supporting the impact of simple practices (summarized in Fig. 6) on the quality and quantity of sleep especially in individuals with or prone to having sleep disorders (Varadharasu and Das 2024; Carrión-Pantoja et al. 2022; Corrêa et al. 2024; Norouzi et al. 2024).

Physical activity and exercise

Engaging in physical activity contributes to improved sleep duration and quality through several mechanisms:

Endorphin release Exercise triggers the release of endorphins, enhancing mood and reducing stress, thereby facilitating better sleep initiation. Additionally, physical activity increases body temperature, and the subsequent post-exercise temperature drop may aid in sleep induction (Basso and Suzuki 2017; Sepdanius et al. 2023).

Fig. 6 Sleep hygiene tips (icons by Falticon.com)

Circadian rhythm regulation Regular physical activity helps synchronize the body's internal clock, promoting more consistent sleep and wake times. This is particularly beneficial for individuals suffering from circadian rhythm sleep disorders, such as delayed sleep phase disorder (Thomas 2020; Weinert and Gubin 2022).

Reduction in anxiety and depression symptoms Since anxiety and depression often contribute to sleep disturbances, exercise serves as a natural remedy to alleviate these symptoms. Physical activity has been linked to increased production of neurotransmitters like serotonin and dopamine, which help regulate mood and improve sleep (Alnawwar et al. 2023).

Muscle relaxation and physical fatigue Engaging in exercise can lead to muscle relaxation and physical fatigue, making it easier to fall asleep. However, the timing of exercise is crucial. While moderate morning and afternoon exercise has positive effects on sleep, high-intensity workouts close to bedtime can increase alertness and hinder the ability to fall asleep (Alkhaldi et al. 2023).

Studies suggest that moderate aerobic exercises such as walking, swimming, or cycling for at least 30 min several times a week yield the most significant sleep benefits. Resistance training and yoga have also been found to be beneficial, particularly in reducing stress-related insomnia (Wang and Boros 2021; Zhou et al. 2022).

Dietary modifications

Diet plays a crucial role in sleep regulation, with specific nutrients influencing sleep quality by affecting neurotransmitters and circadian rhythms. A well-balanced diet that includes essential vitamins and minerals can significantly impact sleep patterns, improving both the duration and quality of rest (Alruwaili et al. 2023). Dietary interventions include as follows:

Melatonin-rich foods Melatonin, a hormone that governs sleep–wake cycles, can be naturally supported by consuming foods rich in melatonin, such as tart cherries, grapes, bananas, nuts, and oats. These foods help promote a natural feeling of sleepiness and can assist in maintaining a steady sleep schedule (Pereira et al. 2020).

Magnesium and calcium These essential minerals contribute to neurotransmitter regulation, promoting relaxation and calmness, which may aid in better sleep. Magnesium plays a role in reducing cortisol levels, a stress hormone that can disrupt sleep. Foods such as leafy greens, almonds, dairy products, seeds, and whole grains are excellent sources (Zhang et al. 2022; Briskey et al. 2024).

High glycemic foods Diets high in refined carbohydrates and sugar can negatively impact sleep quality by causing fluctuations in blood sugar levels and subsequent insulin spikes. These sudden changes can lead to nighttime awakenings and difficulty maintaining a restful sleep. Opting for complex carbohydrates like whole grains, legumes, and fiber-rich vegetables can help stabilize blood sugar levels and support more consistent sleep patterns (Gangwisch et al. 2020).

Nutritional interventions in these areas have demonstrated promising results in enhancing sleep duration and quality, particularly when combined with other lifestyle modifications. Additionally, staying well hydrated and maintaining a consistent eating schedule can further help regulate sleep cycles (Hepsomali and Groeger 2021; Kesztyüs et al. 2021; Arab et al. 2023).

Mindfulness and relaxation techniques

Mindfulness meditation, yoga, and relaxation techniques have emerged as effective complementary strategies for managing sleep disorders. These practices help reduce physiological and psychological stress, which can contribute to sleep disturbances. By promoting relaxation, these methods encourage the body's natural transition into restful sleep (Wang et al. 2019; Rusch et al. 2019).

Mindfulness meditation Engaging in mindfulness techniques that focus on present-moment awareness and acceptance can decrease sleep latency and enhance sleep quality, particularly for individuals with insomnia and anxiety-related sleep issues. Practicing mindfulness before bed can reduce the racing thoughts and mental clutter that often interfere with sleep (Wang et al. 2019).

Yoga Gentle forms of yoga that incorporate breathing exercises and relaxation techniques have been shown to improve sleep quality, especially in individuals suffering from chronic insomnia or high stress levels. Poses such as child's pose, legs-up-the-wall pose, and forward bends help calm the nervous system and prepare the body for rest (Turmel et al. 2022).

Progressive muscle relaxation (PMR) PMR, a technique involving the tensing and relaxing of muscle groups, has proven effective in reducing sleep onset latency and extending sleep duration in individuals with insomnia. This practice helps release physical tension that may be preventing relaxation (Simon et al. 2022).

Breathing exercises Controlled breathing techniques, such as the 4–7–8 method or diaphragmatic breathing, can slow the heart rate and activate the parasympathetic nervous system, signaling the body that it is time to sleep. Practicing these exercises regularly can help establish a bedtime routine that encourages relaxation (Jerath et al. 2019; Laborde et al. 2019).

These relaxation-focused methods foster a state of tranquility, making it easier to fall asleep and maintain restful sleep throughout the night. Integrating them into a nightly routine can enhance the effectiveness of other sleep-promoting strategies (Rusch et al. 2019).

Pharmacological therapy

The list of pharmacological therapy of common sleep disorders is displayed in Table 1.

Natural remedies for sleep disorders

Using natural remedies for the treatment of sleep disorders is a common practice in modern day (Sánchez-Ortuño et al. 2009). Many of these natural remedies are food supplements consisting of different plant extracts taken for improving sleep, and are believed to be generally safe and well tolerated

Table 1 Summary of the pharmacological therapy of insomnia, sleep apnea, restless leg syndrome, and narcolepsy

Sleep disorder	Pharmacological class	Examples	Guidelines and references
Insomnia	Benzodiazepines	Temazepam, triazolam	Riemann et al. 2023; Madari et al. 2021; Sateia et al. 2017
	Benzodiazepine receptor agonists	Eszopiclone, zopiclone, zolpidem, zaleplone	
	Orexin receptor antagonist	Suvorexant, daridorexant	
	Sedative norepinephrine/serotonin enhancers	◦ Tricyclic antidepressants: Doxepin ◦ Serotonin receptor antagonists and reuptake inhibitors (SARI): Trazodone	
	Melatonin and melatonin receptor agonists	Melatonin, ramelteon	
	Histamine receptor antagonist	Diphenhydramine	
	Dopamine (D2)/serotonin (5HT2 A) receptors antagonists	Olanzapine, quetiapine	
Sleep apnea	Carbonic anhydrase inhibitors	Acetazolamide	Randerath et al. 2022; Nobre 2024; Arredondo, et al. 2022; Liu et al. 2024
	Selective norepinephrine reuptake inhibitor/muscarinic receptor antagonist combination therapy	Atomoxetine/oxybutynin combination therapy	
	Selective serotonin reuptake inhibitors	fluoxetine	
	Norepinephrine and dopamine reuptake inhibitors	Solriamfetol	
	Dopamine reuptake inhibitors	Modafinil, armodafinil	
	Glucagon-like peptide- 1 agonists	Tirzepatide	
	H3-receptor antagonist/inverse agonist	Pitolisant	
Restless leg syndrome	Dopamine agonists	Ropinirole, rotigotine	Lv et al. 2021; Winkelman et al. 2016; Silber et al. 2021
	α2δ ligands	Pregabalin, gabapentin enacarbil	
	Iron treatment	Oral ferrous sulphate	
	Low potency opioids	Tramadol, codeine	
Narcolepsy	Norepinephrine and dopamine reuptake inhibitors	Methylphenidate, solriamfetol	Thorpy and Bogan 2020; Bhattarai and Sumerall 2017; Maski et al. 2021
	Dopamine reuptake inhibitors	Modafinil, armodafinil	
	Selective serotonin and norepinephrine reuptake inhibitors	Venlafaxine	
	H3-receptor antagonist/inverse agonist	Pitolisant	
	GABA-B receptor agonist	Sodium oxybate	

by the population (Guadagna et al. 2020). Many natural remedies have been studied in the management of sleep disorders such as kava (*Piper methysticum*), valerian (*Valeriana officinalis*), and passionflower (*Passiflora incarnata*) (Ekor et al. 2013). In this section, examples of natural remedies that have been reported to have potential in the management of sleep disorders are covered and discussed.

***Artemisia* sp.**

Artemisia annua L. (sweet wormwood or Qinghao) has an ethnomedicinal use of as sedative agent. The chloroform fraction of the methanol extract of *Artemisia annua* was found to have sedative effects in mice when injected intraperitoneally, suggested to be mediated via benzodiazepine receptors pathways (Emadi et al. 2011).

Anthemis arvensis (field chamomile) has been reported to be among the most cited Italian plants used for managing sleep disorders although no mechanism of action studies have been carried out yet (Motti and Falco 2021).

Interestingly, de novo formation of benzodiazepines in the plant tissue extract of *Artemisia dracunculus* (estragon) has been reported, with a binding activity to the central human benzodiazepine receptor of IC_{50} 5.7 mg/ml. The reported benzodiazepine in *Artemisia dracunculus were* delorazepam and temazepam, and their amounts ranged from 100 to 200 ng/g cell tissue (Kavvadias et al. 2000).

***Citrus aurantium* (bitter orange)**

In traditional medicine, the *Citrus genus* is used in managing the symptoms of anxiety or insomnia. The essential oil of *Citrus aurantium* L., with its main active components reported to be monoterpene limonene (98.66%), β-pinene (0.41%), and β-myrcene (0.53%), was found to exhibit anxiolytic-like activity mediated by $5\text{-HT}_{1\ A}$-receptors in mice after acute treatment, helping in increasing sleep duration(Costa et al. 2013; de Moraes Pultrini et al. 2006; Carvalho-Freitas and Costa 2002).

In addition to *C. aurantium*, the sedative and anxiolytic-like effects of the essential oils of *C. latifolia*, and *C. reticulata* in mice have similarly been reported (Gargano et al. 2008).

***Crataegus monogyna* (hawthorn)**

Based on the reported traditional uses of hawthorn for its neurosedative activity, the effect of the fruit extract of hawthorn was investigated in mice and was found to have CNS depressant activities (Can et al. 2010). Hawthorn extract was also found to effectively reduce anxiety symptoms in mice (Mandanizadeh et al. 2018). In a randomized controlled trial, hawthorn fruit extract was found to significantly improve the quality of sleep in hypertensive patients when taken as a supplementary medication(Abbasi et al. 2021).

***Eschscholzia californica* (Californian poppy)**

Eschscholzia californica is known to have sedative and anxiolytic effects. Its main compounds are alkaloids such as protopine, californidine, allocryptopine, eschscholtzine, sanguinarine, chelerythrine, reticuline, N-methyllaurotetanine, and caryachine. Based on in vitro studies, alkaloids present in *E. californica* are suggested to act at the $GABA_A$ receptors in the brain mainly at the inhibitory interneurons(Fedurco et al. 2015).

***Humulus lupulus* (hop)**

Hops oil was found to potentiate the $GABA_A$ receptor response elicited by GABA (Aoshima et al. 2006). *Humulus lupulus* CO_2 extract was found to increase the pentobarbital sleep-enhancing property (Zanoli et al. 2005), and both the ethanolic and CO_2 extracts showed a central sedating effect (Schiller et al. 2006). Additionally, a combination of both valerian and hops extract was suggested to achieve it sleep-aiding activity possibly through interaction with melatonin and serotonin receptors (Abourashed et al. 2004). Xanthohumol, a prenylated chalcone derivative extracted from *Humulus lupulus,* was found to achieve its activity by acting at the $GABA_A$ receptors (Abourashed et al. 2004).

***Piper methysticum* (kava-kava)**

Although kava-kava has been shown to have anxiolytic and hypnotic activity suggested to be through acting on GABA in animal experiments, it is not commonly prescribed or used in humans due to its hepatotoxic effects (Guadagna et al. 2020; Jussofie et al. 1994).

***Laurus nobilis* (bay laurel)**

Bay laurel was found to have sedative properties due to its content of phenylpropanoids such as eugenol and methyl eugenol and the monoterpenoid 1,8-cineole; however, mechanisms of actions or clinical data supporting their sleep-inducing activity have not been documented (Sayyah et al. 2002; Santos and Rao 2000).

***Lavandula angustifolia* (lavender)**

The main components of lavender are linalool and linalyl acetate (Guadagna et al. 2020). These molecules interact with NMDA receptors, block serotonin transporter (SERT), and lower voltage-operated calcium channels (VOOCs) (Motti and Falco 2021). Supported by preclinical studies and clinical data, lavender has shown anxiolytic and sedative properties, implying possible use in enhancing the quality of sleep (Guadagna et al. 2020; Woelk and Schläfke 2010; Kasper et al. 2010; Kasper et al. 2015; Uehleke et al. 2012).

Magnolia sp.

Magnolia species, particularly through their bioactive compounds magnolol and honokiol, have been shown to induce REM sleep by modulating $GABA_A$ receptors. These effects have been observed in in vitro studies and intraperitoneal administration in animal models, indicating their efficacy in enhancing sleep (Alexeev et al. 2012; Qu et al. 2012; Squires et al. 1999).

Matricaria chamomilla (chamomile)

Chamomile has shown potential as a natural remedy for sleep disorders, supported by preclinical and clinical studies (Amsterdam et al. 2009; Mao et al. 2016). Apigenin, a flavonoid found in chamomile, was found to act as a ligand for benzodiazepine (BZD) receptors, demonstrating benzodiazepine-like activity (Medina et al. 1998), inhibiting glutamate decarboxylase (GluAD) activity, and leading to sedative and anxiolytic effects (Viola et al. 1995; Avallone et al. 2000; Awad et al. 2007; Zanoli et al. 2000).

Melissa officinalis (lemon balm)

The polyphenolic content of Lemon balm was found to inhibit GABA transaminase, resulting in increased GABA levels in the brain (Awad et al. 2007; Yoo et al. 2011). This mechanism underlies its anxiolytic and sleep-enhancing properties(Kennedy et al. 2004). Both clinical and animal studies support the use of lemon balm in improving sleep quality (Kennedy et al. 2004; Cases et al. 2011; Awad et al. 2009).

Moringa oleifera (drumstick tree)

The key compounds in Moringa oleifera, oleic acid, β-sitosterol, and stigmasterol have been associated with improved sleep quality via $GABA_A$ receptor activity, as demonstrated in oral administration studies in animal models (Liu et al. 2020).

Nelumbo nucifera (lotus)

The alkaloid fraction of the extract of lotus leaves was found to have sedative–hypnotic effects (Yan et al. 2015a). Lotus leaves alkaloids, such as nuciferine, were found to promote sleep through interactions with $GABA_A$ receptors (Yan et al. 2015b).

Ocimum basilicum (basil)

Basil leaves, containing monoterpenoids including linalool and phenylpropanoids such as eugenol, are traditionally used for its sedative properties (Hirai and Ito 2019). Both the volatile oil and the hydroalcoholic extract of basil leaves were found to have anxiolytic and sedative effect in mice, suggested to be due to their phenolic content (Rabbani et al. 2015).

Papaver rhoeas (corn poppy)

The flavonol hyperoside is one of the main primary compounds identified in corn poppy. While it has been found to have anxiolytic and sedative effects, evidence specifically relating to sleep induction is limited (Grauso et al. 2021; Hillenbrand et al. 2004).

Papaver somniferum (opium poppy)

Opium poppy, which contains alkaloids such as morphine, codeine, and noscapine, is known to modulate opioid μ-receptors (Labanca et al. 2018). These opioid compounds are associated with sedative effects, but their use is restricted due to potential for dependency and abuse (Listos et al. 2019).

Passiflora incarnata (passionflower)

Passionflower has been used traditionally to treat a range of sleep disorders (Ekor et al. 2013; Bruni et al. 2021). Passionflower extract was reported to contain alkaloids and flavones that interact with $GABA_A$, $GABA_B$, and possibly $GABA_C$ receptors, reducing sleep latency and increasing sleep duration, as supported by in vitro and animal studies (Appel et al. 2011; Elsas et al. 2010).

Polygala tenuifolia (Yuan Zhi)

Tenufolin, the active compound in the well-known anti-insomnia herb *Polygala tenuifolia,* was found to enhance GABA and GABA transporter levels, resulting in prolonged sleep duration. These effects have been observed in studies using zebrafish and rats (Chen et al. 2020; Ren et al. 2020).

Rosmarinus officinalis (rosemary)

Rosemary extract, rich in rosmarinic acid, caffeic acid, and flavonoids such as cirsimaritin, was found to have sleep-inducing activity via mediation of $GABA_A$ receptors and inhibition of T-type calcium channels (Abdelhalim et al. 2015; Alaoui et al. 2017).

Schisandra chinensis **(Chinese magnolia-vine)**

Schisandra chinensis contains the active lignan schisandrin B and schizandrin, which show notable sedative and hypnotic effects via altering the GABAergic system, raising the GABA/Glu ratio and upregulating $GABA_A$ receptor subunits (Rα1 and Rγ2) in the cerebral cortex, hippocampal, and hypothalamus, yielding lower sleep latency and longer sleep duration (Li et al. 2018; Wang et al. 2020). Furthermore, schizandrin was found to reduce locomotor activity and improve pentobarbital-induced sleep patterns (Zhang et al. 2014).

Tilia platyphyllos **(large-leaved lime)**

Tilia platyphyllos extract, rich in flavonoids including quercetin and rutin, was found to exhibit GABA-like and benzodiazepine-like activity. These effects were found to be mediated through modulation of GABAergic and serotonergic systems (Aguirre-Hernández et al. 2016; Allio et al. 2015; Cavadas et al. 1997).

Valeriana officinalis **(valerian)**

Valerian is well-known for its sleep-inducing activity and is extensively used as a hypnotic and calming agent. Valerian sesquiterpenes, such as valerenic acid and valerenol, have been found to modulate $GABA_A$ receptors and serotonergic systems (Benke et al. 2009; Dietz et al. 2005; Khom et al. 2007; Mineo et al. 2017). Valerian was found to significantly reduce sleep latency and improve subjective sleep quality in both clinical and preclinical studies (Mischoulon 2018; Aliakbari and Alesaeidi 2018).

Withania somnifera **(Ashwagandha)**

Ashwagandha contains withanolide A and withaferin A, which were found to reduce sleep latency and enhance sleep quality through interactions with $GABA_A$ and $GABA_C$ receptors, as demonstrated both in in vitro and clinical studies (Candelario et al. 2015; Langade et al. 2019).

Zizyphus jujube **(jujube)**

Jujube extract, containing sanjoinine A and suanzaorentang, was found to enhance GABA synthesis and act on serotonin receptors contributing to prolonged sleep time and improved sleep quality in animal studies (Yi et al. 2007; Ma et al. 2007).

To summarize the diverse natural remedies explored in this review, Table 2 provides an overview of key phytochemicals, their mechanisms of action, and their reported effects on sleep disorders.

Mechanisms of action of natural products in sleep disorders

Natural products have been traditionally used to aid in sleep disorders, and their importance is growing dramatically due to their lower side effects compared to conventional medications (Hu et al. 2018). These remedies act via various mechanisms: directly by altering neurotransmitter and hormonal pathways in sleep circuits and indirectly by improving sleep quality by relieving stress, inflammation, and oxidative stress. In this section, we aim to investigate into how nutraceuticals aid sleep.

Modulation of neurotransmitters

Nutraceuticals can modulate neurotransmitters that regulate the sleep–wake cycle. For instance, valerian enhances sleep quality by acting on $GABA_A$ receptors and improving the availability of internal GABA by inhibiting its destruction, leading to sedative effects (Murphy et al. 2010). Magnolol, nuciferine, stigmasterol, apigenin, and tenufolin display sedative effects through the GABAergic pathway (Bruni et al. 2021). Moreover, the sedative effect of chamomile extract could be justified, at least in part, by modulating serotonin and dopamine receptors (Yeom and Cho 2024). Inline, lavender interacts with serotonin transporter, exerting a sedative impact (Lopez et al. 2017). Melatonin adjustment explains also the sedative effect of several herbal products, including tart cherry (Howatson et al. 2012), St. John's wort (Salehi et al. 2019), and kiwifruit (Doherty et al. 2023).

Hormonal regulation and stress reduction

Indeed, stress negatively affects individuals' cognitive and physical performance and sleep quality (Kalmbach et al. 2018). Fortunately, herbal products regulate hormones and amend stress, significant mechanisms for addressing sleep disorders. Cortisol, a stress hormone, levels are reduced by several herbal products, including ashwagandha, lavender, and rhodiola (Burns 2023). They, among others, are known for being adaptogenic, relieving stress, and enhancing mindfulness (Tóth-Mészáros et al. 2023). Noteworthy, the sympathetic system's over-activation provokes anxiety, which passionflower could repress with minimal side effects (Janda et al. 2020). Interestingly, a double-blinded clinical study reported the anxiolytic effect of lemon balm on patients after

Table 2 Summary of phytochemical-based natural remedies for sleep disorders, detailing their active compounds, mechanisms of action, notable effects, and supporting study types

Plant name	Active compounds	Mechanism of action	Notable effects	Study type
Artemisia annua	Benzodiazepines	Acts on benzodiazepine receptors	Sedative effects in mice	Animal studies
Citrus aurantium	Limonene, β-pinene, β-myrcene	Anxiolytic via 5-HT_{1A} receptors	Increased sleep duration	Preclinical studies
Crataegus monogyna	-	CNS depressant activity	Improved sleep quality in hypertensive patients	Clinical trial
Eschscholzia californica	Alkaloids (e.g., protopine, sanguinarine)	Acts on $GABA_A$ receptors	Sedative and anxiolytic effects	In vitro, animal studies
Humulus lupulus	Xanthohumol	Potentiates $GABA_A$ receptor response	Enhanced pentobarbital sleep	Preclinical studies
Laurus nobilis	Eugenol, methyl eugenol, 1,8-cineole	-	Sedative properties	Preclinical studies
Lavandula angustifolia	Linalool, linalyl acetate	Interacts with NMDA receptors, blocks SERT	Anxiolytic and sedative properties	Clinical and preclinical studies
Magnolia sp.	Magnolol, honokiol	Modulates $GABA_A$ receptors	Induces REM sleep	Animal studies
Matricaria chamomilla	Apigenin	Benzodiazepine receptor ligand	Sedative and anxiolytic effects	Clinical and preclinical studies
Melissa officinalis	Polyphenols	Inhibits GABA transaminase	Improved sleep quality	Clinical and preclinical studies
Moringa oleifera	Oleic acid, β-sitosterol, stigmasterol	Acts on $GABA_A$ receptors	Improved sleep quality in animal models	Animal studies
Nelumbo nucifera	Nuciferine	Acts on $GABA_A$ receptors	Sedative-hypnotic effects	Preclinical studies
Ocimum basilicum	Linalool, eugenol	-	Sedative and anxiolytic effects	Animal studies
Passiflora incarnata	Alkaloids, flavones	Acts on $GABA_A$, $GABA_B$, and $GABA_C$ receptors	Reduced sleep latency, increased duration	In vitro, animal studies
Polygala tenuifolia	Tenufolin	Enhances GABA and GABA transporter levels	Prolonged sleep duration	Animal studies
Schisandra chinensis	Schisandrin B, schizandrin	Modulates GABAergic system, raises GABA/Glu ratio	Prolonged sleep duration, improved patterns	Animal studies
Tilia platyphyllos	Flavonoids (e.g., quercetin, rutin)	Modulates GABAergic and serotonergic systems	GABA-like activity	Preclinical studies
Valeriana officinalis	Valerenic acid, valerenol	Modulates $GABA_A$ receptors and serotonergic systems	Improved sleep quality, reduced latency	Clinical and preclinical studies
Withania somnifera	Withanolide A, withaferin A	Acts on $GABA_A$ and $GABA_C$ receptors	Enhanced sleep quality	Clinical and preclinical studies
Zizyphus jujube	Sanjoinine A, suanzaorentang	Enhances GABA synthesis, acts on serotonin receptors	Prolonged sleep time	Animal studies

cardiac surgery, improving their sleep quality (Soltanpour et al. 2019).

Anti-inflammatory and antioxidant effects

Although sleep disturbance inflames systemic inflammation (Irwin et al. 2016), the reverse is also correct, and chronic inflammation indirectly lessens sleep quality (Mullington et al. 2010). Subsequently, anti-inflammatory herbal products, including turmeric, ginger, and rosemary, can enhance sleep quality (Ghasemian et al. 2016). This favorable action can be credited to reducing the sleep onset latency and wake time, improving sleep continuity (Wirth et al. 2020).

Moreover, sleep is crucial to clear reactive oxygen species that develop through the day; subsequently, inadequate sleep could provoke oxidative stress (Shah et al. 2023). Interestingly, Hill et al. pointed to a bidirectional connection between sleep and oxidative stress (Hill et al. 2018). This outcome is further supported by a recently reported randomized clinical study in around 25000 adults that concluded reducing the risk of sleep disorder upon consuming dietary antioxidants (Jiang et al. 2024). Dietary antioxidants include polyphenols, flavonoids, vitamins, and minerals (Zujko and

Table 3 The summary of clinical trials of natural products in the management of sleep disorders

Sleep disorder	Study	Study design	No. of participants	Special population	Agent(s) and dose	End point/outcome(s)	Main result(s)
Impaired sleep	Taavoni et al. 2013	Randomized, triple-blind, placebo-controlled clinical trial	**100** (50 in the intervention group, 50 in the control group)	Women undergoing menopause	Valerian/Lemon Balm capsules (160 mg/80 mg)	PSQI	The valerian/lemon balm combination improved sleep quality compared to control
Impaired sleep	Adib-Hajbaghery and Mousavi 2017	Randomized controlled trial	**60** (30 in the intervention group, 30 in the control group)	Older adults	Chamomile extract capsules (200 mg, twice daily)	PSQI	8-week administration of chamomile extract can significantly improve the quality of sleep in elderly patients
Impaired sleep	Haybar et al. 2018	Randomized, Double-blind placebo-controlled clinical trial	**73** (35 in the intervention group, 38 in the control group)	Patients with chronic stable angina	Lemon balm "*Melissa officinalis*" dried aerial parts (3 g)	PSQI DASS- 21	Consumption of *Melissa officinalis* can improve depression, anxiety, stress, and insomnia in patients with chronic stable angina
Impaired sleep	Feyzabadi et al. 2018	Randomized, double-blind, placebo-controlled study	**75** (25 in the Violet oil group, 25 in the Almond oil group, 25 in the control group)	-	Violet Oil (Intranasal drops)	PSQI ISI	Significant improvement in insomnia was noticed across the 3 groups with the Violet Oil intervention being more significant
Impaired sleep	Umigai et al. 2018	Randomized, double-blind, placebo-controlled, cross-over study	**30**	-	Crocetin (7.5 mg)	OSA-MA EEG	Study participants reported improvement in sleepiness on rising and fatigue recovery (subjective sleep parameters) EEG data showed increased delta power during REM sleep latency which enhances sleep maintenance
Impaired sleep	Um et al. 2019	Randomized, double-blind, placebo-controlled, polysomnographic study	**50** (25 in the intervention group, 25 in the control group)	-	Rice Bran Extract Supplement (1000 mg)	PSQI ESS FSS SE TST WASO TWT	Rice bran extract supplement may improve sleep onset and sleep maintenance in patients with impaired sleep

Table 3 (continued)

Sleep disorder	Study	Study design	No. of participants	Special population	Agent(s) and dose	End point/outcome(s)	Main result(s)
Impaired sleep	Ha, et al. 2019	Randomized, double-blind, placebo-controlled trial	**80** (40 in the intervention group, 40 in the control group)	-	*Polygonatum sibiricum* (PS) rhizome extract (500 mg)	AIS (1ry) TST SE WASO	Mild insomnia might be controlled by 4-week administration of PS rhizome extract
Impaired sleep	Taherzadeh et al. 2020	Randomized, double-dummy, double-blind placebo controlled clinical trial	**50** (25 in the intervention group, 25 in the control group)	-	Dried violets (*Viola odorata* L.), saffron (*Crocus sativus* L.) and lettuce seeds (*Lactuca sativa* L.) oil preparation for intranasal administration	ISI (1ry) PSQI	The administration of the herbal intranasal formula decreased insomnia severity and improved quality of sleep
Impaired sleep	Lopresti et al. 2020	Randomized, double-blind, placebo-controlled trial	**63** (33 in the intervention group, 30 in the control group)	-	Saffron extract (14 mg, twice daily)	ISI (1ry) RSQ PSD DASS- 21	8-week supplementation of saffron extract reduced insomnia, and improved sleep quality
Impaired sleep	Elmi, et al. 2021	Randomized, triple-blind, placebo-controlled clinical trial	**76** (38 in Coronary Artery Bypass Graft (CABG) intervention group, 38 in control group)	Patients after CABG surgery	Valerian root extract powder (530 mg)	PSQI PT/PTT	Valerian root extract improved Sleep quality with no effect on coagulation profile
Impaired sleep	Shirazi, et al. 2021	Randomized, double-blind, placebo-controlled clinical trial	**60** (20 in the *Melissa officinalis L.* group, 20 in Citalopram group, 20 in the control group)	Postmenopausal women	lemon balm leaf and fennel fruit capsule (500 mg)	Changes in MENQOL domains	*Melissa officinalis L.* can improve the quality of life of postmenopausal women with sleep disturbances compared to other groups
Impaired sleep	Lopresti et al. 2021	Randomized double-blind placebo-controlled multi-dose study	**120** (40 in 14 mg saffron extract group, 40 in 28 mg saffron extract group, 40 in the control group)	-	Saffron extract (14 mg, 28 mg)	PSD (1ry) ISQ-W FOSQ- 10 POMS-A Salivary Cortisol Salivary Melatonin	Saffron extract can improve sleep quality and mood after awakening in addition to increasing melatonin levels
Impaired sleep	Pachikian, et al. 2021	Randomized double-blind placebo-controlled multi-dose study	**66** (32 in the intervention group, 34 in the control group)	-	Saffron extract (15.5 mg)	SOL SE TIB FRAGI TST WASO LSEQ PSQI SF- 36	Saffron extract supplementation for 6 weeks improved sleep quality-related parameters when assessed by actigraphy or questionnaires

Table 3 (continued)

Sleep disorder	Study	Study design	No. of participants	Special population	Agent(s) and dose	End point/outcome(s)	Main result(s)
Impaired sleep	Langade et al. 2021	Randomized, parallel, double-blind, controlled clinical trial	**80** 40 healthy subjects (20 in the intervention group, 20 in the control group) 40 patients with insomnia (20 in the intervention group, 20 in the control group)	-	Ashwagandha (*Withania somnifera* (L.) Dunal.) root extract (300 mg)	SOL TST WASO TIB SE PSQI	8-week consumption of ashwagandha root extract improved various parameters of sleep quality in healthy and insomnia patients
Impaired sleep	Karimi et al. 2023	Randomized triple-blind placebo-controlled trial	**60** (30 in the intervention group, 30 in the control group)	menopausal women	*Ocimum basilicum* leaf extract (250 mg)	PSQI III	O. basilicum leaf extract improved sleep quality and reduced the severity of insomnia in the study participants
Impaired sleep	Gutiérrez-Romero et al. 2024	Randomized, placebo-controlled trial	**64** (31 in intervention group, 27 control group)	-	Nutraceutical Formulation (green tea, lemon balm, valerian, and saffron extracts)	SE (1ry) PSQI (2ry) WASO (2ry) Salivary Cortisol (2ry) SF- 36 (2ry)	No significant effect on sleep efficiency or quality compared to placebo
Impaired sleep	Chandra Shekhar et al. 2024	Randomized, double-blind, placebo-controlled study	**80** (40 in intervention group, 40 in control group)	-	Valerian root extract (200 mg with 2% total valerenic acid)	PSQI (1ry) SL (1ry) SE (2ry) ESS (2ry) BAI (2ry) VAS (2ry)	Significant improvement in sleep quality, sleep efficiency, sleep latency and total sleep time
Impaired sleep	Pierro, et al. 2024	Randomized double-blind, placebo-controlled, and cross-over study	**30** (14 in the intervention group, 16 in the control group)	-	Lemon balm "*Melissa officinalis*" Phytosome™	Changes in ISI Sleep Quality Parameters	Melissa officinalis extract improved ISI score and extended deep sleep duration
Impaired sleep	Uchida et al. 2024	Randomized, parallel, double-blind, controlled clinical trial	**99** (49 in the intervention group, 50 in the control group)	Older Adults with cognitive decline	Match green tea capsules (2 g)	MoCA-J (1ry) ADCS-MCI-ADL (1ry) Change in PSQI (2ry)	12 months consumption of matcha green tea improved emotional perception and sleep quality
Impaired sleep	Dehghan et al. 2024	Randomized controlled clinical trial	**60** (30 in the intervention group, 30 in the control group)	Mothers of infants admitted to the neonatal intensive care unit (NICU)	Bitter orange blossom distillate syrup	STAI General Sleep Disorder Scale	The intervention had no significantly different effect on the participants' anxiety but improved their sleep disorder state

Table 3 (continued)

Sleep disorder	Study	Study design	No. of participants	Special population	Agent(s) and dose	End point/outcome(s)	Main result(s)
Impaired sleep	Can et al. 2024	Randomized placebo-controlled clinical trial	**63** (21 in the Lavender group, 21 in the rosemary, 21 in the control group)	Older adults with type 2 diabetes	Lavender oil Rosemary oil (for aromatherapy)	BOMCT PSQI STAI	Aromatherapy improved quality of sleep and cognitive functions of the participants while decreasing anxiety
Impaired sleep	Kavuran and Yurttaş 2024	Randomized controlled trial	**66** (33 in the intervention group, 33 in the control group)	Patients with multiple sclerosis (MS)	Lavender oil (for aromatherapy)	FSS PSQI	Aromatherapy improved quality of sleep and reduced fatigue in patients with MS
Impaired sleep	Pérez-Piñero et al. 2024	Randomized double-blind Placebo-controlled study	**71** (33 in the intervention group, 38 in the control group)	-	extract of lemon verbena (*Aloysia citrodora*) capsule (400 mg)	VAS (1ry) SL SE PSQI PSS STAI Plasma cortisol Nocturnal melatonin	The intervention significantly improved sleep quality and elevated nocturnal melatonin levels in participating individuals
Impaired sleep	Xiong et al. 2024	Randomized triple-blind parallel-group placebo-controlled trial	**116** (96 in the intervention group, 20 in the control group)	-	Prescription of Chinese Herbal Medicine	TST (1ry) SOL WASO SE PSQI BDI SAS	Chinese medicine prescribed based on symptom differentiation can improve quality of sleep and total sleep time in patients with insomnia
Impaired sleep	Lucena et al. 2024	Randomized double-blind controlled study	**35** (17 in the intervention group, 18 in the control group)	Postmenopausal women	Lavender oil (for aromatherapy)	ESS Changes in MENQOL domains SOL TST SE	Aromatherapy improved the total sleep time, sleep efficiency and quality of life of the participants with no effect on daytime sleepiness
Impaired Sleep	Yildirim et al. 2025	Randomized, parallel, single-blind, controlled clinical trial	**100** (50 in the intervention group, 50 in the control group)	Patients with hematological malignancies	lavender oil (For aromatherapy)	Changes in RCSQ domains Changes in PFS	Aromatherapy with Lavender oil improved sleep quality and reduced fatigue levels
RLS	Cuellar and Ratcliffe 2009	Randomized, triple-blind, placebo-controlled clinical trial	**37** (17 in the intervention group, 20 in the control group)	-	Valerian capsules (800 mg)	PSQI ESS International RLS Symptom Severity Scale	Valerian capsules improved the sleep quality and RLS symptoms

Table 3 (continued)

Sleep disorder	Study	Study design	No. of participants	Special population	Agent(s) and dose	End point/outcome(s)	Main result(s)
RLS	Hajizadeh et al. 2023	Randomized, cross-over clinical trial	**40**	Hemodialysis patients	Valeriana officinalis L. Capsules (530 mg) compared to Gabapentin	RLS Score	Both agents were able to treat RLS with Gabapentin being more effective Both agents improved sleep quality

SE, sleep efficiency; *PSQI*, Pittsburgh sleep quality score; *WASO*, wake after sleep onset; *SF- 36*, 36-item short form survey score; *SL*, sleep latency; *ESS*, Epworth Sleepiness Scale; *BAI*, Beck Anxiety Inventory; *VAS*, Visual Analogue Scale; *ISI*, insomnia severity index; *DASS- 21*, Depression; Anxiety and Stress Scale – 21 items; *MENQOL*, Menopause-Specific Quality of Life Questionnaire; *RCSQ*, Richards-Campbell Sleep Questionnaire; *PFS*, Piper Fatigue Scale; *MoCA-J*, Montreal Cognitive Assessment-Japanese version; *ADCS-MCI-ADL*, Alzheimer's Disease Cooperative Study Activity of Daily Living; *STAI*, Spielberger State and Trait Anxiety Inventory; *BOMCT*, Blessed Orientation Memory Concentration Test; *PSS*, Perceived Stress Scale; *FSS*, Fatigue Severity Scale; *TST*, total sleep time; *SOL*, sleep onset latency; BDI, Beck Depression Inventory; *SAS*, Self-Rating Anxiety Scale score; *SNSB*, Seoul Neuropsychological Screening Battery; *SGDS*, Short-Form Geriatric Depression Scale; *III*, insomnia intensity score; *ISQ*, Insomnia Symptom Questionnaire; *PSD*, Pittsburgh Sleep Diary; *RSQ-W*, Restorative Sleep Questionnaire- Weekly version; *FOSQ- 10*, Functional Outcomes of Sleep Questionnaire; *POMS-A*, Profile of Moods States – Abbreviated Version; *LSEQ*, The Leeds Sleep Evaluation Questionnaire; *TIB*, time in bed; FRAGI, Fragmentation Index; *HAM-A*, Hamilton Anxiety scale-A questionnaire; *RSQ*, Restorative Sleep Questionnaire; *TWT*, total wake time; *AIS*, Athens Insomnia Scale; *OSA-MA*, Oguri–Shirakawa–Azumi Sleep Inventory; Middle-age and Aged version; *EEG*, electroencephalogram

Witkowska 2023). Noteworthy, the dietary antioxidants effect is credited to a plethora of molecular mechanisms that eventually enhance the levels of antioxidant enzymes (Lu et al. 2010).

Summary of clinical trials and studies

Several clinical trials investigated the effect of different plant extracts on sleep related problems, which are summarized in Table 3.

Conclusions

Natural remedies are commonly used as sleep aids. It is frequently coupled with a general health-promoting lifestyle and may represent the widespread belief that natural goods are always excellent for sleep without risks. Kava-kava (*Piper methysticum*), Valerian (*Valerinana officinalis*), Passionflower (*Passiflora incameta*), and other herbs used to cure insomnia have gained popularity as alternative medicines. Natural products that have been demonstrated to be useful for sleeping disorders. However, preclinical and clinical investigations are required to determine the specific effects of natural compounds in the treatment of insomnia.

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Declarations

Animal ethics declaration Not applicable.

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