Trakia Journal of Sciences, No 3, pp 251-262, 2025
Available online at:
https://trakia-uni.bg

ISSN 1313-3551 (online) doi:10.15547/tjs.2025.03.009

Review

SLEEP MODULATION AND NEUROPROTECTION THROUGH THE PRISM OF HERBAL PLANTS

P. Hristova*, S. Nikolov

Department of Anatomy, Physiology and Animal Sciences, Faculty of Veterinary Medicine, University of Forestry, Sofia, Bulgaria

ABSTRACT

Sleep disorders, such as insomnia, excessive sleepiness, alterations in NREM/REM cycles and breathing problems during sleep affect a large proportion of the population worldwide and contribute to cognitive and emotional disorders. Due to the adverse effects and risk of addiction of synthetic hypnotics, medicinal plants (valerian, passionflower, lemon balm, lavender, etc.) are established as a safe and effective alternative. Studies show that herbal extracts modulate sleep architecture and support neurological function through various pathways of interaction. Among their effects are also facilitated falling asleep and maintaining normal sleep structure, providing neuroprotection by redox regulation, anti-inflammatory and anti-amyloidogenic properties, improvement of cerebral perfusion and stimulation the drainage of waste metabolites, the accumulation of which is associated with the development of neurodegenerative diseases. This review focuses on: the endogenous processes by which herbs modulate sleep; their neuroprotective properties; their role in metabolic clearance and the synergistic effect of combined herbal formulas.

Keywords: medicinal plants, brain health, sleep architecture, GABA, glymphatic system

INTRODUCTION

It is known that the most commonly prescribed sleeping drugs are benzodiazepines or the so-called "Z" drugs that bind to and activate the receptors of gamma aminobutyric acid, which is the main inhibitory neurotransmitter in the central nervous system. However, due to the many serious adverse side effects, it is recommended that drugs from these groups be used for the shortest possible time – no more than 2-3 weeks, as they lead to addiction, and their sudden discontinuation causes withdrawal syndrome with severe adverse reactions and symptoms in patients. That is why in recent years the interest of the scientific community dealing with sleep problems (insomnia, difficulty falling asleep, insufficient sleep duration, etc.) has increasingly been directed specifically towards studying the sleeping pill effect of plant-based drugs (1). Studies on the effects of herbal extracts on sleep architecture and neurological function reveal complex biochemical interactions at the cellular and molecular levels. Effects expressed in neurochemical modulation, neuroprotective mechanisms, and potential for therapeutic impact in sleep disorders and neurodegenerative conditions have been observed. Traditional Chinese medicine and Ayurvedic practices have recognized the neuroprotective properties of herbs for millennia, attributing their efficacy to the diverse bouquet of phytochemicals they contain (2). These compounds, affecting different brain structures and neural pathways, have demonstrated their practical effectiveness by properly modulating sleep architecture and alleviating the symptoms of various neurodegenerative diseases (3).

Most often, the mechanism of action is expressed through their interaction with neurotransmitter systems, in particular with the GABA-ergic system. This system has a key role in the regulation of sleep and neuronal excitability (4). Many herbal therapeutics improve sleep through active ingredients such as polyphenols, alkaloids and terpenoids, modulating the function of GABA receptors (5). The close relationship between sleep and neurological health stimulates the development

***Correspondence to**: *Pavlina Hristova, Department of Anatomy, Physiology and Animal Sciences, Faculty of Veterinary Medicine, University of Forestry, Sofia, Bulgaria, Email: pspiridonova@ltu.bg*

of new research on the topic. It has been found that some herbs with sleep modulating action also have a neuroprotective effect, expressed in improving brain perfusion and drainage of waste metabolites from metabolism during wakefulness (6). These metabolites would be neurotoxic if they accumulate in the form of protein plaques, which is considered one of the prerequisites for the development of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, frontotemporal dementia, epilepsy, etc. Herbs that promote deeper and restorative sleep can indirectly stimulate the drainage of waste metabolites, potentially reducing the risk of developing neuropathologies (7). In their study, Roy et al. (8) point phytochemicals as a reliable alternative in the treatment against neurodegenerative processes, due to their antioxidant and anti-amyloidogenic properties. The therapeutic effects of herbal extracts also extend to their anti-inflammatory actions. This is especially important in the context of neuroinflammation - a common feature of neurodegenerative diseases (9). The chronically ongoing neuroinflammatory process is associated with disruption of neuronal functions. Zeng et al. (10) study the beneficial effects of herbal extracts on the processes of structural and functional neuroplasticity, expressed in supporting neuroregeneration, formation of dendritic spines and new synaptic contacts between neurons. Short-term use of herbal medicines has been found to improve memory in young and elderly individuals, while long-term use has shown improvement in Alzheimer's symptoms in patients with this disease (1, 11).

Sleep disorders include all cases of insomnia or excessive sleepiness, abnormal activity and sleep behaviour, impaired sleep duration and depth, sleep-disordered breathing, interrupted sleep, and difficulty waking up (12). They affect a significant portion of the population globally (13, 14), directly impacting their well-being and work capacity (15, 16). 47% of people over 65 years of age report experiencing sleep disorders (17). The most common pathological form of sleep is insomnia, according to Perlis et al. (18), as it affects one third of the world's population. Chronic sleep deprivation has many undesirable consequences related to physical and neurological health, such as impaired memory and cognitive function, as well as mood regulation (19). There is a growing interest in the development of alternative methods for the treatment of sleep disorders, including phytotherapies (20, 21). The disadvantages of conventional treatment methods - side effects and the risk of addiction, are some of the factors that make herbal medicine a preferred solution for many people (4, 22). Plants such as valerian, passionflower, lemon balm, lavender, California poppy are among the most popular herbs used to improve sleep, due to their safety and effectiveness (4), among other effects. Herbal remedies act on all key stages of sleep – from falling asleep to maintaining sleep and recovering from sleep (23, 24). They preserve the normal architectonics – slow-wave NREM sleep, transitioning into paradoxical REM and their normal duration and cyclicity, without increasing fragmentation or awakenings (25, 26). They lead to better sleep efficiency, in terms of restorative processes, maintaining its depth and quality, without disrupting daytime activity (27). A number of studies have been conducted, proving the relationship between sleep disorders and the development of neurodegenerative diseases (28 - 31). A meta-analysis including 16 studies and the results of a total of 9 million people found a relationship between insomnia and the development of dementia and Alzheimer's disease (32). The same relationship was also mentioned by Xu et al. (33) and Kumar and Khanum (34).

The aim of this review is to address the relationship between sleep and neurological health through the perspective of herbal plants, with a pronounced sleep modulating and neuroprotective effect. Although a number of studies have been published in the literature to date, examining in detail the advantages and specific properties of herbs, as well as their application to alleviate the symptoms of sleep disorders and neuropathologies, the internal mechanisms and processes related to this are still poorly understood. The endogenous systems that allow the implementation of these effects in the CNS will be described in detail. This issue hides many unknowns and needs to be examined in more depth. This review is built sequentially on the basis of the following areas on the topic: 1. Endogenous mechanisms mediating the sleep modulating effect of herbs; 2. Neuroprotective effects of herbs with sleep modulating action; 3. Influence on metabolic clearance; 4. Advantages of multiherbal formulas.

1. Endogenous mechanisms mediating the sleep modulatory effect of herbs

The sleep command centre is located in the hypothalamus, in the ventrolateral preoptic area (VLPO) of the encephalon (1). It is located in the preoptic area of the hypothalamus, medial and ventral to the anterior commissure, near the optic chiasm. It is part of the preoptic area (POA), which is involved in thermoregulation, sexual behaviour, and sleep. The VLPO contains two main types of neurons – GABA-ergic and galaninergic – that inhibit nuclei associated with the wakefulness period. Both types are activated during sleep, while they are inhibited by the latter during wakefulness. Mutual inhibition between the VLPO and the wakefulness nuclei ensures the homeostatic transition from sleep to wakefulness and vice versa. The VLPO has been shown to exhibit heat sensitivity, it is activated by light heat, which indicates the connection between sleep and thermoregulation – therefore, it is easier to fall asleep when the body is warmed. The VLPO is mainly activated during NREM sleep, but also supports REM, through indirect inhibition of REM-suppressing structures. The VLPO interacts with the REM-on and REM-off nuclei in the brainstem, but is not the main generator of REM. Such a role is played by the pons and its nuclei - *sublaterodosal nucleus* (SLD), *precoeruleus* (PC), *pedunculopontine tegmental nucleus* (PPT), *laterodorsal tegmental nucleus* (LDT) (1). The sequence in the transition from wakefulness through NREM to REM is as follows: 1. The VLPO activates the process of falling asleep and entering NREM sleep, through GABA-ergic inhibition of wakefulness (REM-off) nuclei, such as *locus coeruleus* (LC), *raphe nuclei* (RN) and *tuberomammillary nucleus* (TMN); 2. Prolonged NREM activity and inhibition from the VLPO exhausts the REM-off nuclei. Synaptic release of noradrenaline and serotonin decreases, weakening REM-suppression and this leads to gradual activation of REM-on nuclei; 3. PPT and LDT nuclei (cholinergic) gradually increase their activity, stimulating the cortex and thalamus; 4. The SLD is activated and REM sleep begins. This nucleus projects to medullary interneurons, forming synaptic contacts with alpha-motoneurons in the spinal cord. Activation of the former during REM causes the characteristic muscle atony. Other projections of the SLD are to the cortex and thalamus. They underlie the shift of sleep cycles and the process of dreaming. This issue has been discussed in more depth in our previous work (35). Disturbances in this transition lead to common sleep disorders such as REM sleep behavior disorder (RBD), associated with insufficient activation of medullary neuronal circuits terminating on alpha-motoneurons in the spinal cord and the correlated movements during of REM; narcolepsy, associated with autoimmune loss of orexin, leading to sudden REM transitions and catalepsy; and insomnia, difficulty falling asleep and a poor REM cycle due to weak VLPO activity and impaired maintenance of REM on-off tone (12). For this reason, therapies that are being developed to treat sleep disorders should target the potential for regulating the overall structure of sleep, not just separate phases.

The galaninergic neurons in the VLPO, mentioned above, have a role in modulating and stabilizing NREM sleep (36), although their action is less well studied. Galanin is a neuropeptide whose action is slow and is associated with its interaction with metabotropic G-protein coupled receptors. While the effect of some herbal plants is directly related to the synthesis of GABA, there is currently no data proving the same for galanin. Rather, there is talk of coexpression and indirect modulation through GABA pathways (37, 38). However, the GABA-regulating and GABA-mimetic effect of plants with sleep modulating action is well studied. Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the CNS. Its key role is in reducing neuronal excitability, having a sedative effect, reducing anxiety, anticonvulsant and sleep modulatory effect on the body. The mechanism of action of herbal plants affecting GABA can be of several types: 1. By imitating GABA – the plant active substance binds to the GABA receptor; 2. By inhibiting the degradation of GABA – GABA reserves in the synapses are increased; 3. By increasing the release of GABA – GABA-ergic neurons are stimulated; and 4. By stimulating the binding of GABA to the receptor – allosteric modulation of GABA-A (similar to benzodiazepines). GABA exerts its effect by binding to the so-called GABA-receptors, which are divided into three main types – GABA-A, B and C.

GABA-A subtype receptors are the most widespread in the CNS and are ligand-gated ion channels (ionotropic receptors). They are made up of 5 subunits (2α, 2β and 1γ). When the acid binds to its receptor, an influx of chloride ions (Cl^-) begins in the neuron. The latter

hyperpolarize its membrane potential, leading to suppression of the possibility of depolarization and generation of a receptor potential, and subsequently to the propagation of an action potential. The areas where the presence of this type of receptor has been established are precisely the areas involved in the regulation of sleep and wakefulness - hypothalamus, thalamus, brainstem, cortex and spinal cord (4). Activation of GABA-A receptors promotes the process of falling asleep and maintaining sleep by inhibiting neurons responsible for wakefulness – those in the *locus coeruleus* (pons; noradrenergic neurons), *raphe nuclei* (brainstem; serotonergic neurons), *tuberomammillary nucleus* (hypothalamus; histaminergic neurons), and *ventral tegmental area* and *substantia nigra* (midbrain; dopaminergic neurons). Inhibition of these neurons interrupts wakefulness and induces sleep onset (4). In addition to monoaminergic systems, GABA-A receptors are also found on the presynaptic part of pyramidal glutamatergic neurons in the neocortex (especially layers III and V; suppression of cortical arousal) and the hippocampus (especially in the ammonium horn, areas CA1 and CA3; regulation of memory and sleep cycles), orexinergic neurons in the lateral hypothalamus (their suppression leads to the transition to and maintenance of sleep), thalamocortical neurons from *nucleus reticularis thalami* and the ventrobasal complex of the thalamus, associated with sensory processing to the cortex (their suppression leads to the generation of sleep spindles and delta waves), retinal bipolar and ganglion cells associated with the input of photoinformation to the suprachiasmatic nucleus (SCN; regulation of circadian signals and rhythms), alpha-motoneurons and interneurons in the anterior horns of the spinal cord (muscle atonia) (4).

A number of sedative and hypnotic medications (benzodiazepines, Z-drugs, barbiturates and anesthetics) enhance the activity of GABA-A receptors, and thus shorten the time to fall asleep, increase the duration of the N2 phase of NREM sleep and reduce REM (1), respectively, reducing the proportion of low-frequency, at the expense of high-frequency wave oscillations in the brain (4). In a study by Wasowski & Marder, from 2016 (39), is stated the affinity of flavonoids for the GABA-A receptor subtype with subsequent modulation of chloride ion current, making them potential drugs against neurological disorders. Valerenic acid, found in valerian (*Valeriana officinalis*), has been shown to displace GABA-A ligands and bind selectively to their receptors (40, 41), but it also inhibits the enzymatic degradation of GABA, increasing its bioavailability (4). Apigenin, a flavonoid found in chamomile (Genus: *Matricaria*), shows modulatory GABA-ergic and glutamatergic actions, which attribute to its neuroprotective properties against glutamate-induced neurotoxicity (42). The kava plant (*Piper methysticum*), through the kavalactones it contains, potentiates the function of GABA-A subtype receptors without causing resistance, blocks voltage-gated sodium ion channels and leads to reduced release of excitatory neurotransmitters due to blocking calcium transport (43). The same effect has been shown in California poppy (*Eschscholzia californica*) (44). Chua et al. (45) demonstrated that kavain in kava binds selectively to GABA-A receptors and thus exerts its anxiolytic effect. Linalool, a terpenoid in lavender (Genus: *Lavandula*), exerts a modulatory effect on GABA-A receptors in the CNS (46), inhibits the excitatory effect of glutamate (47), and blocks voltage-gated sodium channels in olfactory receptors and Purkinje cells (48), leading to anxiolytic and relaxant effects.

GABA-B subtype receptors are metabotropic or so-called G-protein coupled receptors. This means that they do not directly open an ion channel, but transmit a signal intracellularly through specific (G-) proteins. These receptors are heterodimers made up of two subunits. The first (B1) binds GABA (ligand), while the second (B2) is responsible for interacting with the G-protein and triggering the intracellular signal. Activation of G-proteins leads to the inhibition of the enzyme – adenylate cyclase, which converts ATP to cyclic AMP. Inhibition of the latter reduces the activation of protein kinase A, which leads to reduced phosphorylation of various ion channels and transport proteins, and thus a decrease in neuronal excitability. Another effect is the opening of K^+ channels. Potassium leaves the cell, which has a hyperpolarizing effect on the neuronal membrane. Thus, the postsynaptic potential becomes more negative, which increases the threshold for depolarization. Third, G-proteins inhibit voltage-gated calcium channels, which is associated with reduced exocytosis of vesicles with neurotransmitter (e.g. glutamate) across the presynaptic membrane into the synaptic cleft. GABA-B receptors are found primarily in the thalamus and cortex. They play a major role in

maintaining deep sleep (delta waves) by suppressing neuronal excitability, increasing the duration of both NREM and REM sleep. Among the herbal plants that bind to this subtype of receptors are passionflower (*Passiflora incarnata)* and licorice (*Glycyrrhiza glabra*). Passionflower has been found to bind to all three subtypes of GABA receptors, with this ability being dose-dependent (49). There is still insufficient confirmatory data for other plants with an effect on this type of receptor.

GABA-C subtype receptors are ionotropic Cl^- channels, similar to subtype A, but made up only of p-subunits. They are not modulated by benzodiazepines. These receptors have slower kinetics, but a longer opening, which provides a long-lasting inhibitory effect. Neurons with this type of presynaptic receptors are localized in the retina (bipolar cells; role in the inhibition of visual processing), hippocampus (glutamatergic; role in protection against hyperexcitability, e.g. in epilepsy), hypothalamus (hormone-regulating neurons; participation in sleep-wake cycles), spinal cord (sensory interneurons; suppression of pain signals). This subtype of GABA receptors has not yet been established as a main regulator of sleep, but it is important for the regulation of circadian rhythms and long-term synaptic inhibition. It has been established that Indian ginseng (*Withania somnifera*) exhibits strong agonist activity for binding to GABA-C receptors (4).

2. Influence on metabolic clearance

During wakefulness, as a result of active work processes in the CNS, waste metabolites such as amyloid-β, tau proteins, etc. are formed, the accumulation of which in the form of plaques is directly associated with the development of neuroinflammatory and neurodegenerative processes (50). Functionally analogous to the peripheral lymphatic network, the so-called glymphatic system plays a key role in maintaining brain homeostasis, especially during sleep. This system, first described in 2012, provides a structural framework for understanding the cerebrospinal fluid (CSF) mediated clearance of waste metabolites in the brain (51). This drainage pathway uses a system of perivascular channels formed by astroglial cells for exchange between CSF and interstitial fluid (52). The glymphatic pathway runs through the perivascular spaces that surround arteries and veins. CSF enters the brain parenchyma through the paraarterial spaces, driven by gradients in hydrostatic and colloid osmotic pressure. Astrocytes have the ability to express specific water channels, aquaporin-4 (AQP4), on their surface, thereby regulating fluid flow. During sleep, and especially during slow-wave sleep, characterized by reduced norepinephrine signalling, the glymphatic system becomes highly active, facilitating the removal of neurotoxic waste products that accumulate during wakefulness (53-56). Experimental studies in mice have shown an approximately 60% increase in glymphatic clearance during slow-wave sleep (SWS) compared to the awake state (57). Conversely, sleep deprivation reduces the efficiency of waste product clearance and alters AQP4 expression (58). MRI studies support the notion that poor sleep quality and reduced glymphatic function correlate with increased amyloid β deposition (59). Melatonin (found in *Prunus cerasus*, sour cherry) acts through MT1/MT2 receptors expressed on astrocytes, promoting AQP4 polarization and subsequent fluid exchange (60). AQP4 exhibits circadian polarization, with a peak in polarization during periods of rest and depolarization during wakefulness (60). Furthermore, the effect of melatonin on brain is thoroughly discussed in the comprehensive review of Georgiev from 2020 (1). Herbal remedies such as valerian root and chamomile flower, which have sedative properties, may indirectly affect glymphatic activity by stimulating deeper regenerative phases of sleep (61, 62). However, direct evidence for herbal plants that directly influence AQP4 channel expression or have an effect on the morphology of the perivascular space remains undiscovered, and the topic is largely unexplored. It is known that Indian ginseng (*Withania somnifera*) and valerian (*Valeriana officinalis*) enhance SWS, which is key for glymphatic clearance (63). The leaves of the plant Ginkgo biloba (*Ginkgo biloba*) have vasodilator effects that could improve brain perivascular flow (64). In pathological conditions, curcumin, a polyphenol in turmeric (*Curcuma longa*), exhibits anti-inflammatory and neuroprotective properties, as in a 2015 study by Wang et al. (65) was found that it effectively reduced the expression of AQP4 channels, thereby alleviating symptoms of cerebral edema. A similar study was conducted by Yu et al. in 2016 (66) in rats. Resveratrol and rosmarinic acid, which are found in hops (*Humulus lupulus*), lemon balm (*Melissa officinalis*), and lavender (*Lavandula officinalis*) have shown promise in reducing amyloid accumulation by improving transport

mechanisms (67, 68). Further studies are needed to determine the glymphatic effects of the herbs using imaging and molecular biology methods.

3. Neuroprotective effects of herbs with sleep modulating action

Neuroinflammatory processes are crucial for normal metabolic clearance. Proinflammatory cytokines IL-β, TNF-α and IL-6 disrupt the normal expression of astrocyte AQP4 channels and reduce perivascular integrity. Conversely, anti-inflammatory pathways, including IL-10, TGF-β and microglial activity, preserve metabolic transport by stabilizing astrocyte membrane polarity and reducing oxidative damage (52). The bidirectional interaction between microglia and astrocytes is important in the context of neuroinflammatory responses and metabolic clearance. Physiologically, microglia control the homeostasis of the brain parenchyma and phagocytize waste fragments during sleep (69). In neurodegenerative diseases such as Alzheimer's disease, chronic microglial activation leads to the release of proinflammatory mediators, which compromises glymphatic function. Along with their sleep-modulating properties, some plants also possess neuroprotective properties that contribute to overall sleep quality and cognitive functions of the brain (70). An example of such plant is chamomile (*Matricaria chamomilla*), which demonstrates antioxidant and anti-inflammatory effects and protects neurons from damage, while also stimulating their regeneration (71-74). The benefits of co-administration of valerenic acid, found in valerian (*Valeriana officinalis*), with conventional therapy against Parkinson's disease have been established, which are expressed in reducing the inflammatory response by lowering the levels of proinflammatory cytokines (IL-1β, IL-6, TNF-α, IFN-γ) in *substantia nigra* and the striatum, protecting dopaminergic neurons and reducing astrocyte activity (75), the target sites of damage in this disease. Flavonoids in the passionflower (*Passiflora incarnata*), on the other hand, have shown good results in overcoming memory deficits, preserving synaptic transmission, and improving motor coordination in experimental mice models with neurodegenerative disease (76, 77). Linalool and linalyl acetate present in the chemical composition of *Lavandula angustifolia*, in a study with rats with scopolamine-induced dementia, induced significantly lower levels of neuronal apoptosis, redox regulation, and improvement in behavioural and cognitive functions than the experimental untreated control group (78).

4. Combined action of plants with sleep modulating effect

Combining several herbal plants to improve sleep has a number of advantages over the use of a single phytoproduct. The different active ingredients can act in complementary ways – some modulate the GABA-ergic system, others reduce the levels of stress hormones such as cortisol (*Passiflora incarnata*), and still others improve circadian rhythms (*Whitania somnifera*). Thanks to their synergy, it is possible to achieve the desired effect at lower individual doses, which reduces the risk of side effects and the development of resistance. The combinations often include anxiolytic, sedative and hypnotic effects – for example, when combining passionflower (hypnotic), valerian (sedation) and Indian ginseng (anxiolytic). Clinical studies have shown that many herbal formulas do not cause a return of the initial symptoms after discontinuation of treatment or dose reduction, and do not lead to dependence, making them suitable for long-term use (79). Among the clinically tested herbal combinations is that with valerian and lemon balm, which has shown good efficacy in children exhibiting anxiety and insomnia (80) and in adult women (50-60 years old), after menopause, who exhibit sleep disorders. Valerian and hops are another practically applicable herbal combination that has shown a weak hypnotic effect in insomnia in a controlled study involving 184 participants (79), and in addition to passionflower, in a study by Maroo et al. from 2013 (81), this combination could be used as a long-term alternative to zolpidem.

DISCUSSION

The strong relationship between sleep and brain health is highlighted by their co-occurrence in the symptom complex of neurological diseases (82). Sleep influences memory and thinking through memory consolidation processes, which are particularly active during rest and sleep, and sleep deprivation can lead to neurological dysfunction (83 - 86). Resilience and vulnerability to stress can be represented as two sides of the same coin, because both are closely related to sleep – weaker resilience means higher levels of stress for the body, and this leads to more serious sleep disorders (87, 88). “Improve your sleep to increase your stress resistance” the same authors point out in their study from 2024. Sleep disorders can be a cause

as well as a consequence of neurological disease (89). In Alzheimer's disease, degeneration of the suprachiasmatic nucleus and cholinergic neurons leads to impaired ability to maintain sleep and regulate circadian rhythms (90). In Parkinson's disease, sleep behaviour disorders and the appearance of motor activity, insomnia, or hypersomnia are often observed (91). During deep sleep, the brain's glymphatic system enhances the removal of waste metabolites; chronic insomnia blocks this process, leading to the accumulation of toxins in the extracellular space (92). Fragmented sleep and hypoxia in obstructive sleep apnoea activate microglial inflammatory response and increase the production of reactive oxygen radicals (90). Progressive disruption of circadian biorhythmology in the hypothalamus disrupts the secretion of melatonin and cortisol, which further worsens the quality and structure of sleep (93). Many herbs with anxiolytic and sleep-modulating effects act as phytoanalogues of GABA (the main inhibitory neurotransmitter), which helps reduce neuronal excitation and facilitate the onset of sleep – valerian, hops. Herbs with a high polyphenol profile simultaneously calm and protect brain cells from oxidative stress and inflammation – lemon balm, lavender, ginkgo biloba. Maintaining the correct circadian rhythm is key for sleep and the drainage of neurotoxic waste metabolites. Plants that stimulate endogenous melatonin production, such as echinacea and sour cherry, can help in this regard. Chronic stress and anxiety exacerbate sleep problems and neurodegenerative processes. Herbs such as passionflower and Indian ginseng contain flavonoids that reduce cortisol, calm heart rate and anxiety, and improve sleep. Combined herbal formulas enhance their effects through their synergy and lead to better results. Despite the growing evidence supporting the benefits of herbs for sleep and cognitive function, real-time imaging techniques are needed. Techniques such as fMRI, PET, and EEG can be used to monitor brain activity and neurotransmitter levels in response to herbal interventions, CSF dynamics, sleep architecture and dreams which is the subject of future research.

CONCLUSIONS

The use of herbal extracts is preferred by most people to improve the symptoms of disturbed sleep, restore its normal duration and cyclicity (all phases). At the heart of this process is the overall restoration of the function of the nervous system and brain, for which herbal therapy offers a number of advantages over conventional drug treatment. The use of classic sleeping pills affects only a certain phase of sleep, leading to numerous side effects, the development dose-dependent habituation in long-lasting treatment. Combined herbal formulas potentiate and reinforce each other's effects on improving sleep quality and overall function of the nervous system.

ACKNOWLEDGEMENTS

This research is supported by the Bulgarian Ministry of Education and Science under the National Programme "Young Scientists and Postdoctoral Students – 2".

REFERENCES

1. Georgiev, I. Neurophysiological control of sleep with special emphasis on melatonin. *Thrace Journal of Sciences*, 18, 355-376. 2020.
2. Sa, F.; Guo, B. J.; Li, S.; Zhang, Z. J.; Chan, H. M.; Zheng, Y.; Lee, S. M. Pharmacokinetic Study and Optimal Formulation of New Anti-Parkinson Natural Compound Schisantherin A. *Parkinson's Disease*, 1. https://doi.org/10.1155/2015/951361. 2015.
3. Liu, Y.; Wang, S.; Kan, J.; Zhang, J.; Zhou, L.; Huang, Y.; Zhang, Y. Chinese Herbal Medicine Interventions in Neurological Disorder Therapeutics by Regulating Glutamate Signaling. *Current Neuropharmacology*, 18(4), 260. https://doi.org/10.2174/1570159x17666191101125530. 2019.
4. Bruni, O.; Ferini-Strambi, L.; Giacomoni, E.; Pellegrino, P. Herbal Remedies and Their Possible Effect on the GABAergic System and Sleep. *Nutrients*, 13(2), 530. https://doi.org/10.3390/nu13020530. 2021.
5. Johnston, G. A. R. GABAA Receptor Channel Pharmacology. *Current Pharmaceutical Design*, 11(15), 1867. https://doi.org/10.2174/1381612054021024. 2005.
6. Hu, Z.; Oh, S.; Ha, T.-W.; Hong, J. T.; Oh, K.-W. Sleep-Aids Derived from Natural Products. *Biomolecules & Therapeutics*, 26(4), 343. https://doi.org/10.4062/biomolther.2018.099. 2018.
7. Nahar, L.; Charoensup, R.; Kalieva, K.; Habibi, E.; Guo, M.; Wang, D.; Kvasnica, M.; Önder, A.; Sarker, S. D. Natural products in neurodegenerative diseases: recent advances and future outlook. *Frontiers in Pharmacology*, 16.

https://doi.org/10.3389/fphar.2025.1529194 . 2025.
8. Roy, K.K.; Mehta, D.K.; Das, R. Reevaluating Alzheimer's disease treatment: Can phytochemicals bridge the therapeutic gap? *Neuroscience*, 575, 1-18. 2025.
9. Wang, M.; Wang, C.; Kaiwei, Z.; Ma, S.; Jiajia, S.; Xu, S. Bioactive compounds from Chinese herbal plants for neurological health: mechanisms, pathways, and functional food applications. *Frontiers in Nutrition*, 12.. https://doi.org/10.3389/fnut.2025.1537363. 2025.
10. Zeng, J.; Wang, Z.; Zhang, X.; Zhao, A.; Qi, H.; Jiang, Y.; Cai, D.; Zeng, N. Exploring the neuroplasticity hypothesis in depression: The role of traditional Chinese herbal medicine. *Phytomedicine: international journal of phytotherapy and phytopharmacology*, 143, 156927. 2025.
11. Kennedy, D. O.; Scholey, A. The Psychopharmacology of European Herbs with Cognition-Enhancing Properties. *Current Pharmaceutical Design*, 12(35), 4613. https://doi.org/10.2174/138161206779010387. 2006.
12. Thorpy, M.J. Classification of Sleep Disorders. *Neurotherapeutics*, 9, 687-701. 2012.
13. Chen, C.; Liu, X.; Chiou, J.; Hang, L.; Li, T.; Tsai, F.; Ko, C.; Lin, T.; Liao, C.; Huang, S.; Liang, W.; Lin, Y. Effects of Chinese herbal medicines on dementia risk in patients with sleep disorders in Taiwan. *Journal of ethnopharmacology*, 113267. 2020.
14. Bent, S.; Padula, A.; Moore, D.H.; Patterson, M.; Mehling, W. Valerian for Sleep: A Systematic Review and Meta-Analysis. *The American Journal of Medicine*, 119(12), 1005. https://doi.org/10.1016/j.amjmed.2006.02.026. 2006.
15. Akiyoshi, R.; Wake, H.; Kato, D.; Horiuchi, H.; Ono, R.; Ikegami, A.; Haruwaka, K.; Omori, T.; Tachibana, Y.; Moorhouse, A.J. Microglia Enhance Synapse Activity to Promote Local Network Synchronization. *eNeuro*, 5, 5. 2018.
16. Cho, S.; Shimizu, M. Natural Sleep Aids and Polyphenols as Treatments for Insomnia. 2015.
17. Ohayon M.M.; Reynolds C.F. 3rd. Epidemiological and clinical relevance of insomnia diagnosis algorithms according to the DSM-IV and the International Classification of Sleep Disorders (ICSD). *Sleep Med*. 10(9):952–60. pmid: 19748312. 2009.
18. Perlis M.L.; Posner D.; Riemann D.; Bastien C.H.; Teel J.; Thase M. Insomnia. *Lancet*. 400(10357):1047–60. pmid:36115372. 2022.
19. Guan, D.; Hou, Z.; Fan, B.; Bai, Y.; Wu, H.; Yu, J.; Xie, H.; Duan, Z.; Wang, F.; Wang, Q. The Extract of Piper nigrum Improves the Cognitive Impairment and Mood in Sleep-Deprived Mice Through the JAK1/STAT3 Signaling Pathway. *International Journal of Molecular Sciences*, 26. 2025.
20. Feizi, F.; Namazi, N.; Rahimi, R.; Ayati, M.H. Medicinal Plants for Management of Insomnia: A Systematic Review of Animal and Human Studies. *Galen Medical Journal*, 8. https://doi.org/10.31661/gmj.v8i0.1085. 2019.
21. Acero, N.; Ortega, T.; Villagrasa, V.; Leon, G.; Muñoz-Mingarro, D.; Castillo, E.; González-Rosende, M.E.; Borràs, S.; Ríos, J.L.; Bosch-Morell, F.; Martínez-Solís, I. Phytotherapeutic alternatives for neurodegenerative dementias: Scientific review, discussion and therapeutic proposal. *Phytotherapy Research*, 37, 1176-1211. 2023.
22. Zhang X.Y.; Guo C.Q.; Wu L.Z.; Chang Y.H.; Zhou J.L.; Wang S.M. Clinical observation of Sini San in the treatment of adolescent depression with liver qi stagnation type. Guangming J. Chin. Med., 38 (24) pp. 4783-4786. 2023.
23. Grabowski, W.; Karoń, K.; Karoń, Ł.M.; Zygmunt, A.E.; Drapała, G.; Pedrycz, E.; Pedrycz, D. Unlocking Better Sleep and Stress Relief: The Power of Ashwagandha (Withania somnifera) Supplementation – A Literature Review. *Quality in Sport*. 2024.
24. Kim, G.; Kim, Y.; Yoon, S.; Kim, S.; Yi, S.S. Sleep-inducing effect of Passiflora incarnata L. extract by single and repeated oral administration in rodent animals. *Food Science & Nutrition*, 8, 557-566. 2019.
25. Donath, F.; Quispe, S.; Diefenbach, K.; Maurer, A.; Fietze, I.; Roots, I. Critical evaluation of the effect of valerian extract on sleep structure and sleep quality. *Pharmacopsychiatry*, 33 2, 47-53. 2000.
26. Lee, E.; Chung, W. Glial Control of Synapse Number in Healthy and Diseased Brain. *Frontiers in Cellular Neuroscience*, 13. https://doi.org/10.3389/fncel.2019.00042. 2019.

27. Cheah, K.L.; Norhayati, M.N.; Husniati Yaacob, L.; Abdul Rahman, R. Effect of Ashwagandha (Withania somnifera) extract on sleep: A systematic review and meta-analysis. *PLoS One*, 16. 2021.
28. Shi, L.; Chen, S.; Ma, M.; Bao, Y.; Han, Y.; Wang, Y.; Shi, J.; Vitiello, M.; Lu, L. Sleep disturbances increase the risk of dementia: A systematic review and meta-analysis. *Sleep medicine reviews*, 40, 4-16. 2017.
29. Bubu, O.M.; Brannick, M.T.; Mortimer, J.A.; Umasabor-Bubu, O.Q.; Sebastião, Y.V.; Wen, Y.; Schwartz, S.W.; Borenstein, A.R.; Wu, Y.; Morgan, D.; Anderson, W. Sleep, Cognitive impairment, and Alzheimer's disease: A Systematic Review and Meta-Analysis. *SLEEP*, 40. 2017.
30. Sung, P.; Yeh, C.; Wang, L.; Hung, P.; Muo, C.; Sung, F.; Chen, C.; Tsai, K. Increased Risk of Dementia in Patients with Non-Apnea Sleep Disorder. *Current Alzheimer research*, 14 3, 309-316. 2016.
31. de Almondes, K.M.; Costa, M.V.; Malloy-Diniz, L.F.; Diniz, B. Insomnia and risk of dementia in older adults: Systematic review and meta-analysis. *Journal of psychiatric research*, 77, 109-15. 2016.
32. Meng, M.; Shen, X.; Xie, Y.; Lan, R.; Zhu, S. Insomnia and risk of all-cause dementia: A systematic review and meta-analysis. *PLoS One*, 20. 2025.
33. Xu, W.; Tan, C.; Zou, J.; Cao, X.; Tan, L. Sleep problems and risk of all-cause cognitive decline or dementia: an updated systematic review and meta-analysis. *Journal of Neurology, Neurosurgery, and Psychiatry*, 91, 236-244. 2019.
34. Kumar, G.; Khanum, F. Neuroprotective potential of phytochemicals. *Pharmacognosy Reviews*, 6, 81 - 90. 2012.
35. Hristova, P.; Georgiev, I.P. NEUROPHYSIOLOGICAL BASIS OF DREAMING – A REVIEW. *THRACIAN JOURNAL OF SCIENCES*. 2024.
36. Kroeger, D.; Absi, G.; Gagliardi, C.; Bandaru, S.S.; Madara, J.C.; Ferrari, L.; Arrigoni, E.; Münzberg, H.; Scammell, T.E.; Saper, C.B.; Vetrivelan, R. Galanin neurons in the ventrolateral preoptic area promote sleep and heat loss in mice. *Nature Communications*, 9. 2018.
37. Gallopin, T.; Fort, P.E.; Eggermann, E.; Cauli, B.; Luppi, P.; Rossier, J.; Audinat, E.; Mühlethaler, M.; Serafin, M. Identification of sleep-promoting neurons in vitro. *Nature*, 404, 992-995. 2000
38. Sherin, J.E.; Shiromani, P.J.; McCarley, R.W.; Saper, C.B. Activation of Ventrolateral Preoptic Neurons During Sleep. *Science*, 271 , 216-219. 1996.
39. Wasowski, C.; Marder, M. Flavonoids as GABAA receptor ligands: the whole story? *Journal of Experimental Pharmacology*, 4, 9 - 24. 2012.
40. Murphy, K.; Kubin, Z.J.; Shepherd, J.N.; Ettinger, R.H. Valeriana officinalis root extracts have potent anxiolytic effects in laboratory rats. *Phytomedicine*, 17, 674. https://doi.org/10.1016/j.phymed.2009.10.020. 2009.
41. Cavadas, C.; Araújo, I.; Cotrim, Amaral, T.; Ap, C.M.; Macedo, T.A.; Ribeiro, C. In vitro study on the interaction of Valeriana officinalis L. extracts and their amino acids on GABAA receptor in rat brain. *Arzneimittel-Forschung*, 45 7, 753-5. 1995.
42. Losi, G.; Puia, G.; Garzon, G.; De Vuono, M.C.; Baraldi, M. Apigenin modulates GABAergic and glutamatergic transmission in cultured cortical neurons. European journal of pharmacology, 502 1-2, 41-6. 2004.
43. Singh, Y.N; Singh, N.N. Therapeutic Potential of Kava in the Treatment of Anxiety Disorders. CNS Drugs, 16, 731-743. 2002.
44. Fedurco, M.; Gregorová, J.; Šebrlová, K.; Kantorová, J.; Peš, O.; Baur, R.; Sigel, E.; Táborská, E. Modulatory Effects of Eschscholzia californica Alkaloids on Recombinant GABAA Receptors. *Biochemistry Research International*, 2015.
45. Chua, H.C,.; Christensen, E.T.; Hoestgaard-Jensen, K.; Hartiadi, L.Y.; Ramzan, I.; Jensen, A.A.; Absalom, N.L.; Chebib, M. Kavain, the Major Constituent of the Anxiolytic Kava Extract, Potentiates GABAA Receptors: Functional Characteristics and Molecular Mechanism. *PLoS ONE*, 11. 2016.
46. Milanos, S.; Elsharif, S.A.; Janzen, D.; Buettner, A.; Villmann, C. Metabolic Products of Linalool and Modulation of GABAA Receptors. *Frontiers in Chemistry*, 5. 2017.
47. Silva M.I.; Silva M.A.; de Aquino Neto M.R.; Moura B.A.; de Sousa H.L.; de Lavor E.P. et al. Effects of isopulegol on pentylenetetrazol-induced convulsions in mice: possible involvement of GABAergic system and antioxidant activity. *Fitoterapia* 80, 506–513. 10.1016/j.fitote.2009.06.011. 2009.

48. Narusuye, K.; Kawai, F.; Matsuzaki, K.; Miyachi, E. Linalool suppresses voltage-gated currents in sensory neurons and cerebellar Purkinje cells. *Journal of Neural Transmission*, 112, 193-203. 2005.
49. Elsas S.M.; Rossi D.J.; Raber J.; White G.; Seeley C.A.; Gregory W.L.; Mohr C.; Pfankuch T.; Soumyanath A. Passiflora incarnata L. (Passionflower) extracts elicit GABA currents in hippocampal neurons in vitro, and show anxiogenic and anticonvulsant effects in vivo, varying with extraction method. *Phytomedicine*. 17:940–949. doi: 10.1016/j.phymed.2010.03.002. 2010.
50. Singh, D. Astrocytic and microglial cells as the modulators of neuroinflammation in Alzheimer's disease. *Journal of Neuroinflammation*, 19(1). https://doi.org/10.1186/s12974-022-02565-0. 2022.
51. Aalling, N.; Munk, A.S.F.; Lundgaard, I.; Nedergaard, M. The Glymphatic System: A Beginner's Guide. *Neurochemical Research*, 40(12), 2583. https://doi.org/10.1007/s11064-015-1581-6. 2015.
52. Gędek, A.; Koziorowski, D.; Szlufik, S. Assessment of factors influencing glymphatic activity and implications for clinical medicine. *Frontiers in Neurology*, 14. https://doi.org/10.3389/fneur.2023.1232304. 2023.
53. Adamu, A.; Li, S.; Gao, F.; Xue, G. The role of neuroinflammation in neurodegenerative diseases: current understanding and future therapeutic targets. *Frontiers in Aging Neuroscience*, 16. https://doi.org/10.3389/fnagi.2024.1347987. 2024.
54. Kim, M.E.; Lee, J.S. Mechanisms and Emerging Regulators of Neuroinflammation: Exploring New Therapeutic Strategies for Neurological Disorders. *Current Issues in Molecular Biology*, 47(1), 8. https://doi.org/10.3390/cimb47010008. 2024.
55. Onyango, I.G.; Jauregui, G.V.; Čarná, M.; Bennett, J.P.; Stokin, G.B. Neuroinflammation in Alzheimer's Disease. Biomedicines, 9(5), 524. Multidisciplinary Digital Publishing Institute. https://doi.org/10.3390/biomedicines9050524. 2021.
56. Glass, C.K.; Saijo, K.; Winner, B.; Marchetto, M.C.; Gage, F.H. Mechanisms Underlying Inflammation in Neurodegeneration. *Cell*, 140(6), 918. https://doi.org/10.1016/j.cell.2010.02.016. 2010.
57. Xie L.; Kang H.; Xu Q. et al. Sleep drives metabolite clearance from the adult brain. *Science*. 342(6156):373-7. doi:10.1126/science.1241224. 2013.
58. Simard, M.; Nedergaard, M. The neurobiology of glia in the context of water and ion homeostasis. *Neuroscience*, 129(4), 877. https://doi.org/10.1016/j.neuroscience.2004.09.053. 2004.
59. Eide, P.K.; Pripp, A.H.; Berge, B.; Hrubos-Strøm, H.; Ringstad, G.; Valnes, L. Altered glymphatic enhancement of cerebrospinal fluid tracer in individuals with chronic poor sleep quality. *Journal of Cerebral Blood Flow & Metabolism*, 42, 1676 - 1692. 2022.
60. Yao, D.; Li, R.; Hao, J.; Huang, H.; Wang, X.; Ran, L.; Fang, Y.; He, Y.; Wang, W.; Liu, X.; Wang, M. Melatonin alleviates depression-like behaviors and cognitive dysfunction in mice by regulating the circadian rhythm of AQP4 polarization. *Translational Psychiatry*, 13. 2023.
61. Chen, S.; Wang, H.; Zhang, L.; Xi, Y.; Lu, Y.; Yu, K.; Zhu, Y.; Regina, I.; Yong, B.; Tong, F. Glymphatic system: a self-purification circulation in brain. *Frontiers in Cellular Neuroscience*, 19. https://doi.org/10.3389/fncel.2025.1528995. 2025.
62. Ding, Z.; Fan, X.; Zhang, Y.; Yao, M.; Wang, G.; Dong, Y.; Liu, J.; Song, W. The glymphatic system: a new perspective on brain diseases. *Frontiers in Aging Neuroscience*, 15. https://doi.org/10.3389/fnagi.2023.1179988. 2023.
63. Salve, J.; Pate, S.; Debnath, K.; Langade, D. Adaptogenic and Anxiolytic Effects of Ashwagandha Root Extract in Healthy Adults: A Double-blind, Randomized, Placebo-controlled Clinical Study. *Cureus*, 11. 2019.
64. Mashayekh, A.; Pham, D.L.; Yousem, D.M.; Dizon, M.; Barker, P.B.; Lin, D.D. Effects of Ginkgo biloba on cerebral blood flow assessed by quantitative MR perfusion imaging: a pilot study. *Neuroradiology*, 53, 185-191. 2011.
65. Wang, B.; Cui, Z.; Zhong, Z.; Sun, Y.; Sun, Q.; Yang, G.; Bian, L. Curcumin attenuates

brain edema in mice with intracerebral hemorrhage through inhibition of AQP4 and AQP9 expression. *Acta Pharmacologica Sinica*. 2015.

66. Yu, L.; Fan, Y.; Ye, G.; Li, J.; Feng, X.; Lin, K.; Dong, M.; Wang, Z. Curcumin alleviates brain edema by lowering AQP4 expression levels in a rat model of hypoxia-hypercapnia-induced brain damage. *Experimental and Therapeutic Medicine*, 11, 709 - 716. 2016.
67. Kahle, K.T.; Simard, J.M.; Staley, K.J.; Nahed, B.V.; Jones, P.S.; Sun, D. Molecular Mechanisms of Ischemic Cerebral Edema: Role of Electroneutral Ion Transport. *Physiology*, 24(4), 257. https://doi.org/10.1152/physiol.00015.2009. 2009.
68. Kwong, K.C.N.K.; Mehta, A.R.; Nedergaard, M.; Chandran, S. Defining novel functions for cerebrospinal fluid in ALS pathophysiology. *Acta Neuropathologic Communications*, 8(1). https://doi.org/10.1186/s40478-020-01018-0. 2020.
69. Medeiros, R.; Kitazawa, M.; Passos, G.F.; Baglietto -Vargas, D.; Cheng, D.; Cribbs, D.H.; LaFerla, F.M. Aspirin-Triggered Lipoxin A4 Stimulates Alternative Activation of Microglia and Reduces Alzheimer Disease–Like Pathology in Mice. *American Journal of Pathology*, 182(5), 1780. https://doi.org/10.1016/j.ajpath.2013.01.051 . 2013.
70. Guadagna, S.; Barattini, D.F.; Roşu, Ş.; Ferini-Strambi, L. Plant Extracts for Sleep Disturbances: A Systematic Review. *Evidence-Based Complementary and Alternative Medicine*, 2020(1). https://doi.org/10.1155/2020/3792390. 2020.
71. Kazemi, A.; Shojaei-Zarghani, S.; Eskandarzadeh, P.; Hashempur, M.H. Effects of chamomile (Matricaria chamomilla L.) on sleep: A systematic review and meta-analysis of clinical trials. *Complementary Therapies in Medicine*, 84, 103071. https://doi.org/10.1016/j.ctim.2024.103071. 2024.
72. Lairikyengbam, D.; Wetterauer, B.; Schmiech, M.; Jahraus, B.; Kirchgessner, H.; Wetterauer, P.; Berschneider, K.M.; Beier, V.; Niesler, B.; Balta, E.; Samstag, Y. Comparative analysis of whole plant, flower and root extracts of Chamomilla recutita L. and characteristic pure compounds reveals differential anti-inflammatory effects on human T cells. *Frontiers in Immunology*, 15. 2024.
73. De Cicco, P.; Ercolano, G.; Sirignano, C.; Rubino, V.; Rigano, D.; Ianaro, A.; Formisano, C. Chamomile essential oils exert anti-inflammatory effects involving human and murine macrophages: Evidence to support a therapeutic action. *Journal of ethnopharmacology*, 116391. 2023.
74. Nargesi, S.; Moayeri, A.; Ghorbani, A.; Seifinejad, Y.; Shirzadpour, E. The effects of Matricaria chamomilla L. hydroalcoholic extract on atherosclerotic plaques, antioxidant activity, lipid profile and inflammatory indicators in rats. *Biomedical Research and Therapy*. 2018.
75. Rodríguez-Cruz, A.; Romo-Mancillas, A.; Mendiola-Precoma, J.; Escobar-Cabrera, J.; García-Alcocer, G.; Berumen, L.C. "Effect of valerenic acid on neuroinflammation in an MPTP-induced mouse model of Parkinson's disease". *IBRO Reports*, 8, 28 - 35. 2019.
76. Al-kuraishy, H.M.; A.Al-windy, S.; Al-Gareeb, A.I. Beneficial Neuro-Pharmacological Effect of Passionflower (Passiflora Incarnate L). *Online Journal of Neurology and Brain Disorders*. 2020.
77. Ingale S.P.; Kasture S.B. Antioxidant and antiparkinsonian activity of Passiflora incarnata. *Oriental Pharmacy and Experimental Medicine* 14(3):231-236. 2014.
78. Ayaz, M.M.; Sadiq, A.; Junaid, M.; Ullah, F.; Subhan, F.; Ahmed, J. Neuroprotective and Anti-Aging Potentials of Essential Oils from Aromatic and Medicinal Plants. *Frontiers in Aging Neuroscience*, 9. 2017.
79. Morin, C.M.; Koetter, U.; Bastien, C.H.; Ware, J.C.; Wooten, V. Valerian-hops combination and diphenhydramine for treating insomnia: a randomized placebo-controlled clinical trial. *Sleep*, 28 11, 1465-71. 2005.
80. Müller, S.F.; Klement, S. A combination of valerian and lemon balm is effective in the treatment of restlessness and dyssomnia in children. *Phytomedicine: international journal of phytotherapy and phytopharmacology*, 13 6, 383-7. 2006.
81. Maroo, N.; Hazra, A.; Das, T. Efficacy and safety of a polyherbal sedative-hypnotic formulation NSF-3 in primary insomnia in comparison to zolpidem: A randomized controlled trial. *Indian Journal of Pharmacology*, 45, 34 - 39. 2013.

82. Sutton, E.L. Psychiatric Disorders and Sleep Issues. *Medical Clinics of North America*, 98(5), 1123. https://doi.org/10.1016/j.mcna.2014.06.009. 2014.
83. Patel, A.K.; Reddy, V.D.K.; Araújo, J.F. Physiology, Sleep Stages. 2021.
84. Nollet, M.; Hicks, H.; McCarthy, A.; Wu, H.; Möller-Levet, C.S.; Laing, E.; Malki, K.; Lawless, N.; Wafford, K.A.; Dijk, D.; Winsky-Sommerer, R. REM sleep's unique associations with corticosterone regulation, apoptotic pathways, and behavior in chronic stress in mice. *Proceedings of the National Academy of Sciences*, 116(7), 2733. https://doi.org/10.1073/pnas.1816456116. 2019.
85. Krause, A.; Simon, E.B.; Mander, B.A.; Greer, S.M.; Saletin, J.; Goldstein-Piekarski, A.; Walker, M.P. The sleep-deprived human brain. Nature Reviews. *Neuroscience*, 18(7), 404. https://doi.org/10.1038/nrn.2017.55. 2017.
86. Krystal, A.D. Psychiatric Disorders and Sleep. *Neurologic Clinics*, 30(4), 1389. https://doi.org/10.1016/j.ncl.2012.08.018. 2012.
87. Gallo, G.G.; Curado, D.F.; Machado, M.P.A.; Espíndola, M.I. de; Scattone, V.V.; Noto, A.R. A randomized controlled trial of mindfulness: effects on university students' mental health. *International Journal of Mental Health Systems*, 17(1). https://doi.org/10.1186/s13033-023-00604-8. 2023.
88. Martire, V.L.; Berteotti, C.; Zoccoli, G.; Bastianini, S. Improving Sleep to Improve Stress Resilience. *Current Sleep Medicine Reports*, 10(1), 23. https://doi.org/10.1007/s40675-024-00274-z. 2024.
89. Kim, J. P. W. J. Resilience through Sleep. *Journal of Sleep Disorders & Therapy*, 1(2). https://doi.org/10.4172/2167-0277.1000e105. 2012.
90. Anghel, L.; Ciubara, A.B.; Nechita, A.; Nechita, L.; Manole, C.; Baroiu, L.; Ciubară, A.B.; Musat, C.L. Sleep Disorders Associated with Neurodegenerative Diseases. *Diagnostics*, 13. 2023.
91. Auger, R.R.; Boeve, B.F. SLEEP AND NEURODEGENERATE DISORDERS. *CONTINUUM: Lifelong Learning in Neurology*, 13, 201-224. 2007.
92. Owen, J.E.; Veasey , S.C. Impact of sleep disturbances on neurodegeneration: Insight from studies in animal models. *Neurobiology of disease*, 104820. 2020.
93. Shen, Y.; Lv , Q.; Xie , W.; Gong, S.; Sheng, Z.; Liu, J.; Mao, C.J.; Liu, C.F. Circadian disruption and sleep disorders in neurodegeneration. *Translational Neurodegeneration*, 12. 2023.