

PSYCHOBOTIC POTENTIAL OF SAFFRON (CROCUS SATIVUS): EFFECTS ON GUT MICROBIOTA AND SLEEP ARCHITECTURE IN PATIENTS WITH INSOMNIA

Dr. K.G. Padmanabhan

Medical advisor & Researcher-Khoday Centre for Integrative Medicine and Research, Bangalore. ORCID ID: 0009-0009-4444-5072

ABSTRACT

Insomnia is a prevalent sleep disorder associated with dysregulation of the gut–brain axis, altered microbiota composition, and impaired neurochemical signaling. Emerging evidence suggests that psychobiotics—bioactive compounds influencing mental health via gut microbiota modulation—may offer novel therapeutic avenues. Saffron (*Crocus sativus*), traditionally used for mood and sleep disorders, contains bioactive constituents such as crocin, crocetin, and safranal with demonstrated neuroprotective and anxiolytic properties. This manuscript explores the psychobiotic potential of saffron, focusing on its effects on gut microbiota composition and sleep architecture in insomnia patients. We synthesize current preclinical and clinical evidence and propose mechanistic pathways linking saffron intake to improvements in sleep quality through microbiota-mediated modulation of neurotransmitters and inflammatory pathways. Finally, we outline future research directions and clinical implications.

KEYWORDS: Saffron, Psychobiotics, Insomnia, Gut Microbiota, Sleep Architecture, Gut–Brain Axis, Crocin, Circadian Rhythm.

INTRODUCTION

Insomnia affects approximately 10–30% of the global population and is characterized by difficulty initiating or maintaining sleep, often accompanied by daytime impairment. Conventional pharmacological treatments, including benzodiazepines and non-benzodiazepine hypnotics, are associated with adverse effects and dependency risks, prompting the search for safer alternatives. [2]

The gut–brain axis, a bidirectional communication system involving neural, endocrine, and immune pathways, has emerged as a key regulator of sleep. Alterations in gut microbiota composition have been linked to insomnia, anxiety, and depression. Psychobiotics, defined as probiotics or bioactive compounds that confer mental health benefits via the gut microbiome, represent a promising therapeutic strategy. [3], [5]

Saffron (*Crocus sativus*), a medicinal spice rich in carotenoids and volatile compounds, has demonstrated antidepressant, anxiolytic, and sleep-enhancing effects. However, its role as a psychobiotic remains underexplored. [7] This manuscript investigates the hypothesis that saffron improves sleep in insomnia patients through modulation of gut microbiota and downstream neurophysiological pathways.

Bioactive Components of Saffron and Neurobiological Effects

Saffron contains several key bioactive compounds:

Crocic acid and crocetin: Carotenoids with antioxidant and anti-inflammatory properties

Safranal: A volatile compound contributing to aroma and exhibiting sedative effects

Picrocrocin: Responsible for saffron's bitter taste. These compounds have been shown to:

Modulate neurotransmitters such as serotonin, dopamine, and GABA

Reduce oxidative stress and neuroinflammation

Enhance brain-derived neurotrophic factor (BDNF) expression.

Such effects suggest a potential role in regulating sleep–wake cycles and emotional states.

Gut Microbiota and Insomnia

Recent studies indicate that insomnia is associated with:

Reduced microbial diversity

Altered Firmicutes/Bacteroidetes ratio

Decreased abundance of beneficial genera such as *Lactobacillus* and *Bifidobacterium*

Gut microbiota influence sleep via:

Production of neurotransmitters (e.g., serotonin, GABA)

Regulation of circadian rhythm genes

Modulation of systemic inflammation and hypothalamic–pituitary–adrenal (HPA) axis activity

Disruption in these pathways contributes to impaired sleep architecture, including reduced slow-wave sleep and REM instability.

Psychobiotic Effects of Saffron on Gut Microbiota

Although direct clinical evidence is limited, preclinical studies suggest that saffron and its constituents:

- Promote the growth of beneficial gut bacteria
 - Suppress pathogenic microbial populations
 - Enhance short-chain fatty acid (SCFA) production
- Crocin, in particular, has been shown to:
- Increase Lactobacillus and Bifidobacterium abundance
 - Improve intestinal barrier integrity
 - Reduce gut-derived inflammation
 - These microbiota changes may indirectly influence central nervous system function via the gut–brain axis.

Saffron and Sleep Architecture

Sleep architecture refers to the structure and pattern of sleep cycles, including REM and non-REM stages.

Clinical trials evaluating saffron supplementation have reported:

- Improved sleep latency (time to fall asleep)
- Increased total sleep time
- Enhanced sleep efficiency
- Reduced nighttime awakenings

Mechanistically, saffron may influence sleep architecture through:

- Serotonergic modulation: Increasing serotonin availability, a precursor to melatonin
- GABAergic activity: Enhancing inhibitory neurotransmission
- Anti-inflammatory effects: Reducing cytokines that disrupt sleep
- Microbiota-mediated pathways: Enhancing microbial metabolites that regulate circadian rhythms

Rationale of the Study

The gut–brain axis plays a pivotal role in sleep, mood, and neurochemical homeostasis, as demonstrated by recent developments in the field of neuroscience and microbiome research. Changes in gut microbiota composition are linked with insomnia, anxiety, depression and circadian rhythm disorders. [8], [9] Bioactive compounds or microorganisms that affect mental health by modulating the gut microbiome are known as 'psychobiotics' and are becoming a promising therapeutic area of research. There is accumulating evidence that saffron can impact neurotransmitter dynamics, inflammatory signaling, and gut microbial composition, all of which could lead to an enhancement of sleep quality via gut microbiota action. Although there is growing interest in the scientific community, the psychobiotic effect of saffron in insomnia treatment is not fully explored and there is a lack of comprehensive synthesis of the existing data. [11]

This study aimed to assess the psychobiotic properties of saffron and its potential effects on sleep architecture and modulation of gut microbiota in insomnia patients. The study aims to offer an integrated understanding of the mechanisms involved in the connection between saffron, gut microbiota and sleep regulation and to highlight the gaps that can be targeted for further clinical and translational research.

Importance of Study

This study is worthwhile due to its contribution to the growing interdisciplinary field within which sleep medicine, psychobiotics, gut microbiome research and herbal therapeutics intersect. [5] The characterization of the gut–brain axis modulation by saffron may help to develop safer and more effective non-pharmacological treatments of insomnia. [3]

Furthermore, this study could be of interest to researchers, clinicians, nutritionists and mental health professionals who are interested in the field of psychobiotics and complementary medicine for the treatment of insomnia. The study consolidates emerging evidence and also provides a new perspective for future translational and clinical studies, as well as for microbiome-based therapeutics.

Research Gap

The beneficial effects of saffron as an antidepressant, anxiolytic and antioxidant have so far been the focus of existing studies, but its psychobiotic activity against gut microbiota and sleep architecture has not been well studied. [6], [2] To date, there have been reports that gut microbiota dysbiosis is correlated with sleep issues, but little evidence to suggest that saffron's influence on gut microbiota directly translates to sleep quality and circadian regulation. [7], [8] Very few studies are available that assess the effects of saffron supplementation in patients suffering from insomnia, and these studies typically do not explore mechanisms underlying these effects that are related to the microbiome.

Objective

General Objective

The objective of the present study was to assess the psychobiotic effect of saffron (*Crocus sativus*) on modulation of gut microbiota and sleep architecture in insomnia patients.

Allied Objectives

- To explore the connection between gut microbiome and insomnia via gut–brain axis.

- Assess the neurobiological and psychobiotic effects of saffron and its active ingredients such as crocin, crocetin and safranal.
- To evaluate the effect of saffron on gut microbial composition and production of microbial metabolites.

RESEARCH METHODOLOGY

Research Questions

- Q1. How is gut microbiota dysbiosis related to insomnia in gut–brain axis?
- Q2. Can saffron (*Crocus sativus*) impact mental well-being and sleep functions?
- Q3. What are the effects of the bioactive compounds present in saffron (crocin, crocetin and safranal) on neurotransmitter activity and neuroinflammatory pathways related to sleep?

Study Design

The aim of this study was to undertake a systematic review for evaluating the psychobiotic potential of saffron (*Crocus sativus*) and its impact on gut microbiota and sleep architecture in insomnia. The electronic scientific databases, PubMed, Scopus, Google Scholar, and Web of Science, were used to collect relevant literature. Recently published clinical and preclinical studies were reviewed and analysed to provide a synthesis of current evidence on the mechanisms, therapeutic effects and clinical relevance of saffron for sleep regulation and modulation of the gut–brain axis.

Types of Studies included

All the published clinical and preclinical studies on the effect of saffron *Crocus sativus* on sleep, gut microbiota, psychobiotic and sleep architecture were included in the systematic review. Randomized controlled trials, experimental animal studies, observational studies, pilot clinical studies, and review articles from peer-reviewed journals were included in the review. Studies measuring sleep quality, neurotransmitter regulation, modulation of microbiota, inflammatory pathways and mechanisms of gut–brain axis upon saffron supplementation were included for comprehensive evidence synthesis.

Search Strategy

The electronic databases such as PubMed, Scopus, Web of Science, Google Scholar, and ScienceDirect were used for conducting a comprehensive literature search for relevant studies on saffron (*Crocus sativus*), psychobiotics, gut microbiota, insomnia, and sleep architecture. Only papers published in English from 2021-2026 were included in the studies. To guarantee the comprehensive coverage of the topic, additional relevant articles were identified by manually screening the reference lists of articles selected for the study.

Proposed Mechanistic Model

We propose a multi-pathway model linking saffron intake to improved sleep:

Gut Microbiota Modulation:

Saffron bioactives alter microbial composition and increase SCFA production.

Neurotransmitter Regulation:

Microbial metabolites and saffron compounds enhance serotonin and GABA signaling.

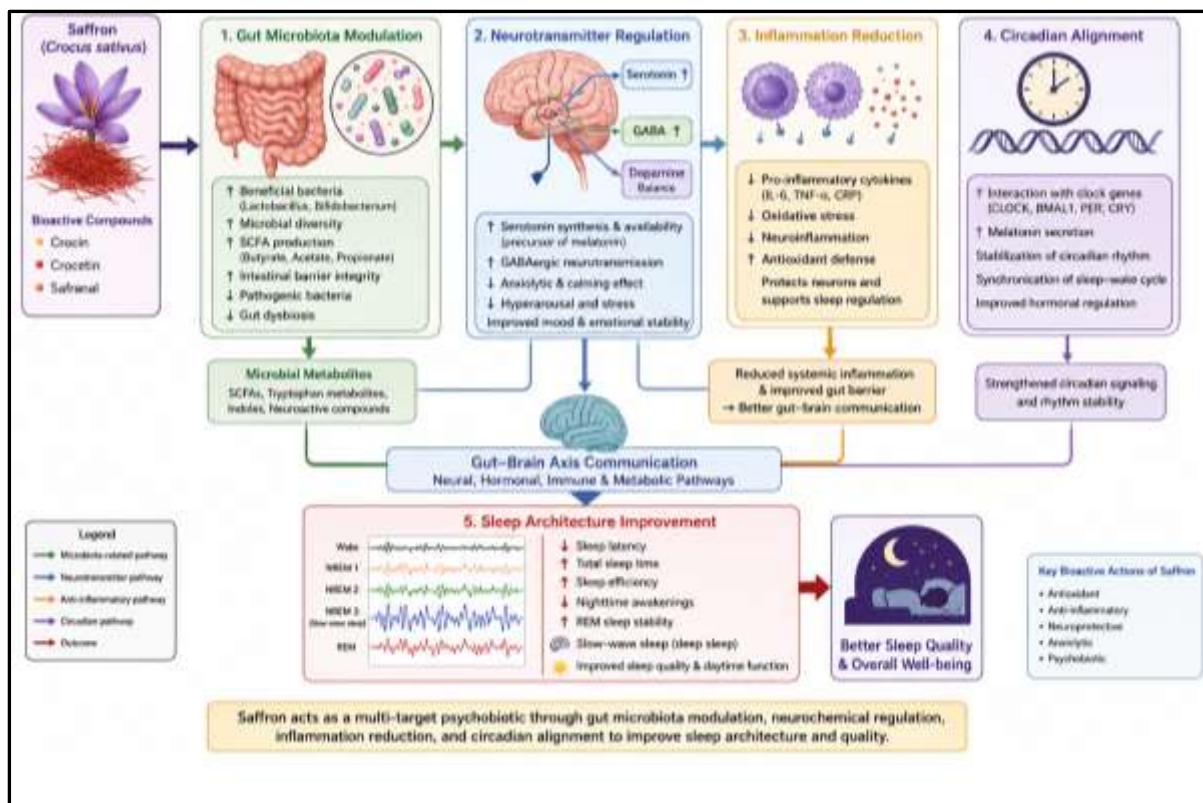
Inflammation Reduction:

Circadian Alignment:

Interaction with clock genes stabilizes sleep–wake cycles.

Sleep Architecture Improvement:

Enhanced REM stability and slow-wave sleep lead to better sleep quality.



Source: Cryan et al (2023); Lopresti et al (2021)

Figure 1: Proposed Mechanistic Model Saffron as a Psychobiotic for Improved Sleep

Clinical Evidence and Limitations

Several randomized controlled trials have demonstrated saffron's efficacy in improving sleep quality and mood. However:

Most studies have small sample sizes

Few assess gut microbiota directly

Variability exists in dosage and formulation

Long-term safety and efficacy data are limited

There is a need for integrative studies combining microbiome sequencing, polysomnography, and neurochemical analysis.

DISCUSSION OF THE PROPOSED MECHANISTIC MODEL

The following is a discussion of the Proposed Mechanistic Model. Based on this proposed mechanistic model, saffron (*Crocus sativus*) could enhance sleep quality by several interconnected pathways in the body, including modulation of gut microbiota, regulation of neurotransmitters, attenuation of inflammation, stabilization of circadian rhythms, and improvements in sleep architecture. This integrative approach emphasizes the emerging importance of saffron as a potential psychobiotic agent that can affect gastrointestinal and neurophysiologic mechanisms of insomnia. [11], [12]

Gut Microbiota

Modulation A key feature of the proposed model is the effect that bioactive compounds from the saffron can have on the composition of gut microbes, including crocin, crocetin and safranal. [7] In recent years, it has been shown how changes in the gut microbiota are strongly linked to sleep disturbances, mood disorders and gut-brain axis dysregulation. Insomniacs typically also have lower levels of microbial diversity and less of beneficial bacterial genera like *Lactobacillus* and *Bifidobacterium*. Saffron might help restore microbial balance by stimulating the growth of beneficial microorganisms and inhibit potentially harmful microbial populations. Experimental studies also indicate that saffron may stimulate the production of short-chain fatty acids (SCFAs), such as butyrate, acetate and propionate. [8] These microbial metabolites are crucial in sustaining the integrity of the gut barrier, decreasing systemic inflammation, and enabling gut-brain communication. Increased production of SCFAs could then lead to better neurochemical signaling and sleep regulation. [13], [7]

Neurotransmitter Regulation

The proposed model also highlights the importance of the modulation of neurotransmitters in the sleep-enhancing action of saffron. Neurotransmitters like serotonin, gamma-aminobutyric acid (GABA), dopamine, and melatonin

are closely linked to sleep regulation. Crocin, safranal inhibit the serotonergic and GABAergic signaling pathways essential for emotional regulation, sleep initiation and relaxation. [6], [7] The serotonin is a precursor of melatonin synthesis which is a hormone that controls circadian rhythms and sleep-wake cycles. Saffron may indirectly boost melatonin production and sleep onset and continuity by boosting serotonin. Furthermore, increasing GABA transmission could play a role in anxiolytic and sedative effects, which could lessen hyperarousal and psychological stress seen in insomnia patients. [13] Another contribution of gut microbiota is the production and metabolism of some neurotransmitters. Beneficial bacteria can produce neuroactive substances such as serotonin and gamma-aminobutyric acid, which help to bolster the two-way communication between the gut and brain. Combination effect of saffron compounds and microbial metabolites can therefore have synergistic effects on neurochemical balance and sleep regulation. [8]

Inflammation Reduction

Saffron has strong anti-inflammatory and antioxidant properties, which could potentially help to lower inflammation and oxidative stress in the brain. Crocin and crocetin have been shown to inhibit inflammatory signalling pathways and the generation of pro-inflammatory cytokines. [6], [5] An increased microbial balance in the gut may also help to further lower permeability and systemic inflammatory responses. Saffron may help to reduce inflammation, which can help to improve the function of neurons, stabilize neurochemical pathways during sleep, and overall sleep quality. Also, decreased inflammation could prevent disruption of circadian rhythm regulatory mechanisms due to chronic stress and immune activation. [11]

Circadian Alignment

The proposed model suggests that the saffron and metabolites produced by its microbiota could have a modulatory effect on the expression of circadian genes and help synchronize biological rhythms. Saffron may positively influence these pathways, such as serotonin and melatonin, which have a key role in circadian regulation. [12] Also, the gut microbiota have circadian oscillations and also communicate with host clock genes. Normalization of healthy microbial patterns can therefore contribute to normalizing the circadian signaling and stabilization of sleep-wake cycles. The relationship between saffron and gut microbiota and circadian regulation is an exciting new direction in psychobiotics. [3],[8]

Sleep Architecture Improvement

Based on clinical evidence, saffron supplementation can help to alter a number of parameters of sleep architecture, such as:

Reduced sleep latency

There is an increase in total sleep time.

Improved sleep efficiency

Reduced sleep fragmentation

Enhanced REM stability

Extended duration of slow-wave sleep.

The combined effects of neurotransmitter regulation, inflammation reduction and modulation of microbiota may be responsible for these beneficial effects. Stable slow-wave sleep is especially vital for physical, memory, and neurocognitive restoration, memory consolidation, and neurocognitive function, and stable REM sleep is vital for emotional processing and mental health. [14]

Integrated Mechanistic Perspective

A proposed mechanistic model shows that saffron can have a multi-dimensional psychobiotic action, including simultaneous modulation of the gut microbiome, immune responses, neurochemical signaling and circadian physiology. Saffron does not act on one specific mechanism but has broad systemic actions which all help to enhance sleep quality and emotional health. This integrative model also helps to explain that insomnia is not only a neurological problem but can also be a combination of various factors involving gastrointestinal function, immune pathways, and central nervous system functions. As a result, microbiota-targeted interventions, like saffron supplementation, could be an exciting new avenue in personalized and integrative sleep medicine. [7], [9], [15]

CONCLUSION

Saffron exhibits promising psychobiotic properties that may benefit insomnia patients through modulation of gut microbiota and sleep architecture. Its multi-targeted mechanisms, encompassing neurotransmitter regulation, anti-inflammatory effects, and microbiome modulation, position it as a compelling candidate for integrative sleep therapy. While preliminary evidence is encouraging, further rigorous clinical research is required to establish its efficacy and mechanistic pathways.

Future Directions

To validate saffron as a psychobiotic intervention for insomnia, future research should:

- Conduct large-scale, placebo-controlled clinical trials
- Utilize multi-omics approaches (metagenomics, metabolomics)
- Investigate dose-response relationships

- Explore synergistic effects with probiotics
- Assess long-term outcomes and safety

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