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# Unveiling the Sleep-Immunity Nexus: Plant Bioresources for Ameliorating Consequences of Sleep Deprivation

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## ABSTRACT

Sleep is a fundamental physiological process that not only supports immune function but also contributes significantly to overall well-being. Because of the established decline in the average amount of sleep due to lifestyle and rise in shift work over the past few decades, exploring the relationship between sleep and immunity has become crucial. Moreover, infections trigger increased sleep as a result of the host's immunological response, particularly the release of proinflammatory cytokines, such as tumour necrosis factor and interleukin-1. Understanding the mechanisms governing the human immune response against different pathogens during sleep, as well as the neuroimmune interconnections, immune regulatory effects of sleep, and the impact of cytokines in sleep deprivation, is crucial. Traditional medicine has employed plant derived preparations for treating various sleep disorders and promoting better sleep. While some plant derived products have shown positive effects on sleep, it is essential to acknowledge the limited scientific research in this area, and altered individual responses to these. In conclusion, recognizing the critical connection between sleep and immunity underscores the importance of prioritizing sufficient and restorative sleep to bolster overall health and well-being. While certain products may offer potential benefits for better sleep, further scientific investigation is necessary to fully understand their effectiveness and applicability on an individual basis.

**Keywords:** Sleep; Immunity; Cytokines; Sedative Herbal plants; Neurotransmitter; Antioxidant.

## INTRODUCTION

Sleep is an indispensable physiological process that consumes approximately one-third of our lives on an average and is crucial for maintaining our physical, mental, and emotional well-being. The intricacies of sleep patterns and requirements are influenced by a complex interplay of factors, including chronological age, developmental stage, genetics, behaviors, environment, and social aspects. Sleep provides an opportunity for our bodies to rejuvenate and recuperate. A restful night's sleep is instrumental in stress management, problem-solving, and promoting health recovery [1]. Nerve communication relies on chemicals called neurotransmitters [2]. These neurotransmitters determine whether we are awake or asleep based on the neurons they interact with. Researchers in the early 20th century proposed the existence of a hypnotoxin that rises during wakefulness and induces sleep, eventually being cleared out during sleep. The first identified hypnotoxin was the bacterial cell wall component muramyl peptide in the 1980s, which, like more than 2,000 years ago, was believed to originate from the gastrointestinal tract [3]. The complex interactions within our brain and the involvement of various substances, including neurotransmitters and cytokines, demonstrate the profound significance of sleep in maintaining a healthy and balanced life. Understanding these mechanisms can aid in promoting better sleep habits and ultimately enhance our overall health and resilience. During the sleep; brain undergoes regular cycles of activity, which consist of two main periods and a total of four stages of sleep:

1. The first period is non rapid eye movement (NREM) sleep, encompassing three phases (Fig. 1). As individuals progress into the final two stages of NREM sleep, they enter a deep sleep state that is particularly challenging to awaken from.

2. Approximately an hour to an hour and a half after falling asleep, the second period called rapid eye movement (REM) sleep begins. This stage is characterized by vivid dreams [4].

Understanding the significance of REM sleep highlights the vital role it plays in maintaining the well-being and underscores the importance of ensuring sufficient and uninterrupted sleep to promote a robust immune system and overall health. Consistent sleep deprivation can lead to a gradual decline in our immune systems, elevating the risk of infections and other diseases [5]. 'Sleep deprivation' refers to a condition where an individual consistently gets less sleep than their body requires for optimal functioning. The use of electronic devices with screens before bedtime can interfere with the production of melatonin, a hormone that regulates sleep. Blue light emitted by screens can suppress melatonin

release, making it harder to fall asleep [6]. Some medications can interfere with sleep patterns or cause insomnia as a side effect. An uncomfortable mattress, noisy environment, excessive light, or improper room temperature can hinder quality sleep. Consuming caffeine or alcohol close to bedtime can disrupt sleep patterns and lead to fragmented sleep [7]. The immune system plays a pivotal role in safeguarding overall health and defending the body against pathogens and diseases. Furthermore, sufficient sleep has been shown to bolster vaccination-induced antibody responses, implying that adequate rest both before and after receiving a vaccination can enhance its effectiveness [8]. Plant bioresources hold significant promise as natural remedies for sleep disorders. A diverse range of plants, have been traditionally used for their sedative and sleep-enhancing properties [9]. These plants contain bioactive compounds like flavonoids, alkaloids, and terpenes that interact with the GABAergic (Gama aminobutyric acid) system, modulating neurotransmission and promoting relaxation, ultimately leading to improved sleep quality [10]. The review intends to examine the potential of natural plant compounds, such as those found in herbs like chamomile, valerian root, passionflower, and jujube, to promote better sleep quality and support immune function. By providing a comprehensive analysis of the sleep-immunity connection and the potential benefits of plant bioresources, the review seeks to contribute to the understanding of holistic approaches to addressing sleep-related issues and their impact on immune health.

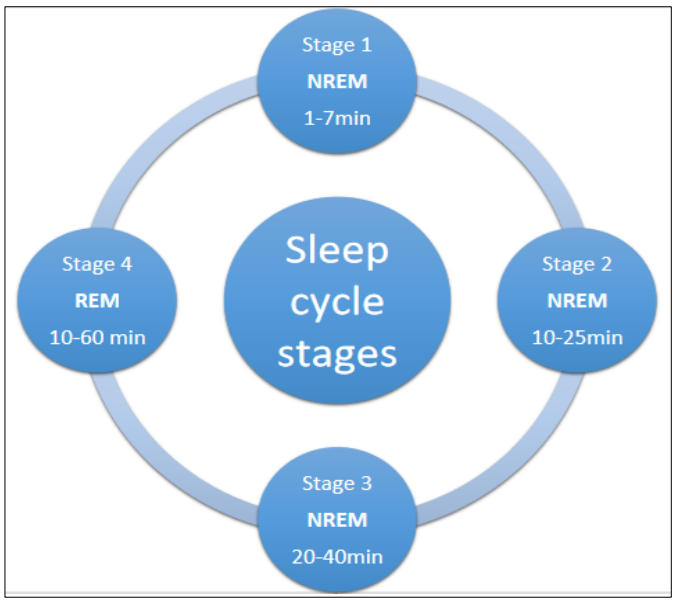


**Figure 1:** Sleep Cycle Progression.

## Sleep Deprivation and Immunological Imbalance: Enhanced Disease Suseptibility

Lack of sleep and immune-related diseases are intricately connected, with growing evidence highlighting the profound impact of sleep deprivation on immune function and the development of various health conditions. Studies have shown that insufficient sleep can lead to a decrease in immune function, impairing the body's ability to defend against infections and leaving individuals more susceptible to illnesses. During sleep, anti-inflammatory cytokines, such as interlukin-10 (IL-10) increases, promoting immune system balance and tissue repair. On the other hand, sleep deprivation can lead to an elevation of pro-inflammatory cytokines, such as IL-6 and tumour necrosis factor-alpha (TNF-α), contributing to chronic inflammation [11, 12]. Thus, sleep loss can disrupt the balance of pro-inflammatory and anti-inflammatory cytokines, leading to a state of chronic inflammation, which has been linked to the development of various immune-related diseases, including autoimmune disorders, neurodegenerative disease, cardiovascular diseases, metabolic disorders, and even certain cancers such as breast cancer and prostate cancer [13]. Sleep is crucial for antibody generation. During sleep, B cells mature and differentiate into antibody-producing cells. Sleep deprivation can impair this process, reducing the body's ability to generate specific antibodies to fight infections [14]. Researchers have established a connection between longer sleep durations and reduced levels of parasitism, while poorer sleep quality is linked to a higher risk of infection and less favourable infection outcomes [15]. Epidemiological studies have indicated a direct association between insufficient sleep and an increased likelihood of developing cancers such as breast, colorectal, and prostate cancer [16]. In this context, the hormone melatonin, which possesses anti-cancer benefits through various pathways, may have a shorter duration of nocturnal production due to increased exposure to artificial light at night. Melatonin's anti-cancer potential lies in its antimitotic, oxidative, apoptotic, anti-estrogenic, and anti-angiogenic properties [17]. It can also suppress the pro-inflammatory nuclear factor-B (NF-B)/NLRP inflammasome pathways, enhance T/B-cell activation, and boost macrophage function [18]. However, research has shown that inadequate and poor-quality sleep leads to insufficient cytokine production, rendering our bodies more vulnerable to infections.

## Use of Plant-Derived Compound to Treat Sleep Disorders

The term ‘sleep disorders’ encompasses a wide range of conditions, including difficulties in falling asleep, staying asleep for an adequate duration, experiencing frequent awakenings or early waking, restless legs syndrome (RLS), and obstructive sleep apnea (OSA). These conditions are often collectively referred to as ‘insomnia’ by patients [19]. The impact of insomnia on patients' quality of life often results in frequent medical prescriptions, leading some individuals to seek alternative treatment options such as traditional herbal medicine products [20]. Consequently, there is growing interest in using plant-derived compound for the treatment of sleep disorders. Plants have been used for centuries in traditional medicine to address various health issues, including sleep disorders [21]. Several plants and their derivatives contain compounds that can influence the mechanisms underlying sleep and contribute to improving sleep quality. Some of the key mechanisms by which plants can impact sleep disorders include:

1. Sedative and Anxiolytic Effects: Many plants possess sedative and anxiolytic properties, which can help promote relaxation and reduce anxiety, leading to better sleep. Compounds like flavonoids, alkaloids, and terpenoids found in plants such as valerian root, chamomile, passionflower, and lavender can act on the GABA receptors, a neurotransmitter that promotes relaxation and sleep [22].

2. Regulation of Neurotransmitters: Some plant compounds can influence neurotransmitters like serotonin, melatonin, and dopamine, which play essential roles in sleep-wake cycles and mood regulation [23]. For example, plants like *Griffonia simplicifolia*, which contains 5-HTP (5-hydroxytryptophan), can increase serotonin levels and, subsequently, melatonin levels, promoting better sleep [24].

3. Anti-Inflammatory and Antioxidant Effects: Inflammation and oxidative stress can disrupt sleep patterns and contribute to sleep disorders. Certain plant compounds, such as polyphenols found in green tea and curcumin in turmeric, exhibit anti-inflammatory and antioxidant properties [25] that may indirectly promote better sleep by reducing inflammation and cellular damage.

4. Regulation of Circadian Rhythms: Some plants and plant-derived products can influence the body's internal clock and circadian rhythms, helping to synchronize sleep-wake cycles with the natural light-dark cycle [26]. Melatonin-rich plants such as banana and tart cherries may help in the regulation of circadian rhythms [27] and improve sleep quality [28].

5. Cortisol Reduction: Elevated cortisol levels caused by stress can disrupt sleep. Certain plants, such as *Withania somnifera* and

*Rhodiola rosea*, have adaptogenic properties [29] that help reduce stress and lower cortisol levels, potentially improving sleep [30].

**Plant Bio-Resources Used in the Management of Sleep Disorders**

Sleep conditions have a significant influence on society and the economy, which can lead to decreased work productivity. The most common sleep disorder is insomnia, which is caused by an interruption in circadian rhythm control at the hypothalamus level [31]. Plant bioresources have been utilized for centuries in the management of sleep disorders, offering natural and potentially effective remedies. Preclinical researches focus on the *in vitro* and *in vivo* impacts of beneficial plants to comprehend and modify the possible applications of these substances for usage in humans [32]. In animals, a small number of taxa were examined for sedative and anxiolytic properties [33] for *e.g.* Valerian, passionflower, jujube, hops, chamomile *etc*. (Table 1). GABA synthesizing and metabolizing enzymes that affect sleep quality are primarily involved in the mechanisms of action of herbal medications for treating insomnia [34]. Some such plants are described below:

**Table 1:** Bioresources used as relaxants for the treatment of common sleep conditions.

| S. No. | Plants | Common Name | Active components | Uses | Reference |
|---|---|---|---|---|---|
| 1 | *Passiflora incarnata* | Passiflora/ Passion flower | Chrysin | It is generally taken as tea or also as medicines as it makes the neurological system less active. | [46] |
| 2 | *Lavandula angustifolia* | Lavender | Monoterpen (linalool, linalyl acetate) | Inhaling essential oil infused with lavender reduces stress, anxiety and promotes sleep. Has ability to modulate glutamate, GABA, and acetylcholine. | [62] |
| 3 | *Matricaria chamomilla* | Chamomile | Apigenin | Chamomile tea acts as sedative due to the presence of flavanoids in it. Also chamomile's aroma gives calming effect. | [39] |
| 4 | *Withania somnifera* | Winter cherry | Triethylene glycol | Ashwagandha leaves are mostly used in conditions such as insomnia and stress. Also its root extract contain certain compound that promote sleep. | [63] |
| 5 | *Valeriana officinalis* | Valerian | Monoterpenes and sesquiterpenes (valerenic acids) | Valerrian roots are mainly used to treat insomnia. It usually functions by preventing the breakdown of GABA neurotransmitter. | [64] |
| 6 | *Lactuca virosa* | Wild Lettuce | Lactucarium | Milky latex has astringent chemical that affects CNS to produce laxative and sedative properties. | [65] |
| 7 | *Humulus lupulus* | Hops | Methylbutenol, Myrcene | Active component of the plant strengthens neuroendocrine response via GABA and stimulates sleep induction. | [66,67] |
| 8 | *Melissa officinalis* | Lemon Balm | Rosmarinic acid | Leaves component of lemon balm helps in insomnia and gives calming effect and also used to treat anxiety and nervousness. | [68] |
| 9 | *Jasminum officinale* | Jasmine | Ketones (Jasmone), linalool | It is consumed as tea also aromatherapy is used in anxiety and insomnia. | [69] |
| 10 | *Chrysanthemum morifolium* | Chrysanthemum | Linarin | It is widely consumed as medicinal herbal tea. Dried in herbal tea has traditionally been used for the treatment of insomnia. | [70,71]. |
| 11 | *Panax quinquefolius* | Ginseng | Saponins (protopanaxatriol ginsenoside) | Plant component Ginsenoside Rb1 is mainly involve in sedation. Traditionally ginseng roots are used as sedative. | [72] |
| 12 | *Salvia rosmarinus* | Rosemarry | Luteolin, apigenin | Rosemary may have sedative effects because of its antioxidant capacity. | [73] |
| *13* | *Cannabis sativa* | Hemp | Cannabidiol | Active component of plant is used in variety of products such as oils and capsules and serves as an effective sleep supplement. | [74] |
| 14 | *Crataegus monogyna* | Hawthorn | Vitexin | Active component present in leaf and flower has sedative properties and acts as natural anxiolytic. | [75] |
| 15 | *Ginkgo biloba* | Maidenhair tree | Ginkgolide B and Bilobalide | Leaf extract of the plant contain phytochemicals that acts as sedative. | [76,77] |
| 16 | *Piper methysticum* | Kava | Kavalactones | Kava extract is an effective sedative and sleep-inducing stimulant. | [78] |
| 17 | *Hypericum perforatum* | St. John's wort | Hyperforin | Flower and leaves consist of active ingredient used in the treatment of insomnia and anxiety. | [79] |
| 18 | *Actaea racemosa* | Black cohosh | Magnoflorine | Pills and extracts of roots and rhizomes are used to induce sleep and treat irregular menstruation. | [80,81] |
| 19 | *Sambucus nigra* | Elderberry | Conicineand Sambucine | Active components present in the bark of elderberry possess sedative and laxative properties. | [82] |
| 20 | *Eschscholzia californica* | California poppy | N-Methyllaurotetanine | Plant component potentially attach to GABAA receptors, which could lead to sedation. | [83] |
| 21 | *Verbena officinalis* | vervain | Verbenalin and Aucubin | Flowers and leaves are used to make vervain tea. Active components act as natural sedative and relaxants. | [84] |

**Valerian (*Valeriana officinalis*)**

For many years, the valerian plant, particularly its root, has been utilized for various medicinal purposes, including the improvement of sleep. Valerian root contains a range of bioactive compounds, such as alkaloids, terpenes, organic acids, valepotriates, and flavonoids, which may exert physiological effects. Among these compounds, actinidine, valerenic acid, and velerenal aldehyde have garnered particular attention for their ability to influence GABAergic transmission, a process involving the neurotransmitter GABA that plays a crucial role in promoting relaxation and sleep [10]. The diverse array of bioactive components present in valerian root suggests its potential as a natural remedy to aid in sleep improvement and also in regulating menopausal system [35].

**Chamomile *(Matricaria chamomilla/ Matricaria recutitia)***

Chamomile is an annual herbaceous plant native to South Asia and South-Eastern Europe, [36] its infusion is widely used across the world, and its effectiveness is attributed to various flavonoids and phenolic compounds present in its bloom head parts, including apigenin, quercetin, patuletin, and luteolin [37]. These compounds have been linked to modulating benzodiazepine receptor activity, which can have calming effects on the nervous system [38]. In a research trial focused on improving sleep quality in elderly individuals, the impact of chamomile was studied. Participants consuming 200 mg of chamomile extract twice daily for about 4 weeks had considerably improved sleep than a control group [9]. The use of chamomile as a natural remedy to promote better sleep is supported by its rich content of beneficial compounds. Thus, the promising results of the chamomile trial highlight its potential as a safe and effective option to enhance sleep quality [39], particularly for elderly individuals.

**Jujube (*Ziziphus jujuba)***

Chinese medicine has a long history of utilizing *Ziziphus jujuba* as a natural sedative, relaxant, and hypnotic substance. Jujube contains several bioactive compounds, including saponins, alkaloids, and flavonoids, which are believed to contribute to its calming effects [40]. Among these compounds, jujuboside A (JuA) stands out as the primary active ingredient. In China, jujube seeds are used as sedatives[41].Researchers propose that JuA exerts its effects through the GABAergic system, a complex network involving the neurotransmitter GABA known for its role in promoting relaxation and reducing anxiety [42]. The diverse array of bioactive components found in *Ziziphus jujuba* highlights its potential as an herbal remedy to induce relaxation and improve sleep quality.

**Passionflower (*Passifora incarnata*)**

*Passiflora incarnata* is believed to possess sedative and anxiolytic properties, making it an effective remedy for treating restlessness and having spasmolytic effects. Unlike valerian, passiflora acts differently on the GABA transmission system [43]. Research suggests that passiflora inhibits both the binding of GABA to GABAA and GABAB receptors and the reuptake of GABA, which results in an alteration of the GABA transmission system [44]. This modulation of the GABA system contributes to its sedative and anxiolytic characteristics. The use of *Passiflora incarnata* as a natural sedative and anxiety-relieving remedy highlights its potential as an alternative option for promoting stability [45] and managing stress-related conditions. The unique mode of action of *Passiflora incarnata* on the GABA transmission system distinguishes it from other herbal sedatives [46], making it a promising natural alternative for those seeking non-pharmacological approaches to support relaxation and well-being.

**Winter cherry (*Withania somnifera*)**

*Withania somnifera* commonly known as winter cherry or ashwagandha, found throughout India is a recognised plant in ancient Indian *Ayurveda* [47] and is used as ‘’Rasayana’’ and an adaptogen for treating variety of ailments [48]. Winter cherry root extract's influence on sleep quality when seen in insomnia patients, significantly improved sleep start latency and lowered anxiety levels [49]. As per the study conducted by Kaushik and colleagues, the active component present in winter cherry leaves, tryethylene glycol, can promote sleep in mice [50]. It predominantly functions by increasing NREM and reducing the length of the waking period [51] and also through GABAergic and serotonergic pathway [52].

**Gamma-Aminobutyric Acid (GABA): Neurotransmitter Regulating Sleep**

GABA is the primary inhibitory neurotransmitter in the CNS, responsible for reducing activity in the postsynaptic neuron. This essential neurotransmitter is produced by the enzyme glutamic acid decarboxylase (GAD), [53] which converts glutamate into GABA. It exerts its effects by binding to two different types of receptors present in both pre-and postsynaptic neurons: the ionotropic GABAA receptor and the metabotropic GABAB receptor [54] (Fig. 2). The ionotropic GABAA receptor not only has binding sites for GABA but also for other substances like benzodiazepines [55], barbiturates, and neurosteroids, which can modulate its activity [56]. Approximately 20–30% of all neurons in the brain are GABA-containing neurons, commonly known as GABAergic neurons [57]. These neurons play a crucial role in regulating neural activity and maintaining the delicate balance between excitatory and inhibitory signals in the brain. Understanding the function and distribution of GABAergic neurons and their receptors is essential as it has implications for various neurological and psychiatric conditions. Modulating GABAergic transmission is a key target in the development of medications for conditions such as anxiety, epilepsy, and sleep disorders, highlighting the significance of GABA in maintaining brain function and overall mental well-being. GABA, the primary inhibitory neurotransmitter in the brain, is stored in synaptic vesicles through the GABA transporter (VGAT) in presynaptic neurons [58]. When these neurons are activated, calcium channels open, leading to an influx of calcium. This influx causes the vesicles containing GABA to fuse with the presynaptic membrane, resulting in exocytosis. The released GABA then binds to GABAA receptors on postsynaptic neurons. The activation of GABAA receptors leads to the opening of a central pore, allowing chloride ions ($Cl^-$) to enter the neuron. This influx of chloride hyperpolarizes the neuron's membrane potential, lowering the likelihood of action potentials and ultimately inhibiting neurotransmission [59]. Furthermore, certain drugs like benzodiazepines can bind to the GABAA receptor at an allosteric site, enhancing its affinity for GABA (Fig. 3). This potentiation of GABA's inhibitory effect contributes to the relaxation and sedative properties associated with benzodiazepine use. Interestingly, while the brain contains five wake-promoting transmitters, GABA stands as the sole neurotransmitter that actively promotes sleep. Its role in inhibiting neural activity plays a vital part in facilitating the transition to a restful state, making it a key player in the regulation of sleep-wake cycles. GABA is found naturally in a variety of foods, including tomato, soybean, tea as well as some fermented foods, and can be acquired through a healthy diet [60,61].

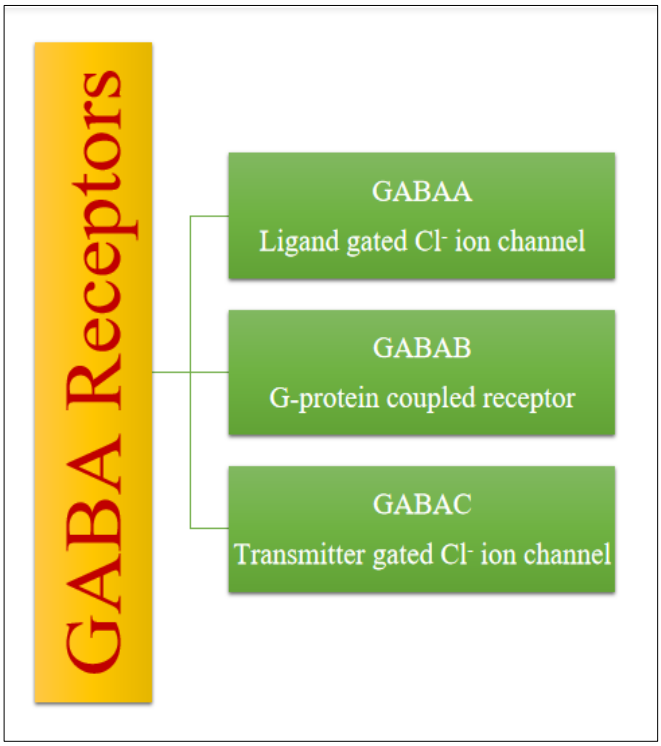


**Figure 2:** Type of GABA receptors

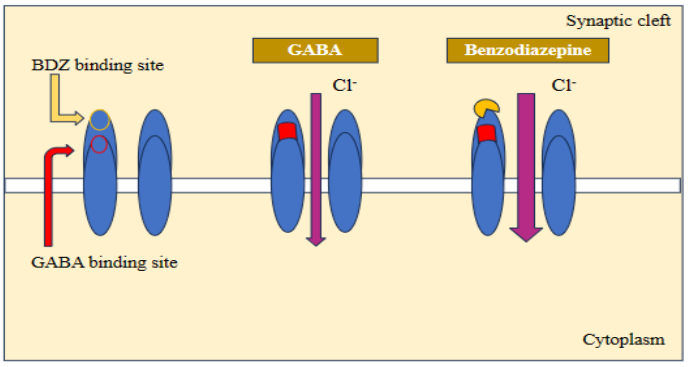


**Figure 3:** Benzodiazepine (BDZ) action on gaba receptor causes increase in $Cl^-$ ion influx.

## CONCLUSION

Sleep is essential physiological process for overall well-being, with intricate brain interactions and the role of substances like neurotransmitters and its profound importance in maintaining health. In conclusion, the sleep-immunity nexus is a complex interplay between sleep and the immune system, where sleep plays a crucial role in maintaining immune function and overall well-being. Sleep has a profound impact on the production and function of immune cells, such as T cells, B cells, and natural killer cells, which are essential for defending against illnesses. Adequate sleep promotes a well-coordinated immune response and reduces the risk of chronic inflammation by ensuring a balanced synthesis of pro-inflammatory and anti-inflammatory cytokines. Sleep deprivation can lead to a decrease in immune function and antibody production, impairing the body's ability to combat infections. Plant bioresources offer promising potential as natural remedies for ameliorating the consequences of sleep deprivation. Traditionally, various plants like valerian root, chamomile, passion flower, lemon balm, jujube, hops, and jasmine have been used to treat sleep disorders and promote better sleep. These plants possess sedative properties and can improve sleep quality and reduce the time it takes to fall asleep. Through their bioactive compounds and interactions with the GABAergic system, various plants have shown to enhance sleep quality and mitigate the adverse effects of sleep deprivation on the immune system. However, individual reactions to these plants may vary, and it is essential to exercise caution when using herbal remedies and consult a healthcare professional if needed. Further research into these plant bioresources could lead to valuable interventions in the realm of sleep health, benefiting individuals seeking natural and effective solutions for sleep-related concerns.

### Conflict of interest

The authors declare that they have no conflict of interest.

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