



## An Innovative Experimental Method to the Therapies of Psychotic Disorders

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### Abstract

Sleep is a restorative time that is very important for the body's physiological functions, like how the immune system, memory, and cognition work. Numerous mental, physical, and social issues can lead to sleep problems. Sleep has recently been the subject of increasing interest. The female maize flower known as maydis stigma (MS, corn silk) is traditionally utilized as a medicinal plant to treat a variety of conditions, including diabetes, edema, and hypertension. Additionally, it is utilized in tea and other supplements as a functional food. BS is a phytosterol and a naturally occurring micronutrient found in higher plants. Its structure is comparable to that of cholesterol. It has anti-inflammatory, antidepressant, and sedative properties and is a major component of MS. However, it is still unclear how MS might affect how sleep is controlled. Here, we examined the impacts of MS on rest in mice. The mouse models of pentobarbital-induced sleep and caffeine-induced sleep disruption were used to investigate the effects of MS on sleep induction. When compared to the positive control, valerian root extract, MS extracts increased sleep duration and decreased sleep latency in both the caffeine-induced sleep disruption model and the pentobarbital-induced sleep induction model. MS extracts' butanol fraction increased sleep duration and decreased sleep latency time. Additionally, -sitosterol increases sleep duration and latency. The EEG analysis revealed that both -sitosterol and MS extract increased alpha activity. Using qRT-PCR, we determined the mRNA expression of MT1/2 (melatonin receptors 1 and 2). MS extract and -sitosterol treatment increased the mRNA expression of melatonin receptors 1 and 2 in the brain and primary cultured neurons of rats. In addition, *per1/2*, *cry1/2*, and *Bmal1* expression in the brain was increased by MS extract. ERK1/2 and CaMKII phosphorylation was enhanced by MS extract and -sitosterol. Through the expression of melatonin receptors, our findings for the first time demonstrate that MS has a sleep-promoting effect. This suggests that MS could be used as a potential therapeutic agent to treat and prevent sleep disturbances.

**Keywords:** Sleep; Melatonin Receptors; Maydis Stigma; Nutraceuticals; New Therapeutics

### Introduction

Sleep is necessary for mental, physical, and emotional well-being. After an activity, sleep has a restorative effect, allowing for optimal performance. Homeostasis in the brain is maintained by sleep, and sleep disturbances like sleep deprivation and loss are closely linked to cognitive decline, systemic inflammation, and neurodegeneration. As a result, sleep disturbances are significant risk factors for a variety of neurological conditions, such as neurovascular diseases, depression, attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and neurodegenerative diseases. Additionally, they are common symptoms of these conditions [1].

Sleep apnea, narcolepsy, insomnia, and restless leg syndrome (RLS) are among the most common sleep disorders. The inability to fall asleep and stay asleep, which results in sleep loss and poor quality, is a hallmark of insomnia, the most common sleep disorder. Worldwide, the prevalence of insomnia ranges from 10 to 30 percent, with some estimates reaching 50 to 60 percent. Insomnia has significant negative effects on one's overall quality of life, including depression as well as a reduction in one's ability to perform at work and make decisions. As a result, the burden on society and the economy rises as a result of sleep disorders' significant impairment of social and professional function [2].

The majority of treatments for sleep disorders like insomnia include both medication and non-medical treatments. The easiest and fastest-acting medications are benzodiazepines, barbiturates, antidepressants, and melatonin agonists; Overuse of drugs, on the other hand, has been linked to negative outcomes like resistance over time, reactions to disruption, and withdrawal symptoms [3]. Cognitive behavioral therapy for insomnia (CBT-i), a type of therapy used to change behavior

and lifestyle, and complementary medicines like herbal remedies and natural sleep aids are used in non-pharmacological treatment of insomnia. Despite the fact that medication treatment has a quick and effective effect on insomnia, there is a high potential for abuse and dependence, which is why there has been an increase in interest in alternative medicines like medicinal plants and dietary supplements in recent years. Many medicinal plants, including herbal remedies, can be used to treat a variety of human health issues [4]. In patients with sleep disorders, natural plants like chamomile and valerian are well-known alternatives to sleeping pills. By and large, the systems of restorative plants in treating a sleeping disorder are generally connected with gamma-aminobutyric corrosive (GABA) neurotransmission that controls rest results. Additionally, they are frequently linked to the production of the sleep-regulating hormone melatonin. Lately, with expanding interest in rest enlistment and support, new, powerful, and safe dozing pills have been created. Specifically, there has been developing interest in considering the utilization of melatonin as a resting chemical in patients with rest problems as it doesn't prompt mental trips or result in reliance [5].

The pineal gland releases melatonin (N-acetyl-5-methoxytryptamine),

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an endogenous hormone, into the bloodstream [6]. By activating the high-affinity G protein-coupled receptors MT1 and MT2, melatonin has a variety of beneficial effects on sleep and circadian abnormalities, mood disorders, learning and memory, neuroprotection, drug abuse, and cancer. Endogenous oscillators in the suprachiasmatic nucleus (SCN) control melatonin synthesis, which is influenced by daily and seasonal shifts in the environmental light–dark cycle. Melatonin enhances sleep onset latency, duration, and quality by synchronizing with circadian rhythms. Antioxidative, anti-inflammatory, sleep-regulating, and neuronal survival effects have also been demonstrated [7]. By stimulating the MT1 and MT2 melatonin receptors, melatonin and melatonin agonists aid in the treatment of insomnia. By mimicking the natural endogenous melatonin, binding to MT1 and MT2 receptors, and activating the same downstream pathways, exogenous melatonin can be effective in the absence of melatonin release. Ramelteon, a melatonin receptor agonist, may have an impact on sleep duration via MT2 and promotes sleep by reducing wake-promoting signals by acting on MT1. Melatonin agonists and exogenous melatonin supplementation had no obvious short- or long-term side effects. This means that exogenous melatonin and melatonin agonists that work on functional melatonin receptors could be used to treat sleep disorders, learning and memory problems, neurodegeneration, drug addiction, and other conditions. However, it is still necessary to develop sleeping aids that are highly effective, low in dependence, and have few side effects [8].

Proteins, vitamins, alkaloids, tannins, mineral salts, carbohydrates, steroids, and flavonoids, as well as volatile chemicals, are all found in the silk threads that make up *Maydis stigma*, also known as corn silk. Corn silk is a plant that has been used for centuries to treat a variety of ailments in traditional Chinese medicine. It has been shown to have a number of beneficial effects, including hypotensive, anti-diabetic, anti-fatigue, antidepressant, and hypolipidemic properties. Additionally, it is a potent antioxidant with neuroprotective properties. There are numerous advantages to using corn silk and its bioactive components in ethanol and methanol extracts for healthcare purposes. For medicinal purposes, numerous commercial products made from corn silk are available on the market. However, the possibility of *Maydis stigma* improving sleep is unknown. *Maydis stigma*'s sleep-promoting properties and potential signaling mechanisms toward MT1 and MT2 melatonin receptors were the focus of our current investigation [9].

### MS extracts increased sleep duration and decreased sleep onset latency

Induced sleep model to investigate how MSE influences sleep regulation. Mice that were four weeks old were given MSE orally at doses of one, ten, and one hundred milligrams per kilogram for seven days, with water serving as the vehicle. Valerian root extract (10 mg/kg) was used as a positive control [10]. After seven days, 42 mg/kg pentobarbital sodium was infused intraperitoneally into each exploratory mouse, and an estimated amount of time was given for rest, arousal, and awakening. The MSE-treated group fell asleep 30 seconds earlier than the vehicle control group (202.1 9.6 s) and did so for approximately 1000 seconds longer than the control group (2043.77 147.8 s). MSE mice fell asleep faster and stayed asleep longer than vehicle-treated mice, according to these findings, which were dose-dependent. Also, mice given valerian root extract experienced more limited rest beginning times and longer rest lengths. Our findings, which are intriguing, demonstrated that MSE treatment improved and maintained sleep [11].

Utilizing a pentobarbital-incited rest test on mice, we likewise took a gander at what MSE meant for caffeine-initiated rest unsettling

influence. Insomnia was brought on by administering 10 mg of caffeine per kilogram intravenously. 30 minutes before injecting 42 mg/kg of sodium pentobarbital intravenously, mice treated with caffeine took significantly longer than the vehicle control to fall asleep (237.2 14.8 s). Additionally, compared to the vehicle control, the mice treated with caffeine slept for significantly less time (1523.0 175.9 s). Be that as it may, mice pretreated with MSE at 1, 10, and 100 mg/kg recuperated essentially from the caffeine-actuated expansion in rest idleness (195.2 5.6 s, 174.5 5.9 s, and 161.3 7.5 s, separately), and mice treated with MSE at 100 mg/kg recuperated altogether from the caffeine-prompted decline in rest upkeep (1983.61 113.4 s). In both sleep-inducing and sleep-disorder models, these findings demonstrated that MSE lengthens sleep duration and reduces sleep latency [12].

### Circadian Clock Gene Expression Was Increased by MS Extracts

Melatonin, according to previous research, acts on the SCN to directly regulate circadian rhythms [13]. The mind's guideline of the outflow of clock qualities like *Bmal1* and *Clock* additionally requires a working MT1 receptor. Circadian rhythms are regulated by the transcriptional feedback loop of clock genes like *Per*, *Cry*, *Clock*, and *Bmal1*. In order to investigate the molecular mechanism of MSE in relation to clock genes, we used qRT-PCR to determine the mRNA expression of markers that are controlled by the circadian clock, such as *Per*, *Cry*, *Clock*, and *Bmal1*. Our results demonstrated that MSE (100 mg/kg) significantly increased clock gene expression in the hypothalamus (3.3/3.78-, 2.07/2.37-, and 2.46-fold, respectively) in comparison to the vehicle control. These findings demonstrated that MSE regulates the expression of circadian clock genes by activating melatonin receptors, thereby increasing the quantity and quality of sleep [14].

### The Butanol Fraction of MSE Enhanced Sleep Duration and Reduced Sleep Onset Latency

In order to investigate the nature of the compounds that are responsible for the effects of MS extracts, three fractions were prepared: The polar agents and water-soluble plant constituents (such as glycosides, quaternary alkaloids, and tannins) are solubilized by the ethyl acetate fraction (EAF), which extracts compounds of intermediate polarity, and the butanol fraction (BuF), which carries non-polar agents such as sterols, alkanes, and some terpenoids. The rest term expanded from 2299.5 188.3 to 3466.76 169.6 s ( $p < 0.001$ ) when BuF was directed, and the dormancy time diminished from 172.4 23.47 s (vehicle) to 145.45 26.95 s ( $p < 0.05$ ). We found that the butanol fraction (BuF) of MS extracts significantly increased sleep duration and decreased sleep latency. Non-polar agents may be to blame for MS-induced sleep improvement, as BuF increases sleep parameters [15].

### Discussion

Lack of sleep influences a many individuals, and as friendly and financial advancement has sped up, its commonness has likewise been rising. Consequently, numerous efforts have been made to develop chemical drugs, functional foods, nutraceuticals, and nutraceuticals that are free of toxicity and side effects like addiction as treatments for sleep disorders. Melatonin receptors 1 and 2 are two examples of receptors that are thought to be linked to them. Melatonin is a hormone that regulates sleep. In this study, we demonstrated that MS extracts could increase the expression of melatonin receptors 1 and 2 and clock genes in the brain, reduce sleep latency, protect against neurotoxicity, and prolong sleep. Additionally, we investigated the chemicals that contributed to the effects of MS extracts. According to our findings,

the butanol fraction (BuF) containing non-polar components like -sitosterol significantly increased sleep duration and decreased sleep latency. In addition, our findings demonstrated that -sitosterol also has an effect on sleep improvement, which is consistent with previous studies that demonstrated -sitosterol's effects on narcotics and sleep improvement. MS extracts may be a novel treatment option for sleep disorders like insomnia and other sleep-related neurological disorders, according to these findings. This study is said to be quick to investigate the original application of MSE to improve sleep and target melatonin receptors. Despite the fact that sleep deprivation is associated with gender-specific differences and that a number of clinical studies have demonstrated sex differences in insomnia and other sleep disorders, the majority of studies on sleep deprivation were either carried out primarily with male subjects or failed to account for gender factors. suggested that sleep deprivation experiments on mice did not show a gender difference. During their estrous cycle, however, female rodents, like humans, exhibit changes in sleep and locomotor activity. Additionally, gonadectomy and the removal of sex hormones eliminated sex differences in sleep in rodents, as demonstrated by sleep studies. In this study, we only used male mice as experimental subjects to avoid the effects of the estrus cycle.

Maydis stigma, also known as corn silk, has the potential to be a useful food due to its numerous uses. Corn silk has traditionally been used to treat a wide range of conditions, including diabetes, obesity, cystitis, gout, kidney-related conditions, neurodegenerative conditions, and neurodegenerative diseases. Other ingredients include volatile chemicals, saponins, tannins, alcohols, terpenoids, glycosides, proteins, carbohydrates, vitamins, mineral salts, anthocyanins, protocatekin, quercetin, beta-carotene, stigmasterol, and beta. Furthermore, late examination has exhibited that corn silk has against oxidative, energizer, and mitigating properties. We found that MS extracts increased sleep duration and decreased sleep latency in this study. In addition, these results demonstrated novel characteristics of Maydis shame, corn silk, particularly its effects on rest advancement.

The expression "dietary" is gotten from the words "nourishment" and "drug," and it alludes to a part of food that gives wellbeing and health advantages. Nutraceuticals, which include herbal products, dietary supplements, and isolated nutrients, are utilized as potential treatments for a variety of diseases due to their non-toxic properties. Herbal medicine has recently been used worldwide to treat insomnia due to its sedative and anxiolytic properties. Compound blends make up home grown meds, and their instruments of activity habitually stay a secret. Nonetheless, various examinations have shown that, like pharmacological medicines like benzodiazepine receptor agonists, the anxiolytic and narcotic impacts of natural plants are displayed through GABAergic neurotransmission. From this vantage point, the CPP test was used to determine whether MS extracts cause dependency. As these findings demonstrated, Maydis stigma did not result in dependence, it may be an option for treating insomnia and other sleep disorders as a nutraceutical. Despite our recognition of the difficulties inherent in using an animal model to accurately replicate human physiology, our research sheds light on the mechanisms by which Maydis stigma affects sleep and opens up a new area of inquiry.

## Conclusions

Taken as a whole, our findings indicate for the first time that Maydis stigma may have a positive impact on quality and quantity of

sleep without causing addiction or toxicity. Additionally, our findings demonstrated a connection between the sleep-inducing properties of Maydis stigma and the circadian clock genes and melatonin receptor 1/2. As a result, when developing new treatments, the new possibilities of utilizing Maydis stigma to promote sleep and reduce sleep disorders by targeting melatonin receptors 1 and 2 may be taken into consideration. As a whole, our study provided some evidence that Maydis stigma may be a safe and potential nutraceutical for a variety of sleep-related psychiatric disorders; However, its clinical efficacy cannot be determined without additional research.

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