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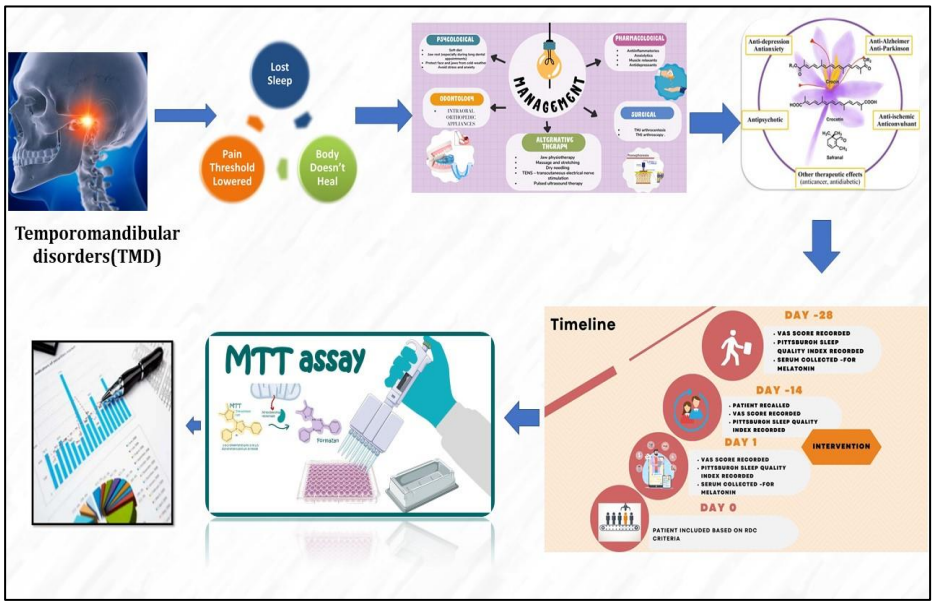
# Effect of Saffron Extract on Sleep Quality and Melatonin Concentrations in Adults with Temporomandibular Disorders-an Observational Study

Nishanthi Raja*, Anuradha Ganesan, Krithika C. L, Yesodha Aniyan
*SRM Dental College, Bharathi Salai, Chennai, Tamil Nadu, India*

## *Abstract*

*Temporomandibular Disorder (TMD) patients experience deterioration in their quality of sleep. Targeting these problems may include a wide variety of treatment options, such as the use of plant- and herbal-based medications, which have the potential to improve sleep. Numerous meta-analyses and systematic reviews have established that saffron is a useful natural treatment for mild-to-moderate insomnia. Hence, the present study aimed to determine the effect of saffron extract on sleep quality by altering the melatonin concentration in adults with TMDs. Thirty-four patients were recruited and divided into two groups equally (Group A study group, Group B -Control group) and advised to take saffron (15 mg once daily) or a placebo. Outcome measures include severity of pain collected at baseline and days 0,14 and 28 and the Pittsburgh Sleep Diary (PSD) collected. On day 0 and day 28 serum melatonin concentration will be evaluated using the ELISA kit method. Patients with temporomandibular dysfunction experienced significant reductions in pain after taking saffron supplements as opposed to a placebo. On comparing day 1 and day 28, the saffron-treated participants had substantially improved sleep quality, elevated melatonin levels, and a lower VAS score. The study concluded that Saffron is a potent, safe substitute in the management of TMD pain that has deterioration in sleep quality for its effectiveness in the management of sleep by altering the melatonin concentration. Further studies should be conducted to assess the possible benefits of saffron extract in large clinical settings with a larger number of patients.*




***Keywords:*** *Melatonin, Saffron, Sleep Quality, Temporomandibular Disorders.*

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****Corresponding Author: nisha442013@gmail.com***

## Introduction

Overall, sleep helps many physiological systems work at maximum efficiency and maintain homeostasis. Pain and sleep are essential for human survival, but persistent issues with both systems can be harmful to an individual's overall health and well-being. The most common sleep impairment condition, insomnia, is found in 67–88% of chronic pain disorders, and at least 50% of those with insomnia have chronic pain [1].

The onset of pain as a side effect occurs concurrently with the development of sleep disturbance throughout the majority of medical interventions, and vice versa. Furthermore, several medical and psychological disorders, including obesity, type 2 diabetes, and sleep apnea, occur together with chronic pain and sleep disturbances. Epidemiological research indicates that inadequate sleep duration and poor sleeping patterns are risk factors for the development of chronic pain [2].

Over the past few decades, there has been an increase in stress-related ailments due to sleep disorders [3]. There is also strong evidence to support the concept that sleep deprivation can cause hyperalgesia or an increased sensitivity to unpleasant stimuli, and can also cause or exacerbate spontaneous pain symptoms, such as headaches and tenderness in the muscles. Numerous experimental models of sleep loss that involve sleep restriction or disruption and assess the consequences using subjective pain ratings and/or quantitative sensory evaluations have demonstrated the association. A wide variety of disorders affecting the masticatory muscles, temporomandibular joints (TMJs), and/or associated structures are collectively referred to as "temporomandibular disorders" (TMDs) [4].

The prevalence of temporomandibular dysfunction (TMD) in adults is 10 to 15 %. Sleep difficulties, which have been connected with increased levels of clinical pain and emotional distress, were reported by over 50% of patients. As sleep disturbance is associated with TMDs, interventions targeted at regulating sleep have been aimed at relieving TMD pain. For pain associated with loss of sleep, medications such as benzodiazepines, tricyclic antidepressants (TCA), and maybe opioids are frequently used [5].

Although hypnotics are commonly used to treat insomnia in pain patients, they do not produce peaceful sleep or reduce pain. While tricyclic antidepressants are effective in reducing pain and enhancing sleep, they are also known to have common anticholinergic side effects, including constipation, drowsiness, and dry mouth. On the other hand, a meta-analysis showed that patients on cyclobenzaprine significantly more often experienced dry mouth and sleepiness regarding medication dosage [6]. However, tolerance and the significant risk of dependency, side effects, and mortality associated with long-term use of these sleeping tablets limit their use.

Melatonin, or N-acetyl-5-methoxytryptamine, is an endogenous indoleamine that is produced during the night by the pineal gland and released exclusively into the bloodstream at night by the circadian rhythm. Melatonin is used by humans as a dark signal and a sleep regulator [7, 8]. Low-dose exogenous melatonin does not cause reliance or tolerance [9]. Natural remedies have become more popular nowadays. Due to their natural abundance, safety, and affordability, they may have been tried for a variety of health-related issues. Because a single herb contains a variety of phytoconstituents, herbal medicine has the advantage of having diverse pharmacological effects [10]. The flower of Crocus sativus, sometimes referred to as the "saffron crocus," is the source of saffron. Several active ingredients, including carotene, crocetin, and crocin, are found in saffron. Insomnia is linked to the glutamatergic, γ-aminobutyric acid (GABA), and serotonergic systems and saffron is used in treating these problems. The present study aims to determine the effect of saffron

extract on sleep quality and melatonin concentration in people with TMJ disorders as saffron has been shown throughout various trials to affect melatonin [11].

## Materials and Methodology

This study was approved by the ethical board. Institutional Ethical committee clearance approval was obtained. IRB APPROVAL NUMBER: SRMU/M&HS/SRMDC/2023/PG/006. This study was carried out in the Department of Oral Medicine and Radiology. Based on the study by *Vidor et al.*, [12] sample size was calculated. The resulting sample size of a total number of 34 participants was divided into two groups, A (the study group) and B (the control group), Experimental therapy using saffron extract capsules was given to group A while group B patients received placebo therapy. The patients who attended the outpatient department with a complaint of TMDs were recruited. The study was double-blinded, and the participants were randomly allocated into one of the two groups. Both the saffron extract capsules and placebo capsules were dispensed in transparent sterile bottles and were distributed to the patients. Randomly. Sleep quality assessment was done by the Pittsburgh Sleep Quality Index, and severity of pain was assessed by VAS Score, Patients with alteration in sleep quality were assessed by the Pittsburgh Sleep Quality Index. Respondents rated their sleep quality on a 5-point scale ranging from very bad (1) to very good (5). According to previous literature TMDs are classified based on the severity of pain and severity was assessed using VAS scores and were categorized into VAS scale: 1-4 -Mild,5-7-Moderate,8-10 -Severe.

### Inclusion Criteria

Patients above the age of eighteen, both male and female Participants in this study were recruited. Individuals suffering from temporomandibular joint diseases classified by RDC/ICD-10 M79.1, M26.62, G44.89) for TMJ disorders who self-reported symptoms of disturbed sleep lasting more than four weeks. Patients with symptoms of pain along with clicking, deviation during jaw movement, pain and difficulty in opening the mouth, pain in the preauricular area, and spreading to surrounding areas were also recruited for this study. Patients experiencing changes in their sleep quality were evaluated using the Pittsburgh Sleep Quality Index, while the VAS Score was used to gauge the intensity of their pain. The respondents used a 5-point rating system, with 1 representing really poor sleep and 5 representing very good sleep.

### Exclusion Criteria

Patients with allergies to ayurvedic medications, neuralgias, neuromuscular problems, jaw tumours, injuries, trauma and patients already receiving anti-inflammatory, muscle relaxant, analgesic and other pharmacological treatments were among the patients who were excluded. Physically challenged and mentally retarded persons, any systemic illness, patients with a previous history of trauma or who have undergone any treatment for temporomandibular disease or ongoing treatment currently were not included in the study. Individuals working night shifts or rotating shifts, those who suffer from sleep conditions other than mild insomnia persistent, severe sleep disturbance for more than 1 year, and diagnosed with a mental health disorder were not allowed to take part in the study. Additionally, individuals who were already taking saffron supplements had a history of current or past 12-month illicit drug abuse or had a diagnosis of a medical condition that included but was not limited to diabetes, hyper- or hypotension, cardiovascular disease, a gastrointestinal disease that required regular medication use were excluded.

**Intervention:** Commercially available Saffron pure extract was procured and used saffron extract-15 mg/day (Crocus sativus-15mg), and commercially available

maltodextrin was procured and used in the trial in the form of capsules. For 28 days, each participant in both groups was given instructions to take one tablet, either a placebo capsule or 15 mg of saffron extract, orally, one hour before bedtime. Dosage is optimized based on a clinical trial article by *Pachikian et al., (2021)* [13], where they administered a capsule containing 15.5 mg/day of a saffron extract. All patients were treated with a placebo or saffron extract and assessed on regular visits on Day 0,14 day 28. Blood (5 ml) was drawn from these subjects in two phases, before and after treatment in both the groups with saffron extract and the placebo group. On the day of analysis, the blood drawn was centrifuged at 3000 rpm for 10 minutes. Serum melatonin was determined immediately using the collected serum. Melatonin hormone levels were measured based on commercially available Human MT(Melatonin) Enzyme-Linked Immunosorbent Assay Kit procured from (https://www.elabscience.com/) by the manufacturer's specifications. An online survey that looked for side effects assumed to be connected to tablet consumption was used every seven days to assess participants' capacity to tolerate and safely take tablets. In addition, participants were instructed to immediately contact the researchers in case they had any adverse reactions.

### Outcome Measures

On days 0–14 and for a total of 28 days, participants were called back, and the patient's assessment form was collected. The Pittsburgh Sleep Quality Index was used to evaluate the quality of sleep. Additionally, self-reported sleep quality and circadian type are correlated with scores. Sleep quality assessment (5-point Likert rating ranging from very bad [1] to very good [5]), mood rating at final awakening (5-point Likert rating ranging from very calm [1] to very tense [5]), total sleep time (hours), sleep latency (minutes), number of awakenings after sleep onset, and alertness rating at final awakening (5-point Likert rating ranging from very sleepy [1] to very alert [5]) are all taken into account when calculating scores. The severity of pain was assessed using VAS scores categorized into -VAS scale: 1-4 -Mild, VAS scale: 5-7-Moderate, VAS scale: 8-10 -Severe, and serum melatonin concentration was assessed. On day 0 and day 28, serum melatonin concentration was evaluated.

## Statistical Analysis

In this research article, a comprehensive array of statistical analyses was applied to elucidate the underlying patterns and relationships within the dataset. The analytical toolkit encompassed prominent methods such as the Chi-square test, facilitating the exploration of categorical variables and uncovering potential associations between them. Additionally, the One-way ANOVA was employed to discern significant variations among multiple independent groups, shedding light on potential differences in means. Moreover, the Paired t-test was utilized to investigate changes within related samples, enabling the assessment of pre- and post-intervention effects. These statistical approaches collectively provided a robust framework for the examination of data, enhancing the depth and validity of the study's findings.

## Results

From 57 individuals who completed the initial online screening questionnaire. Thirty-four patients (65% female) were diagnosed with TMDs. The age of the patients, of which 34 were included in the study with a mean age of 20–50 years, 20 being female and 14 being male, is included in the baseline data of these thirty-four participants. Occupational details of the patient were recorded, which shows more than 26 per cent of students were mostly affected by TMDs. Pain was the most common preoperative symptom (88%), according to our patients. Clicking sounds rated second in

prevalence among our patients' preoperative symptoms (75%), and restricted mouth opening (67%).

For the PSQI scores, compared to baseline, 4 weeks of saffron supplementation, led to an increase in the melatonin score and an increase in sleep duration. The daytime dysfunction score was decreased after 4 weeks of intervention in both the placebo ($p < 0.001$) and saffron ($p < 0.001$) groups. Figure 1 depicts the mean melatonin levels for participants with disturbed and good sleep quality on Day 1 and Day 28 respectively. Higher the melatonin level participants acquired good sleep quality after 4 weeks of saffron supplementation. The Boxplot depicts the melatonin levels for group A respectively, on day 28. The boxplot indicates that there is a statistically significant melatonin level in Group A on Day 28 than in Group A on Day 1 with a p-value less than 0.05(Figure 2). The p-p plot mark indicates that there is a statistically significant in the TMD Vas score in Group A on Day 28 is statistically significantly higher than Group A on Day 1 with a p-value less than 0.05 (Figure 3). Table 1 depicts the correlation of the VAS Score on Group A and Group B. For the VAS scores, there was significant interaction between the treatment groups. Figure 4 depicts the mean melatonin levels for Group A and Group B- on day 28. When comparing day 1 and day 28, the saffron-treated participants had substantially improved sleep quality, elevated melatonin levels, and a lower VAS score (Table 2).

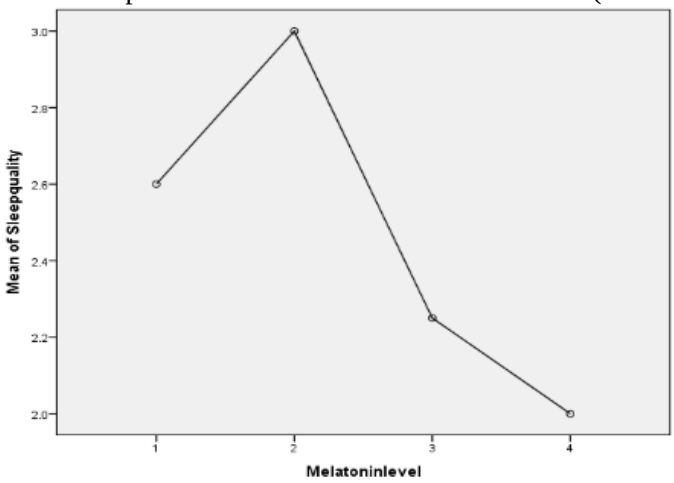


**Figure 1.** Mean Values of Sleep Quality and Melatonin Levels on GROUP -A

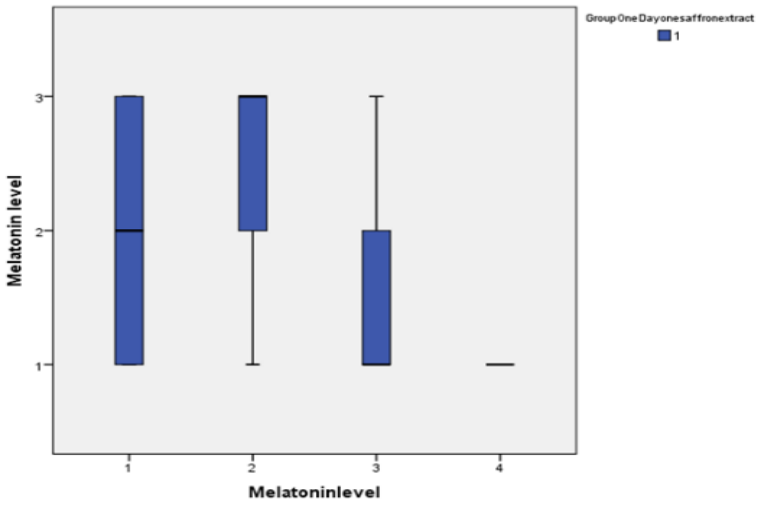


**Figure 2.** Comparison of Day 1 and Day 28 Serum Melatonin Level-GROUP A

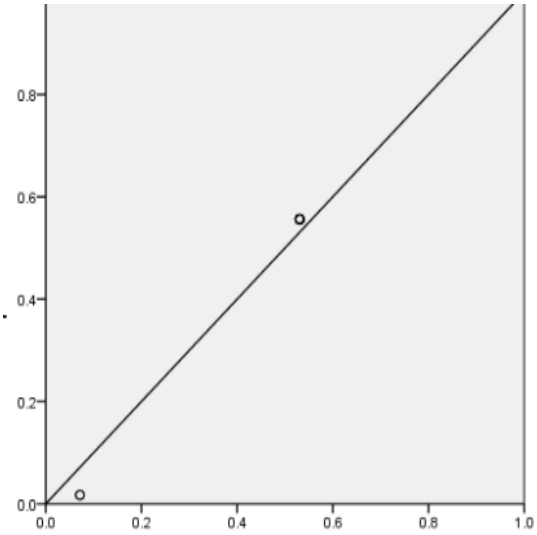


**Figure 3.** Comparison of day 1 and day 28-vas score on GROUP A

**Table 1.** Correlation of VAS Score on Group A and Group B

| | | Paired Differences | | | | | T | df | Sig. (2-tailed) |
|---|---|---|---|---|---|---|---|---|---|
| | | Mean | Std. Deviation | Std. Error Mean | 95% Confidence Interval of the Difference | | | | |
| | | | | | Lower | Upper | | | |
| Pair 1: Saffron days and 28 | TMD vas score – TMD vas score | 1.529 | .624 | .151 | 1.208 | 1.850 | 10.101 | 16 | .000 |
| Pair 2. Placebo days 1 and 28 | TMD vas score – TMD vas score | .706 | .588 | .143 | .404 | 1.008 | 4.951 | 16 | .000 |

**Table 2.** Paired Samples Test Group A Day 1 between Group 1 day 28

| | | Paired Differences | | | | | T | df | Sig. (2-tailed) |
|---|---|---|---|---|---|---|---|---|---|
| | | Mean | Std. Deviation | Std. Error Mean | 95% Confidence Interval of the Difference | | | | |
| | | | | | Lower | Upper | | | |
| Pair 1 | TMD vas score - sleep quality | .235 | .664 | .161 | -.106 | .577 | 1.461 | 16 | .163 |
| Pair 2 | melatonin level – TMD Vas score | 1.471 | 1.231 | .298 | .838 | 2.103 | 4.927 | 16 | .000 |
| Pair 3 | Sleep quality - Melatonin level | -1.529 | 1.068 | .259 | -2.078 | -.981 | -5.907 | 16 | .000 |

The graph depicts the melatonin levels for group A and group B, respectively, on day 28. Melatonin level in Group A on Day 28 is statistically significantly higher than in Group

B with a p-value less than 0.05.VAS score in Group B on Day 28 is statistically insignificantly than Group A on Day 1 with a p-value less than 0.05 (Figure 5).

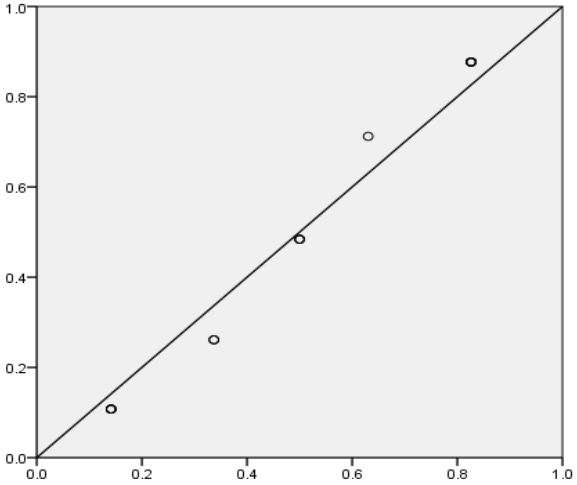


**Figure 4.** Mean Melatonin levels for group A and group B - on day 28

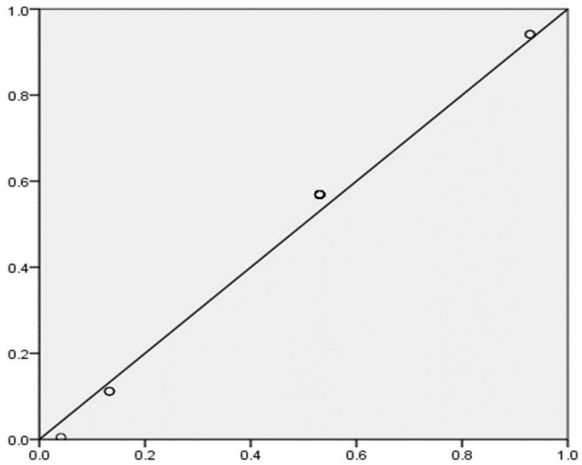


**Figure 5.** Comparison Day one and Day 28-vas Score on GROUP B

## Discussion

In this observational study, patients with mild to moderate temporomandibular disorders showed greater improvements in sleep quality and parameters related to melatonin levels when they received standardized saffron extract (15 mg daily for 4 weeks) and as a result, the patient's VAS score was reduced. The findings of this study are consistent with those found in a previous study by Lee et al [4] on the sleep quality of patients with chronic TMD diagnosed using DC/TMD Axis I. The results of this study indicate that individuals with chronic TMD experienced worse sleep quality than subjects in the healthy control group and that the degree of this worse sleep was associated with age and female sex. The current study demonstrates that women were more likely to report TMD symptoms and individuals with chronic TMD had lower-quality sleep compared to healthy controls. As far as we believe, this is the first study to look at the effects of a saffron extract on melatonin concentration and sleep quality in TMJ patients. Many studies have been conducted on the effects of saffron, which is derived from the dried stigmas of the Crocus sativus L. plant and used in traditional medicine, as well as its components safranal, crocins, and crocetin, on depression and anxiety in humans [14]. Furthermore, prior studies using a variety of methodologies have demonstrated that saffron

seems to have positive benefits on both the quantity and quality of sleep. While some studies examined the effects of saffron as a primary ingredient, crocetin, others utilized the extract in its whole [15]. In the present study saffron consumption significantly improved sleep quality by altering the serum melatonin level. These findings are consistent with previous trials by Lopersti et al., [16] which assessed the sleep-enhancing effects of 28 days of saffron supplementation in adults with unsatisfactory sleep. Recent research indicates that saffron's influence on melatonin may be one factor underlying its ability to improve sleep. The pineal gland secretes the circadian hormone melatonin, which peaks between three and four in the morning. Numerous biological processes, including immunity, reproduction, sleep, and circadian rhythms, are regulated by melatonin. Adults with insomnia exhibited lower melatonin concentrations than those who slept normally in several studies. Additionally, the research conducted by Vidor et al. suggests that melatonin's analgesic advantages on pain scores and analgesic consumption in people with mild-to-moderate chronic myofascial TMD pain may be connected to its involvement in regulating circadian rhythms [17]. Melatonin may therefore be a helpful tactic for treating the pathophysiologic mechanism underlying TMD.

Saffron may have numerous impacts on melatonin. The essential block of melatonin production is the amino acid tryptophan (TRP). Since the gut microbiota can metabolize TRP, saffron may influence the gut microbiota to enhance the availability of tryptophan [18]. Furthermore, because inflammatory cytokines like interferon and interleukin-1b can affect melatonin production and secretion, saffron anti-inflammatory properties may raise melatonin concentrations [19, 20]. This study implies that saffron extract may have a direct effect on the concentration of melatonin in pain pathways or the quantity of signaling molecules that regulate pain and be pertinent to its beneficial effects in TMD patients.

## Conclusion

The results of the present study reveal that saffron extract showed a very good effect in chronic Temporomandibular disorder patients with alteration in sleep quality compared with the placebo group. The study also shows management of altered sleep quality has been very successful in controlling pain associated with temporomandibular disorders.

### Limitations and Future Aspects

The findings of this study corroborate the analgesic effects on pain scores in individuals with chronic TMD, and they are also consistent with the results of an earlier experiment on the benefits of saffron for improving sleep by regulating melatonin levels [19]. Subjective pain scores and self-report questionnaires were employed as outcome measures in the current study. Further research is needed to determine the safety and effectiveness of longer-term saffron supplementation. It will be essential for employing objective sleep measurements like polysomnography or even commercial sleep tracks worn on the wrist in future trials. Therefore, more trials with a greater number of patients are required to evaluate the potential advantages of saffron extract in large clinical settings.

## Declaration

### Ethics approval and Consent to Participate

Proper ethical clearance was obtained from the Institutional Review Board (IRB) (SRMU/M&HS/SRMDC/2023/PG/006) of SRM Dental College, Ramapuram, Chennai – 600089. Following the guidelines, participants who volunteered for the study and met the inclusion criteria were chosen. Informed consent was obtained from the participants in the study.

## Consent for Publication

Proper consent is obtained from the participants for the publication of study results without revealing personal information.

## Competing Interests

The authors declare no competing interests.


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