

# Importance of Addressing Sleep Problems in Epilepsy Patients: Focusing on Phytochemicals that Show Potential Treatment Effects.

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## Abstract

Epilepsy is a central nervous disorder that is the most common severe brain disease that can affect brain activity. Anti-seizure drugs (ASDs) are the first-line treatment for epilepsy. However, approximately one-third of patients report not achieving adequate seizure control with significant side effects. One of the most promising therapeutic fields that can complementarily help solve this is plant-based medicines, which have demonstrated their worth and effectiveness over a lengthy period. This study aimed to analyze recent research on plant extracts and nutraceuticals that are taken orally and are safe and effective for treating both sleep disturbances and epilepsy. We used data from the National Library of Medicine (PubMed) to evaluate each herbal therapy's feature, which leads to positive impacts to not only effectively promote decent quality of sleep but also reduce the number of seizures caused by epilepsy. Herbal medicines investigated in this paper are curcumin, chamomile, mugwort, and ashwagandha, which seem to help with sleep problems and epilepsy control based on literature research. This study may suggest herbal medicine as a complementary means of helping epilepsy patients who are experiencing sleep problems.

## Keywords

Medicine; Epilepsy; Sleep Disorder; Insomnia; phytochemical; seizure.

## Introduction

Epilepsy is a central nervous disorder that is the most common severe brain disease that can affect brain activity.<sup>1</sup> In 2019, it has been reported that over 70 million people were affected by this disease worldwide.<sup>1</sup> Symptoms of epilepsy include epileptic seizures and the associated cognitive, psychological, and social consequences.<sup>2</sup> Anti-seizure drugs (ASDs) are the first-line treatment for epilepsy, with over 20 drugs approved by the US Food and Drug Administration.<sup>3</sup> Even though many ASDs are available, approximately one-third of patients report not achieving adequate seizure control.<sup>2</sup> As a result, neurostimulation devices, dietary therapies, or clinical trials of new ASDs are alternatives for those for whom epilepsy surgery has failed to control seizures.<sup>2</sup>

Since seizures entail how electrical activity in various parts of the brain tends to synchronize during non-rapid eye movement (NREM) sleep, sleep and epilepsy are intimately intertwined.<sup>4</sup> Moreover, It is critical for people with epilepsy to get enough sleep. While this link does not exist in all patients, sleep deprivation can increase the frequency of seizures in people with epilepsy.<sup>5</sup> One explanation for why sleep deprivation may cause seizures is neuronal excitability. Neurons in the brain are more likely to produce significant changes in electrical activity when sleep-deprived. These significant changes in electrical activity in a person with epilepsy can become abnormal and cause a seizure.<sup>6</sup> Several types of sleep disorders that link to epilepsy are insomnia, obstructive sleep apnea, NREM-related parasomnias, and REM-related parasomnias.<sup>4</sup>

Numerous studies and clinical trials are presently being conducted to address the sleep-related problems that epilepsy patients are experiencing. However, most of the drugs used to treat sleep disorders are habit-forming and have a propensity to cause withdrawal symptoms. Additionally, sleep medications list adverse effects like dementia, which for people with epilepsy may be a whole cycle back to another brain issue.<sup>7</sup> This insufficiency in sleep medication has prompted many to look for more recent, superior treat-

ments. One of the most promising therapeutic fields is plant-based medicines, which have demonstrated their worth and effectiveness over a lengthy period. The molecular mechanisms of traditional plant-based treatments are now known thanks to advancements in modern science.<sup>8</sup> Therefore, this study aimed to analyze recent research on plant extracts and nutraceuticals that are taken orally and are safe and effective for treating both sleep disturbances and epilepsy.

## Discussion

Phytotherapy is a new emerging field in complementary and alternative medicine and is one of the most well-studied and used treatment modalities.<sup>9</sup> They can be obtained from various sources, including whole grains, fruits, vegetables, nuts, and herbs, and thousands of phytochemicals have been found to date.<sup>10</sup> Different phytochemical applications such as improving immunity, anticancer, sleep disorders, and anxiety, have been studied.<sup>11</sup>

### ***Curcumin for sleep disorders and epilepsy patients***

Curcumin is one of the most extensively researched natural compounds, pleiotropic, and a natural polyphenolic active component derived from turmeric.<sup>12</sup> Turmeric has been used for almost 2,000 years as a traditional cure in Chinese and Indian Ayurvedic medicine.<sup>13</sup> Sleep is one of the most well-known applications for curcumin. When it comes to the effects of curcumin on sleep, modern science has discovered that serotonin is the most important factor. Curcumin boosts serotonin and promotes dopamine synthesis, which causes a more positive mindset and less stress.<sup>14</sup> In addition, curcumin exerts an anti-inflammatory and antioxidant effect. Ezz, Khadrawy, and Noor clarified the antioxidant influence of curcumin in pilocarpine-challenged rats. They gave rats curcumin a dose of 80 mg/kg po for 21 days.<sup>15</sup> Another study from H. Kaur et al. suggested the antiinflammatory potential of curcumin in animal models resulted in a reduction of both GFAP-1 and Iba-1 markers because of the increase in the expression of cytokines and chemokines, which could be seen in cortex and hippocampus regions of the brain according to the animal experiment.<sup>12</sup>

Curcumin has been demonstrated to minimize seizure intensity by protecting neurons and improving cognitive functions in animal models of epilepsy.<sup>16</sup> Affecting various antioxidant and anti-inflammatory actions are the key advantageous effects of curcumin. Moreover, curcumin has been shown to have a beneficial effect by influencing various neurotransmitters and neuromodulators. Notably, in animal models of epilepsy, doses above 100 mg/kg are found to be anticonvulsant. Using curcumin as a treatment of epilepsy could be an add-on therapy with stand anti-epileptic drug molecules.<sup>17</sup>

Patients with epilepsy may experience other comorbid disorders, such as loss of sleep duration and insomnia. Curcumin is demonstrated as a treatment that can also help these somniphathic disorders. It affects insomnia by leading the patients to decrease stress levels since a more positive mentality and reduced stress in the natural consequence is often a more comfortable, relaxed sleep. Curcumin also impacts sleep disorders by enhancing serotonin and increasing the production of dopamine.<sup>14</sup> Both dopamine and serotonin are involved in people's sleep-wake cycle. Dopamine can inhibit norepinephrine, which can cause people to feel more alert. Serotonin is engaged in wakefulness, sleep onset, and even preventing REM sleep. It's also in charge of producing melatonin.<sup>18</sup>

Curcumin, therefore, is likely to have antidepressant effects as it increases the release of dopamine. In fact, taking 1 gram of curcumin had a similar impact to Prozac (one of the antidepressant treatments) on improving mood in people with major depressive disorder. According to research, when mice took 5 and 10 mg/kg(p.o.) curcumin, it notably minimized the duration of immobility in both the tail suspension and forced swimming test.<sup>19</sup> Moreover, neurochemical research clarified that it produced a marked inflation of serotonin and noradrenaline levels at 10 mg/kg in the frontal cortex and hippocampus. At the same time, dopamine rose in the striatum and frontal cortex. Ultimately, the improvement of serotonin and dopamine levels by curcumin could lead to the reduction of sleep disorders.<sup>19</sup>

There has been limited animal research that showed fewer seizures in epilepsy patients. One study found that injecting curcumin into rats reduced seizure scores, as well as seizure duration and oxidative stress.<sup>17</sup> In clinical trials with young patients, nanomicelle curcumin significantly reduced the number of seizures.<sup>20</sup>

### ***Chamomile for sleep disorders and epilepsy patients***

Chamomile (*Matricaria recutita*) is a natural herb of Europe, Africa, and Asia that is known to ancient Greek, Roman, and Egyptian cultures.<sup>21</sup> Chamomile contains terpenoids, flavonoids, and lactones, including matricin and apigenin. Chamomile's sleep-promoting impact has a lot of scientific data to the point that it is involved in a clinical practice guideline, and its mild sedative effect may be due to flavonoid, apigenin that binds to benzodiazepine receptors in the brain.<sup>22</sup>

Basic research regarding chamomile extracts has proved that chamomile's hypnotic properties are similar to benzodiazepine.<sup>23</sup> Moreover, one clinical trial on chamomile extract on sleep quality among elderly people reported significantly better sleep quality; it also reported safe use of chamomile among the elderly.<sup>24</sup> How chamomile affects the brain is mainly through the neuroactive ligand-receptor interaction, serotonin synapse, cAMP signaling pathway, calcium signaling pathway, and other pathways while regulating the key target proteins of LRRK2.<sup>25</sup>

Apigenin has also been proven to have an anticonvulsant effect.<sup>26</sup> In one study, apigenin was orally administered at 5mg/kg for six days to the kainite temporal epilepsy model and significantly reduced convulsant activity.<sup>26</sup> Moreover, the research concluded that this herb also restored memory deficit. Another study explored apigenin's anticonvulsant effect through brain imaging. According to this study, myeloperoxidase(MPO)-mediated oxidative stress can be relieved by apigenin. Further research is needed to elucidate this concept.<sup>27</sup>

A recent study that successfully identified bioactive chemicals from chamomile extracts used the Artificial Neural Network Model to determine the best extraction conditions, which revealed when chamomile can promote apigenin expression.<sup>28</sup>

### ***Valerian for sleep disorders and epilepsy patients***

Valerian (*Valeriana officinalis*) is the most researched plant for insomnia.<sup>29</sup> According to an Australian neurologist, the herbal medication valerian may have been the first epilepsy drug in the world.<sup>30</sup> According to research from the National Institutes of Health, Valerian, as an herb, has been used for treatment since ancient Greece and Rome, at the very least. Historically, Valerian was consumed as an herbal infusion of the dried root or in capsule or tablet forms. Italian author Fabio Colonna was the first to mention using valerian to manage seizures in 1592 in his botanical work *Phyto Basanos*. Moreover, Valerian was often used as a treatment for handling seizures by the late 18th and early 19th centuries.

To define whether Valerian is permanent in sleep disorder treatment, based on the clinical trials, studies demonstrated an advancement in sleep quality after administration of valerian at doses from 160 to 60mg a day. However, some studies show mixed outcomes. In improving sleep latency and duration, valerian presented a reduction in wake time after sleep onset. Valerian acts as a sedative on the brain and nervous system. Studies have also shown that valerian root can reduce the time to fall asleep by 15-20 minutes.<sup>31</sup> On the other hand, measured with the Pittsburgh sleep quality index, others reported no improvement in sleep quality when using Valerian for treatment.<sup>29</sup> Specifically, the research from Jacobs and collaborators in a minimal study found no changes in polysomnographic parameters or psychometrics measures after one dose of 300 mg or 600 mg valerian. Sleep hour or how many times people awake nocturnally in the participant's responses in a n-of-1 analysis of 24 subjects. The study from Mineo and collaborators also demonstrated that the single oral dose of the "Valeriana officinalis" extract caused a noteworthy decline in intracortical facilitation, a transition affiliated with decreased anxiety.<sup>29</sup>

One reason Eadies demonstrated the fact that the current medical field doesn't use valerian as frequently as in the past is because of the smell and taste. When exposed to dry valerian roots, the researcher recorded that they smelled like sweaty socks or dirty underwear. It is because of the formation of isovaleric acid in the body, which is one of the valerian's active compounds. The preliminary experiments on isovaleramide have been conducted by U.S. company NPS Pharmaceuticals. According to the result, the positive aspect is that if isovalerate works with few side effects, it also can replace other treatments according to Eadies.<sup>30</sup>

In light of the interaction between dopamine and its positive effect on the sleep-wake cycle, and the significant increase in dopamine levels in dichloromethane extracts of valerian roots, we can conclude that valerian positively impacts the rate of sleep disorder in the end.

### ***Mugwort for sleep disorders and epilepsy patients***

Mugwort (*Artemisia*) is well-known as a medication frequently used for digestive problems, irregular menstruation, and high blood pressure. This plant also promotes sedative effects among its many impacts on the human body.<sup>32</sup> This has been scientifically proven with modern science. This herb contains magnesium, potassium, and calcium phosphates that calm the nervous system, eventually reducing insomnia.<sup>33</sup> Fatemeh Emadi, Narguess Yassa, Abbas Hadjiakhoondi, Cordian Beyer, and Mohammad Sharifzadeh researched possible benzodiazepine receptor involvement by finding sedative effects of Iranian *artemisia annua* in mice. It is paramount that, according to the research, since *Artemisia* supports benzodiazepine receptor involvement, it also affects reducing seizures, which is a huge necessity to cure epilepsy.<sup>34</sup> To be more specific, with mugwort collected from Gilan Province in Iran, in male mice with different concentrations, which were 50, 100, and 200 mg/kg, and for evaluation of sedative reaction, immobility time was illustrated, chloroform, petroleum and ethyl acetate were administered intraperitoneally. To confirm the mechanism of activity, a benzodiazepine receptor, flumazenil (3 mg/kg), was inserted around 15 minutes before chloroform fraction (200 mg/kg).<sup>34</sup> In Comparison with saline-treated mice as a control group, the chloroform fraction significantly raised immobility time in a dose-dependent manner. The result came as flumazenil declined immobility time, persuaded by chloroform fraction second to none. This experiment concluded that *Artemisia annua* produced in Iran activates sedative effects, probably leading to mediation via benzodiazepine receptor pathways.<sup>34</sup>

In the aspect of epilepsy, mugwort is a second-to-none herb to treat the seizure. The National Library of Medicine found out that experimental studies demonstrated *artemisia* extracts offer a momentous antiepileptic potential from their bioactive components through diverse ways of action.<sup>35</sup> Current research shown that oxidative stress and neuroinflammation play significant roles in the pathophysiology of obtained epilepsy.<sup>35</sup> Following this illustration, oxidative stress and neuroinflammation pathways could be desirable therapeutic objectives in epilepsy. Genus *Artemisia* is a well-studied herb containing compounds such as flavonoids, which reduce or even abolish neuroinflammation and oxidative damage.<sup>35</sup> By linking Genus *Artemisia*'s role of eliminating neuroinflammation and oxidative damage and the fact that those two play important roles in the pathophysiology of obtained epilepsy, we can define mugwort as one of the herbal treatments for epilepsy.

Another research also confirms that the genus *Artemisia* has neuroprotective and antiepileptic potentials, which stem from their antioxidant, anti-inflammatory, neurotransmitter-modulating, and anti-apoptotic properties by modulating oxidative stress caused by mitochondrial ROS production and an imbalance of antioxidant enzymes.<sup>35</sup>

Protecting mitochondrial membrane potential required for ATP production is as weak as upregulating GABA-A receptor and nACh receptor activities and interfering with various anti-inflammatory and anti-apoptotic signaling pathways.<sup>36</sup>

In a status quo that today's antiepileptic treatment is not ideal, a therapeutic approach is urgently needed, which perfectly fits with mugwort for the medication, further having positive effects on sleep disorder.

## ***Ashwagandha for sleep disorders and epilepsy patients***

Ashwagandha is well known as India's traditional plant - a prevalent sleep disorder that profoundly impacts mental well-being and physical health. Ashwagandha is proven "Rasayana" from ancient Ayurveda has the necessary potential to nurse insomnia and anxiety.<sup>37</sup> Compared to the placebo group, 300 mg extract twice a day, Ashwagandha, especially Ashwagandha roots, notably increased sleep efficiency quality, according to The National Library of Medicine. A double-blind, randomized, Placebo-controlled study experiment by Prakruti Hospital conducted 60 randomized people in two groups, 40 for test and 20 for control. Using a high concentration of Ashwagandha extract 300mg, The important development of sleep quality was observed with the test compared to placebo; the lab showed that there was a significant improvement in sleep quality, observed in SOL, SE, PSQI, and anxiety (HAM-A scores) with Ashwagandha root extract treatment for ten weeks. In conclusion, Ashwagandha may be of potential use to enhance sleep parameters in patients with insomnia and anxiety.

In addition, the leaf of Ashwagandha comprised triemthylene glycol (TEG), which positively affected rapid eye movement(REM) sleep.<sup>38</sup> According to a study that proved Ashwaganha's ability to improve sleep two application methods of this product are alcohol-based(Ethanol) extraction and water-based extraction(named water & cyclodextrin extracts). According to the experiment, they concluded that the water and cyclodextrin extract enhances NREM sleep profoundly as compared to the alcohol-based extract. The total amount of NREM sleep over 12 hours also increased significantly after administration of those extracts. Consequently, the Ashwagandha leaves are the potential sleep, including tiny molecules.

The idea of using Ashwagandha for epilepsy patients came from Indian Ayurvedic medicine, which has been used in India for centuries.<sup>39</sup>

We must emphasize that Ashwagandha, a significant constituent of BR16A formulation, is used in Ayurvedic medicine.<sup>40</sup> BR-16A (Mentat) is widely used in conjunction with AEDs in current Indian medical practice. This BR16A has been discovered to be valuable in alcohol withdrawal seizures. In addition, Ashwagandha, along with rich sources of omega-3 fatty acids like flax seeds, is known to delay the occurrence of Epileptic Seizures.<sup>41</sup> In conclusion, Ashwagandha, an Ayurvedic classical formulation, is a remedy for Apasmara (epilepsy).

Epilepsy, defined as a chronic noncommunicable disease of the brain, is shown in all age ranges. According to the Epilepsy Foundation, "at least 1 million people in the United States have uncontrolled epilepsy".<sup>42</sup> The estimated proportion of the general population with active epilepsy (i.e., continuing seizures or with the need for treatment) at a given time is between 4 and 10 per 1000 people".<sup>43</sup> Although this disease is a chronic medical problem that for many people, can be treated with a favorable prognosis, currently available treatments do not work for every epilepsy patient. There are some circumstances in which people cannot take medicine because of other treatments they take because of other illnesses. For instance, for a person who takes a medication that contains diphenhydramine and other antihistamines it is hard for them to get cured since those are used for treating allergies but can increase seizure susceptibility, with the increased risk extending beyond the course of treatment.<sup>44</sup> Therefore, the development of complementary and alternative treatment methods is required.

The author identified five natural treatments containing a potential herbal therapy for epilepsy and sleep disorders: curcumin, chamomile, valerian, mugwort, and ashwagandha. These five herbal plants can potentially aid in managing sleep problems in epilepsy patients in different ways. Curcumin enhances serotonin and promotes dopamine synthesis, which causes a more positive mindset and less stress — serotonin and dopamine impacts positively in epilepsy and sleep disorder. Chamomile, a tea, contains terpenoids, flavonoids, lactones, matricin, and apigenin. Chamomile's hypnotic properties are similar to benzodiazepine. Chamomile's components may reduce epilepsy symptoms and sleep disorders. Valerian is a well-researched plant for insomnia. This plant has the power to not only help with insomnia but also impact positive results on diminishing epilepsy syndromes.

Throughout the constant treatment of consuming Valerian, we can look forward to reducing seizures, which leads to recovery of epilepsy while minimizing insomnia. Mugwort is an herb that cures the ability to sleep well and begins to treat years of chronic insomnia resulting in acute exhaustion and depletion.<sup>45</sup> Given the interaction of dopamine and its beneficial influence on the sleep-wake cycle and the significant increase in dopamine levels in dichloromethane extracts of valerian roots, we can conclude that valerian positively affects the rate of sleep disorder in the end. Mugwort extracts offer a momentous antiepileptic potential from their bioactive components. Current research demonstrated that oxidative stress and neuroinflammation play significant roles in the pathophysiology of obtained epilepsy. Mugwort is a nervine tranquilizer and alleviates nervousness, anxiety, and tension. Thus, this makes it highly demonstrated for both deficient or degenerative nerve conditions, as well as undue nervous system activity such as nervousness, anxiety, and insomnia.<sup>46</sup>

While some herbal therapies show promise, more study, particularly clinical trials involving human participants, is required to validate their efficacy and safety in treating sleep problems and epilepsy. Individual responses to these herbs may also vary, so their usage should be reviewed with a healthcare practitioner, especially if you are also using epilepsy medication. Furthermore, it is critical to adopt a holistic approach to managing epilepsy and sleep issues, which may involve lifestyle changes, stress reduction strategies, dietary changes, and herbal therapies. Various complementary techniques can help individuals living with multiple conditions enhance their overall well-being and quality of life. The dosage and procedures of herbal remedies should be evaluated. As with all chemical and herbal medications, selecting the correct dosage and techniques before administering the medicine to patients is critical, which includes analyzing acceptable mechanisms and doing advanced research.

There are several limitations to this study; there is a limitation of actual precise experiments for the specific arguments that are needed and had to be analyzed by connecting each of different organizations' results, which can lead to the lack of accuracy against the ideal research results. In addition, this review does not include any degree paper or unpublished data, which might cause bias when reviewing literature.

## Conclusion

In conclusion, the research suggests that herbal alternatives have the potential to offer relief for individuals with sleep disorders and epilepsy. While further research is needed, these natural remedies provide a promising avenue for those seeking complementary and alternative therapies to manage their conditions.

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