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SLEEP-INDUCING EFFECTS OF MULBERRY LEAVES TO TREAT INSOMNIA NATURALLY

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Keywords:

Mulberry leaves, GABA A receptors, 5-HT receptors, Sleep disturbances, Insomnia

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ABSTRACT: Sleep disorders are a prevalent health concern, impacting overall well-being and cognitive function. Natural compounds like flavonoids have garnered attention for their potential therapeutic effects on sleep regulation. Mulberry leaves (Morus spp.) are rich in bioactive flavonoids that exhibit sleep-improving properties by modulating key neurotransmitter systems. This study explores the effects of mulberry leaves on sleep regulation through their interaction with gamma-aminobutyric acid (GABA) and serotonin (5-hydroxytryptamine, 5-HT) receptors. Evidence suggests that these flavonoids enhance GABAergic transmission, promoting relaxation and sedation, while also modulating 5-HT receptors, that contribute notably to the regulation of sleep-wake cycles. Many flavonoids, including quercetin, rutin, and kaempferol, are able to interact with GABAA receptors and serotonin receptors, promoting relaxation and reducing sleep latency. By influencing these neurotransmitter pathways, mulberry leaf flavonoids may serve as a natural and effective alternative for managing sleep disturbances or insomnia. Additional studies are required to better understand the exact mechanisms as well as potential clinical uses of these bioactive compounds in sleep therapy.

INTRODUCTION: In today's rapidly moving world, insomnia has become a common sleep disorder, impacting millions of people across the world. Characterized by difficulty falling asleep, staying asleep, or achieving restful sleep, insomnia can lead to a range of negative consequences, from impaired cognitive function and mood disturbances to lowered immunity and long term health complecations.

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While conventional treatments like prescription medications and behavioural therapies are commonly employed to manage insomnia, they often come with side effects, dependency risks, or limited long-term effectiveness [1].

In the current era, there has been a growing interest in natural and plant-based alternatives for the treatment of insomnia. Herbal remedies, traditional botanicals, and plant-derived compounds have been used for centuries across cultures for their calming and sleep-inducing properties. As people increasingly seek holistic and sustainable solutions to health concerns, plant products are gaining recognition for their potential in promoting better sleep without the drawbacks associated with synthetic medications [2, 3].

Natural agents such as valerian root, chamomile, passionflower, lavender, and CBD from cannabis, offer a promising and integrative approach to treating insomnia, addressing both the physiological and psychological factors involved in sleep disturbances.

As research into these alternatives continues to expand, plant-based sleep aids could become an essential component of a balanced, long-term strategy for managing insomnia and improving overall well-being [4, 5].

Sleep Disorders And Insomnia: Sleep is a vital function for overall health and well-being, but various disorders can disrupt it. Sleep disorders affect the ability to get quality rest, leading to daytime fatigue, poor performance, mood issues, and health risks. Sleep disorders can take several forms, with insomnia being one of the most common [6-8]. There are several major categories of sleep disorders **Table 1** and each of these disorders can lead to significant disruption in both sleep quality and daily life.

TABLE 1: SLEEP DISORDERS AND IDENTIFYING SYMPTOM

Disorders	Symptoms
Insomnia	Challenges with falling asleep or remaining asleep throughout the night
Sleep Apnea	Disrupted breathing patterns while sleeping
Restless Legs Syndrome (RLS)	An uneasy feeling in the legs that causes a strong urge to move them [9]
Narcolepsy	Experiencing extreme drowsiness during the day along with unexpected episodes of falling asleep
Circadian Rhythm Disorders	Disruption of the internal body clock, leading to issues like jet lag or shift work disorder.
Parasomnias	Unusual behaviors occurring during sleep, including sleepwalking, vivid nightmares, and episodes of night terrors [10,11]

Insomnia is a frequent sleep disorder marked by trouble falling asleep, staying asleep, or waking up too early and being unable to return to sleep. It may be short term (acute) or persist over time (chronic).

Acute Insomnia: Acute insomnia often occurs due to stress, traumatic events, or significant life transitions and generally persists for a few days to a few weeks.

Chronic Insomnia: Occurs at least three nights a week for three months or more. Chronic insomnia may be linked to medical or psychological conditions [13-14].

Typical symptoms of insomnia may include, difficulty falling asleep, frequent awakenings throughout the night, waking up earlier than desired, feeling unrefreshed in the morning, experiencing tiredness or lack of energy during the day, trouble focusing, increased irritability, and persistent concerns about not getting enough sleep [15].

Pharmacological Treatment of Insomnia: Pharmacological treatment of insomnia typically involves the use of medications aimed at promoting sleep, improving sleep quality, and addressing the underlying causes of sleep disturbances. Commonly prescribed medications include benzodiazepines, non-benzodiazepine hypnotics, melatonin receptor agonists, and certain antidepressants [16-18]. Benzodiazepines, act on GABA receptors in the brain to induce sedation, but they are generally recommended for short-term use due to risks of tolerance, dependence, and withdrawal symptoms. Non-benzodiazepine hypnotics are frequently used for short-term insomnia management and tend to have fewer side effects than traditional benzodiazepines. These medications primarily target specific GABA receptors to help with sleep initiation [19, 20].

Melatonin receptor agonists mimic the action of the natural sleep hormone melatonin, helping to regulate the sleep-wake cycle without as much risk of dependency. Some antidepressants, particularly those with sedating properties, may be used off-label to treat insomnia, particularly when it is associated with depression or anxiety. However, several of these medications may cause side effects such as drowsiness during the day, reduced cognitive function, and the possibility of tolerance developing with prolonged use. Medications are typically advised for managing short-term or acute cases of insomnia, whereas cognitive-behavioral therapy for insomnia (CBT-I) is considered the

most effective approach for long-term treatment. Medication selection depends on factors like the patient's age, existing health conditions, and whether the insomnia involves trouble falling asleep or staying asleep. The potential risks associated with long-term use of sleep medications dependency and tolerance, cognitive and memory impairment, daytime drowsiness and impaired function, mood and behavioral changes and altered sleep architecture [21-22].

Mulberry Leaves in the Treatment of Insomnia: Mulberry leaves come from *Morus alba* (White mulberry), *Morus nigra* (Black mulberry), *Morus rubra* (Red mulberry). Mulberry leaves have shown potential in the treatment of insomnia, offering a natural remedy for improving sleep quality. These leaves are rich in bioactive compounds such as flavonoids, polysaccharides, and antioxidants, which are believed to contribute to their sedative and calming effects [23]. One of the key mechanisms through which mulberry leaves may alleviate insomnia is by promoting the regulation of neurotransmitters, particularly gamma-aminobutyric acid (GABA) **Fig. 1** and serotonin **Fig. 2** both of which play a critical role in sleep regulation **Fig. 3**. Serotonin, often referred to as the "feel-good" hormone, helps to stabilize mood and promotes relaxation, thereby making it easier to fall asleep [24]. GABA, on the other hand, is an inhibitory neurotransmitter that reduces brain activity and encourages a state of calm, helping to combat restlessness and anxiety that often accompany insomnia. Studies have also shown that mulberry leaves may have an impact on oxidative stress, which is known to affect sleep patterns [25].

By reducing oxidative stress and inflammation, mulberry leaves can improve overall sleep quality and duration. Additionally, mulberry leaves are thought to support the regulation of blood sugar levels, and stabilizing blood sugar can be beneficial for sleep, as fluctuations in glucose levels can interfere with restful sleep. This natural remedy is gaining popularity due to its minimal side effects compared to conventional medications, making it an appealing alternative for those seeking to address insomnia through holistic means. However, while promising, more research is needed to fully understand the scope of its benefits and the ideal dosages for therapeutic use [26, 27].

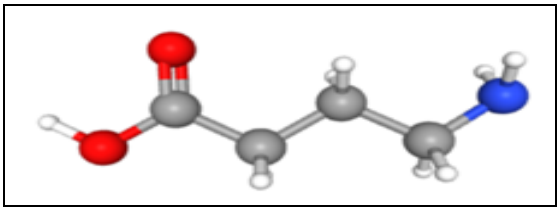


FIG. 1: 3D STRUCTURE OF ACID GAMMA-AMINOBUTYRIC

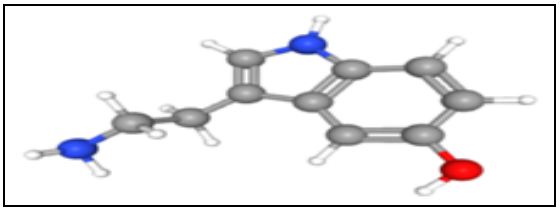


FIG. 2: 3D STRUCTURE OF SEROTONIN

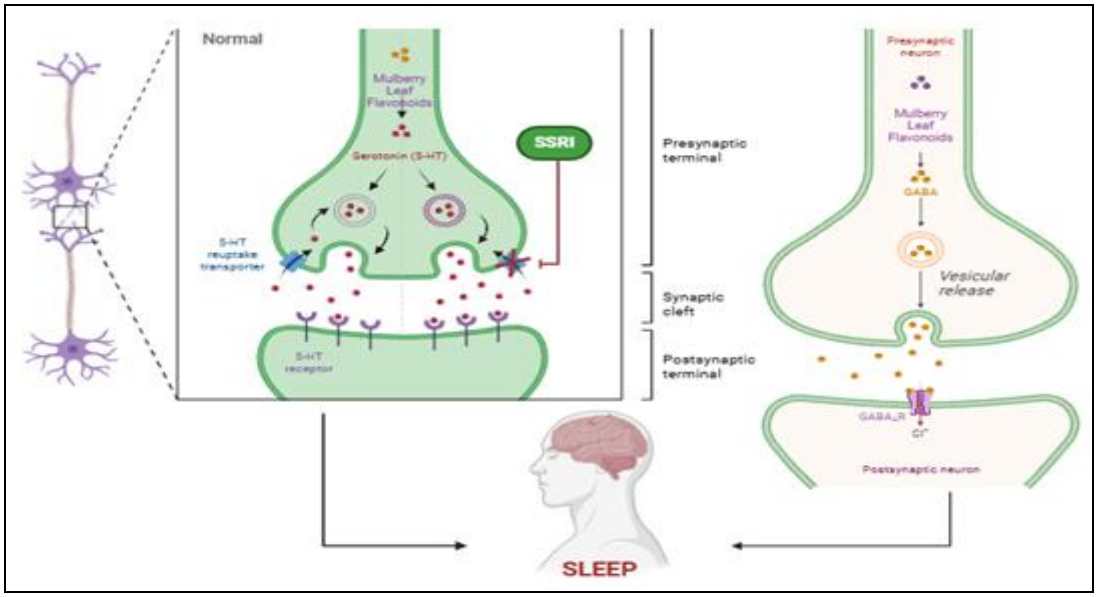


FIG. 3: MECHANISM OF ACTION OF FLAVONOIDS PRESENT IN MULBERRY LEAVES

Flavonoids Present in Mulberry Leaves in the Treatment of Insomnia: Flavonoids from mulberry leaves show promising potential as a natural aid for insomnia, particularly through GABAergic modulation, antioxidant action, and neuroinflammation control. May interact with sedatives, antihypertensives, or blood sugar medications. Flavonoids reduce levels of pro-inflammatory cytokines like IL-6 and TNF-α, helping restore sleep homeostasis. Mulberry flavonoids may influence levels of serotonin and melatonin, which are key regulators of circadian rhythms and sleep architecture. However, more robust clinical trials are needed to confirm efficacy and establish guidelines for therapeutic use. Some clinically established flavonoids **Fig. 4-9** of mulberry leaves that can induce sleep arequercetin-3-o-(6-malonyl glucoside), nicotiflorin, rutin, isoquercetin, and myricetin. Moreover, some non-flavonoids also there which can induce sleep, chlorogenic acid is one of the most important among them [28-32].

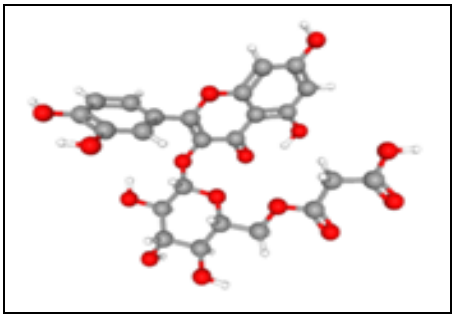


FIG. 4: QUERCETIN-3-O-(6-MALONYL GLUCOSIDE)

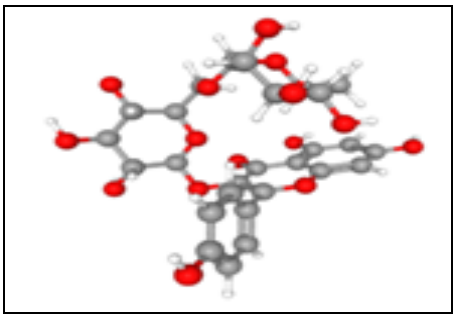


FIG. 5: NICOTIFLORIN

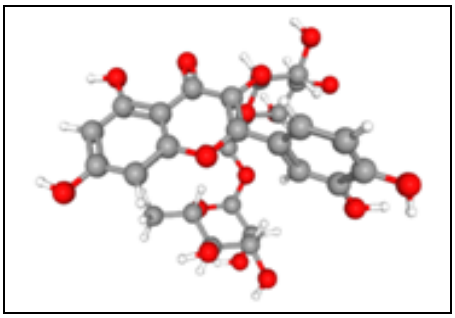


FIG. 6: RUTIN

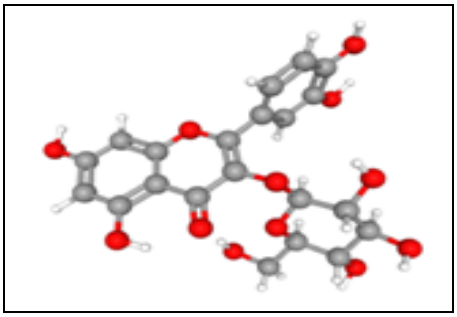


FIG. 7: ISOQUERCETIN

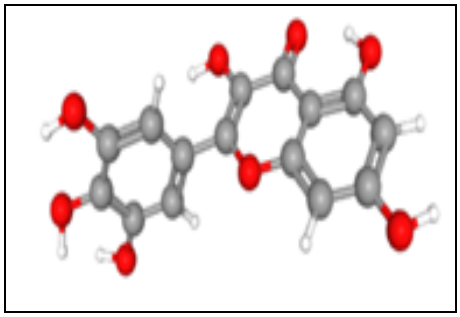


FIG. 8: MYRICETIN

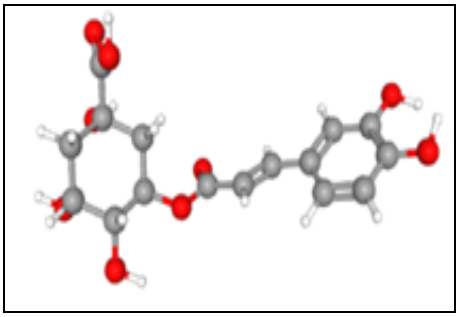
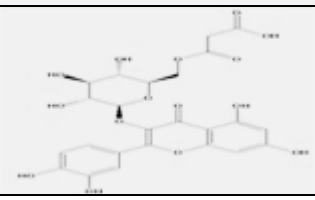
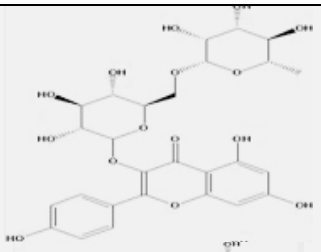
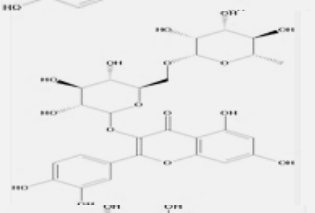
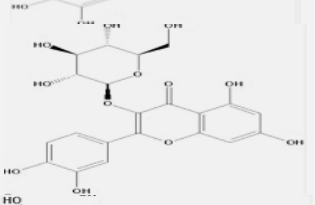
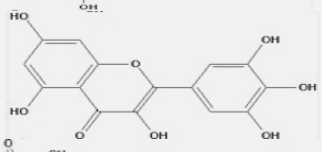
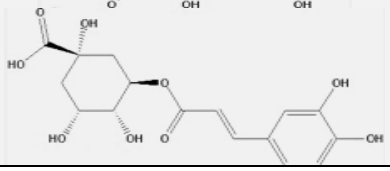


FIG. 9: CHLOROGENIC ACID

Mulberry leaves have several types of flavonoids shown to have an effect on insomnia by different mechanisms of action, some of them are discussed in **Table 2**.

TABLE 2: PHYTOACTIVE CONSTITUENT OF MULBERRY LEAVES IN THE TREATMENT OF INSOMNIA

Sl. no.	Phytoactive constituent	Chemical structure	Mechanism
1	Quercetin-3-O-(6-malonylglucoside)		It possesses anti-inflammatory and antioxidant effects, which can help promote relaxation and improve sleep quality.

2	Nicotiflorin		Known for its neuroprotective effects, which may help with stress and sleep disorders.
3	Rutin		Enhances blood circulation and has calming effects on the nervous system, aiding sleep.
4	Isoquercetin		Isoquercetin supports relaxation and may help to regulate sleep.
5	Myricetin		Has sedative-like effects and supports cognitive health, reducing anxiety-related insomnia.
6	Chlorogenic Acid		Though not a flavonoid, this polyphenol can promote relaxation and improve sleep quality.

Drug-Likeness Prediction: SwissADME is an online resource developed by the Swiss Institute of Bioinformatics (SIB) that helps scientists evaluate the Absorption, Distribution, Metabolism, and Excretion (ADME) properties of small molecules. It provides insights into drug-likeness, physicochemical properties, pharmacokinetics, and more, making it a valuable tool in drug discovery and development. Physicochemical properties, pharmacokinetics, drug-likeness of mulberry leaf flavonoids are developed by the web tool Swiss ADME is mentioned below.

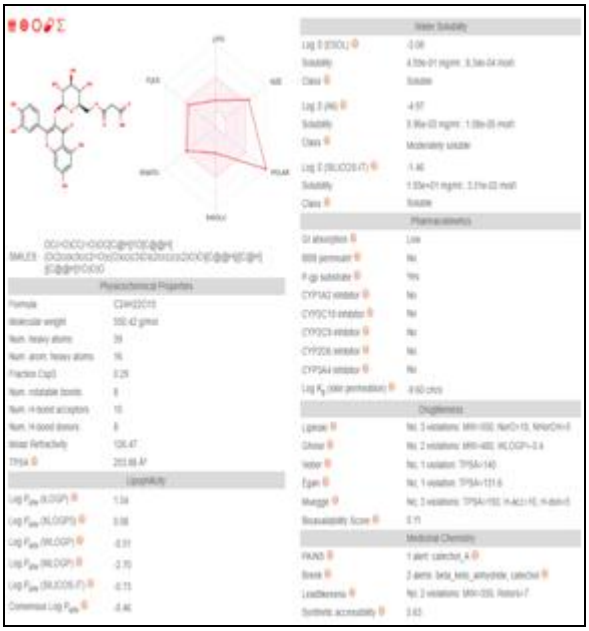


FIG. 10: ADME PROPERTIES OF QUERCETIN-3-O-(6-MALONYL GLUCOSIDE)

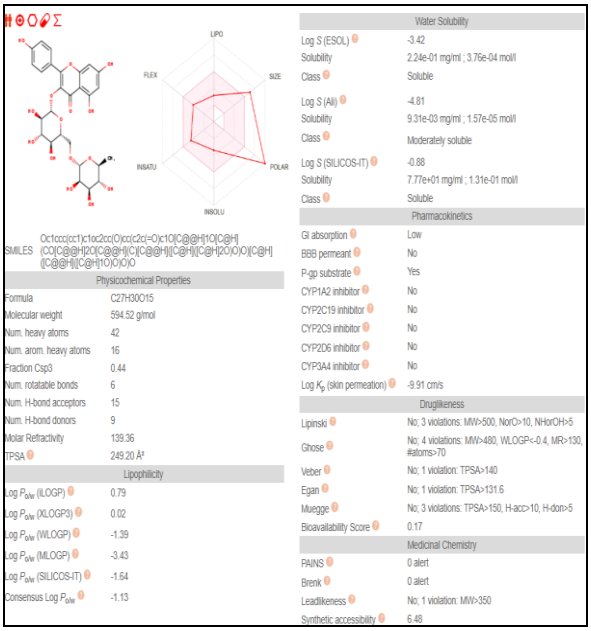


FIG. 11: ADME PROPERTIES OF NICOTIFLORIN

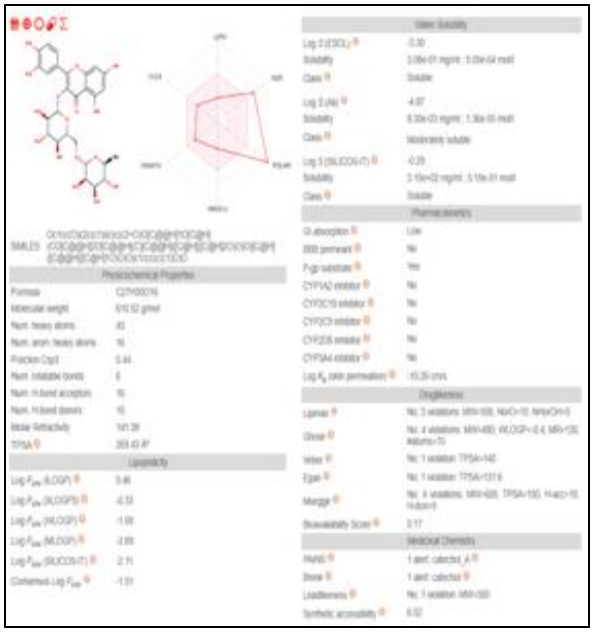


FIG. 12: ADME PROPERTIES OF RUTIN

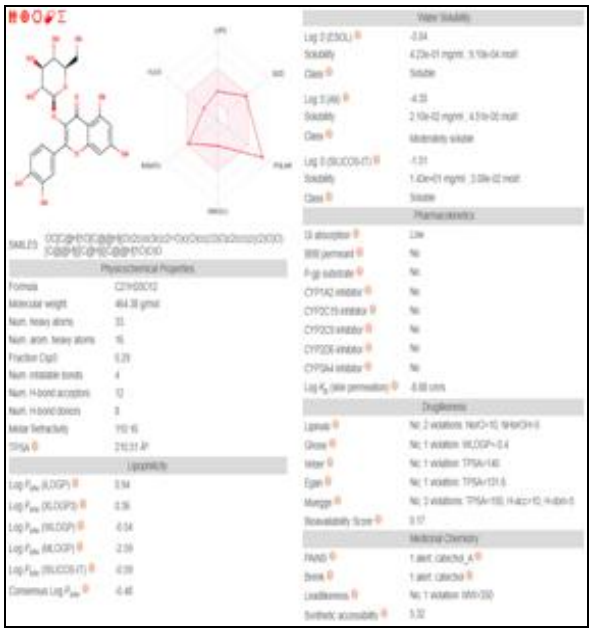


FIG. 13: ADME PROPERTIES OF ISOQUERCETIN

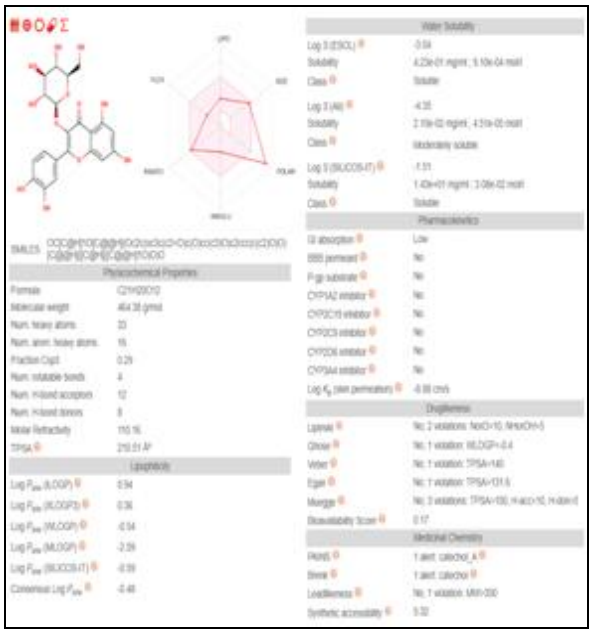


FIG. 14: ADME PROPERTIES OF MYRICETIN

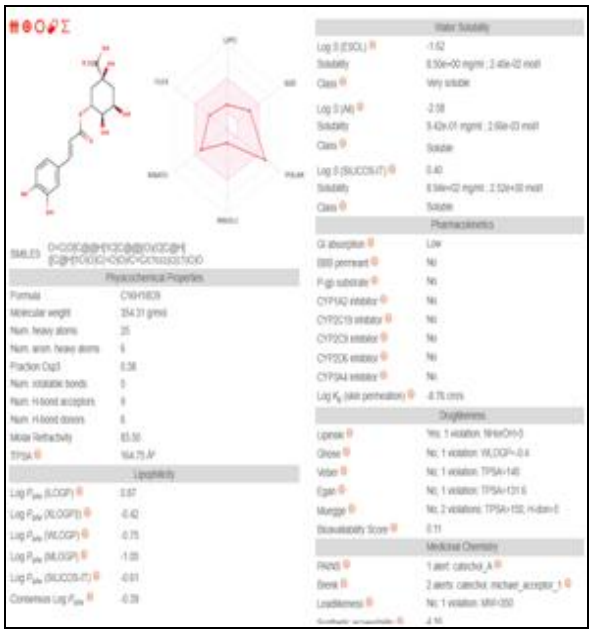


FIG. 15: ADME PROPERTIES OF CHLOROGENIC ACID

DISCUSSION: Sleep disorders, including insomnia and poor sleep quality, have been linked to disruptions in neurotransmitter systems, particularly the gamma-aminobutyric acid (GABA) and serotonin (5-hydroxytryptamine, 5-HT) pathways. Flavonoids derived from mulberry leaves have gained attention for their potential role in improving sleep through the modulation of these neurotransmitter systems. The flavonoids in mulberry leaves contribute to sleep regulation by enhancing GABAergic and serotonergic neurotransmission. Many flavonoids, including quercetin-3-o-(6-malonylglucoside), nicotiflorin, rutin, isoquercetin, myricetin and chlorogenic acid are able to interact with GABA A receptors, promoting relaxation and reducing sleep latency. Similarly, the 5-HT system plays a crucial role in sleep-wake regulation, with increased serotonergic activity being associated with improved sleep quality and duration. Mulberry leaf flavonoids may enhance serotonin synthesis or receptor sensitivity, thereby facilitating the transition into deeper sleep stages. On the other hand, the Swiss ADME helped in enlightening different physicochemical properties and pharmacokinetics properties of flavonoids and non-flavonoids (chlorogenic acid), which are going to be important for the development of novel drugs.

Several animal and *in-vitro* studies have demonstrated that mulberry flavonoids can increase the expression of GABAA receptors and 5-HT receptors, leading to prolonged sleep duration and improved sleep architecture. These effects may be comparable to those of conventional sedative-hypnotic drugs but with fewer side effects. Additionally, flavonoids possess antioxidant and anti-inflammatory properties, which may further contribute to their neuroprotective and sleep-enhancing effects.

CONCLUSION: The literature search suggests that flavonoids from mulberry leaves hold promising potential as natural sleep aids due to their ability to modulate GABA and 5-HT receptor activity. By enhancing inhibitory neurotransmission and regulating serotonin pathways, these bioactive compounds may offer an alternative approach for managing sleep disorders.

Future research should focus on clinical trials to confirm these effects in humans and to determine optimal dosages and formulations for therapeutic use. If validated, mulberry leaf flavonoids could serve as a safe and effective alternative over synthetic sleep medications, benefiting individuals suffering from insomnia and other sleep-related disorders.

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