

# *Safleep<sup>TM</sup>*

**Sleep quality improvement  
& the necessary motivation maintenance  
for getting things done**

- **Safleep<sup>TM</sup>**  
(Water-soluble powder, Food Grade)



**ORYZA OIL & FAT CHEMICAL CO., LTD.**

ver. 1.0 WY

**Sleep quality improvement**  
**The necessary motivation maintenance for getting things done**  
**Safleep™**

## 1. Introduction

Saffron (*Crocus sativus*) is perennial plant of the family Iridaceae. Saffron is made by drying only the pistil (stigma) in the bright purple flowers. Crocin is a red carotenoid glycoside generated in saffron. Only about 100 g of stigma tissue can be obtained from about 16,000 flowers, and saffron flowers bloom only once a year and last only 48 hours.<sup>1)</sup> It is called ‘the most expensive spice’ because it is hand-picked during flowering time. Currently in modern life, people are becoming extremely night owls, and their sleeping hours are getting shorter. More than 20% of people are dissatisfied with their sleep, and the decline in productivity due to the lack of sleep and insomnia what is a problem.<sup>2)</sup> Crocin, derived from saffron has been reported to increase non-REM sleep in mice, and is an ingredient that has been accepted as “Foods with Functional Claims”. Oryza Oil & Fat Chemicals Co., Ltd. has conducted a new Systematic Review (SR) regarding Safleep™ as “Foods with Functional Claims”. Safleep™ is recommended to be added to all kinds of foods promoting sleep aimed at people who want a good night's sleep and want waking up refreshed and take action without feeling sleepy.



Fig1. Saffron (stigma)

1) Kakutani K, *Functions and Applications of Spices and Herbs*, 29-35 (2022)、CMC

2) Ministry of Health, Labor and Welfare, Health Japan 21

( [https://www.mhlw.go.jp/www1/topics/kenko21\\_11/top.html](https://www.mhlw.go.jp/www1/topics/kenko21_11/top.html) )

## 2. Components of Safleep™

Saffron (pistil stigma) contains crocin, picrocrocin, and safranal as its main components. The unique color of saffron is attributed to crocin, which is a glycoside structure. The distinctive taste, including bitterness and pungency, comes from picrocrocin. The characteristic aroma is believed to be due to the volatile compound safranal. Crocin possesses distinctive water-soluble characteristics as carotenoid. This unique feature among carotenoids due to the presence of gentiobiose, a disaccharide, which is esterified at both two ends of 20-carbon crocetin (with two glucose molecules connected by a  $\beta$ 1-6 bond) as below structural formula. It is known that volatile safranal is generated during the breakdown process of crocin, where gentiobiose is converted.<sup>1)</sup>

The carotenoid components found in saffron have been reported in various pharmacological studies to have not only sleep-enhancing effects but also improvements in memory capacity and alleviation of PMS symptoms.<sup>3)</sup>

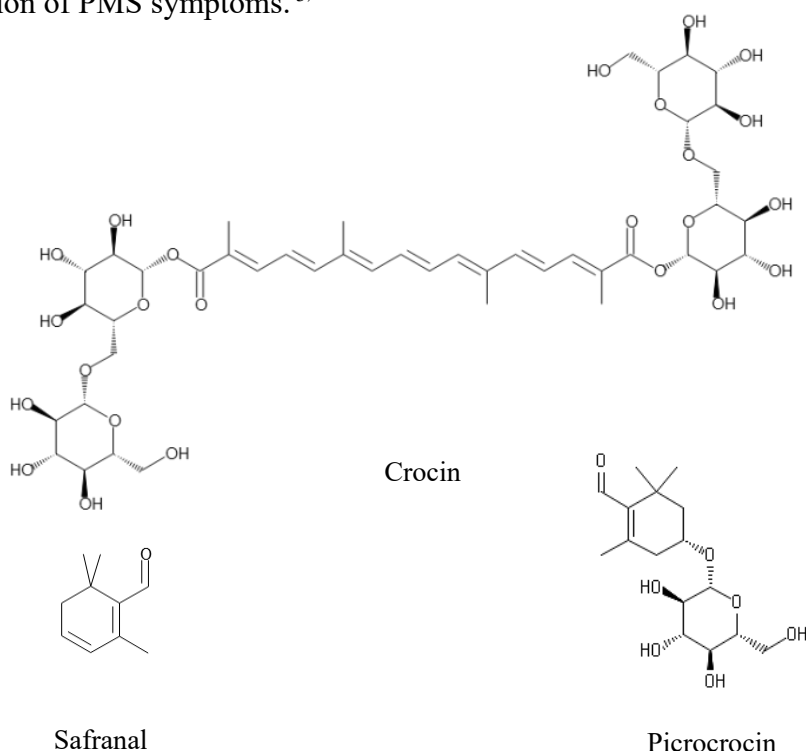


Fig 2. Structure of carotenoid components in saffron

3) Hashiguchi T, *Food Style*21, 26 (9), 85-91, 2022

### 3. Sleep Quality improvement of Safleep™ (from systematic review)

ORYZA has prepared notification documents to submit to the Consumer Affairs Agency to make Safleep™ an approved “Foods with Function Claims”. Based on our research review, we have included the following declaration in the notification: "This product contains crocin derived from saffron. Crocin derived from saffron has been reported to have the functions of shortening the time to fall asleep and improving sleep onset, supporting quality sleep (being able to sleep quickly, deeply and soundly), promoting refreshed awakening, reducing daytime sleepiness, and maintaining the motivation necessary to accomplish tasks."

Below is a summary of the three papers that served as the basis for the above declaration:



Fig3. Safleep™ improves sleep quality & maintains motivation at 6 points

## REFERENCE ①

Takeda R et al., Improvement in quality of sleep by the intake of saffron-derived crocin and safranal. Japanese pharmacology and therapeutics, 48(3), 497-504 (2020)

**【Participants】** 52 healthy adult men and women (ages 20-64) were enrolled in the study

**【Study Design】** Randomized, Placebo-controlled, Double-blind, Parallel-group comparison trial.

**【Outcome Measures】** OSA-MA sleep questionnaire, EEG measurements.

**【Test Samples】** Saffron extract-containing tablets (0.66 mg/day of crocin derived from saffron), Placebo tablets (not containing saffron-derived crocin).

**【Duration of intake】** 4 weeks

**【Result】** Saffron intake group, compared to the placebo intake group, showed significant increases in various parameters measured by brain wave and electromyography (EMG). These parameters included the time to fall asleep, duration of deep sleep, frequency of nighttime awakenings, duration of REM sleep, and duration of non-REM sleep. Furthermore, there were significant improvements observed in the scores of the OSA-MA Sleep Questionnaire's Factor I (morning sleepiness), Factor II (sleep onset and maintenance), and Factor III (dreaming).

## 3.2 REFERENCE②

Nishide A et al., Sleep enhancement by saffron extract in randomized control trial. Japanese pharmacology and therapeutics, 46(8), 1407 - 1415 (2020)

**【Participants】** 21 healthy adult men and women were enrolled (ages 21 or older)

**【Study Design】** Randomized, Placebo-controlled, Double-blind, Parallel-group comparison study

**【Outcome Measures】** Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI).

**【Test Samples】** Participants were randomly assigned to receive either saffron extract-containing tablets (providing 0.6 mg/day of crocin derived from saffron) or placebo tablets (which did not contain crocin derived from saffron).

**【Duration of intake】** 4 weeks

**【Result】** Based on the pre-intake PSQI scores, participants were divided into two groups: the good sleeper group and the poor sleeper group. In the stratified analysis, a significant improvement in the change in the factor "daytime difficulty wakefulness" was observed between the saffron intake group and the placebo intake group.

### 3.3 REFERENCE③

Lopresti AL et al., Effects of saffron on sleep quality in healthy adults with self-reported poor sleep: a randomized, double-blind, placebo-controlled trial. *J Clin Sleep Med.*, 16(6):937-947 (2020).

**【Participants】** 63 healthy adult men and women were enrolled (ages 18-70)

**【Study Design】** Randomized, Placebo-controlled, Double-blind, Parallel-group comparison study

**【Outcome Measures】** Insomnia Severity Index (ISI)、Restorative Sleep Questionnaire (RSQ)、Pittsburgh Sleep Diary (PSD)

**【Test Samples】** Sample tablet (containing Saffron Extract 28 mg with a crocin content of 0.76mg) , 1 tablet/day or Placebo tablet (non-containing saffron extract) ,1 tablet/day

**【Duration of intake】** 4 weeks

**【Result】** The saffron intake group, compared to the placebo intake group, showed significant improvements in the Insomnia Severity Index (ISI), the total score of the Perceived Stress Scale (PSD), and the "sleep quality" item of the PSD.

## 4. Mechanism of Safleep™

### 4.1 Sleep quality improvement

In in-vivo experiment, compared to control, intraperitoneal administration of crocin derived from saffron significantly increased the duration of non REM sleep.<sup>4)</sup> The significant decrease in non-REM sleep time observed in histamine H1 receptor knockout mice suggests that the increase in non-REM sleep time induced by saffron-derived crocin is likely due to a mechanism involving the modulation of the histamine neurotransmitter system. This finding suggests that saffron-derived crocin may interact with the histamine pathway to regulate non-REM sleep duration.<sup>4)</sup>

In the previously cited reference ①, it was found that the extension of non-REM sleep duration leads to a decreases in proportion of REM sleep duration in saffron-derived crocin intake group. It is said that the brain wave is highly active and dreaming often occurs during REM sleep (light sleep state).<sup>5)</sup> This is consistent with the clinical trial results that the third factor “Dreaming (the frequency of dreaming)” in the OSA-MA sleep survey has a significant decrease which supported a good sleep quality. Furthermore, it has been reported that the administration of histamine H1 receptor antagonists has a shortening effect on sleep onset.<sup>6)</sup> It is believed that the ability to facilitate faster sleep onset and improve sleep initiation which is also attributed to a similar mechanism suggested by in vivo test results using histamine H1 receptor knockout mice.

### 4.2 Necessary motivation maintenance for getting things done

It is reported that sleep deprivation, poor sleep initiation, and loss of restorative feeling from sleep which leads to a decline in daytime attention, concentration, and motivation, among other things.<sup>7)</sup> It is believed that saffron-derived crocin, as mentioned earlier, can help maintain motivation by improving sleep quality.

Furthermore, it is known that dopamine, one of the neurotransmitters, plays a role in motivation.<sup>8)</sup> A decrease in dopamine levels can contribute to a decrease in motivation.<sup>8)</sup> The

intake of saffron-derived crocin has been reported to contribute to the induction of dopamine release by interacting with NMDA receptors (N-methyl-D-aspartate) in various parts of the brain.<sup>9)</sup> Therefore, it has been suggested that the increase in dopamine levels can help maintain the necessary motivation during activities.

Based on the above, it is believed that saffron-derived crocin can help maintain the necessary motivation for accomplishing tasks by improving sleep quality and increasing dopamine levels.

#### References

- 4) Masaki M *et al.*, *Molecular Nutrition and Food Research*. 2012. 56(2):304-308.
- 5) Ministry of Health, Labor and Welfare, e-health net, mechanism of sleep
- 6) Terao A *et al.*, *Folia Pharmacol. Jpn.*, 129, 35-41.
- 7) Ministry of Health, Labor and Welfare, Sleep Guidelines for Health Promotion, 2014
- 8) Kuroda K *et al.*, *Japanese Journal of Biological Psychiatry* . , 28 (3) :127– 131. 2017
- 9) Ettehadi H *et al.*, *J Behav Brain Sci.*, (3):315–319. 2013



## 5. Product stability of Safleep™

### 5.1 Heat Stability

As shown in Fig. 4, content of anthocyanins was stable upon heating at 80°C and 100°C while 30% decrease in the content was observed upon heating at 120°C.

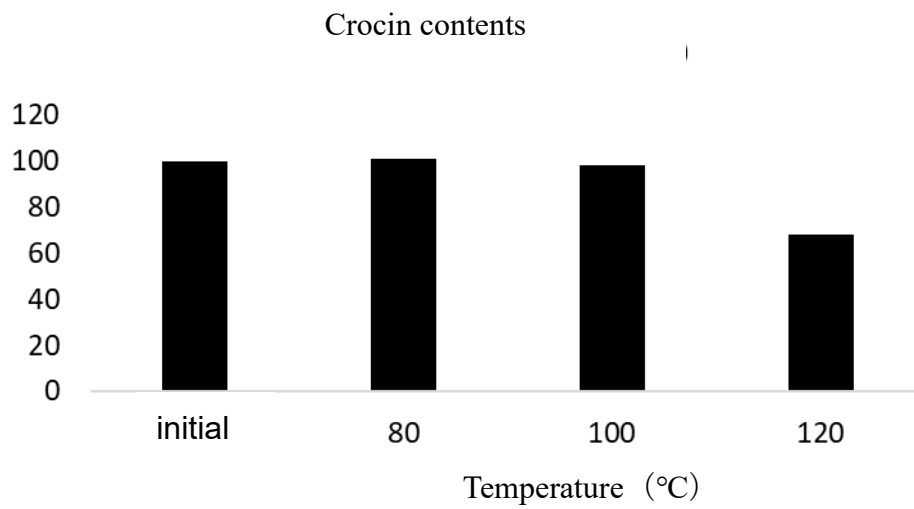


Fig4. Heat stability of Safleep™

## 5.2 pH stability

Figure 5 illustrates the color variation of Safleep™ aqueous solution based on its pH. The Safleep™ solution transitions from a pale yellow color to yellow and then to a deep yellow shade as the pH shifts from acidic to alkaline.

Although Safleep™ exhibits high water solubility, it demonstrates instability across the entire pH range from acidic to alkaline in water. In acidic conditions, crocin undergoes complete decomposition, while in alkaline conditions, it undergoes hydrolysis to form crocetin. Therefore, liquid products are not suitable for Safleep™. However, it can be used in the form of powdered beverages by dissolving it in water and consuming it immediately.

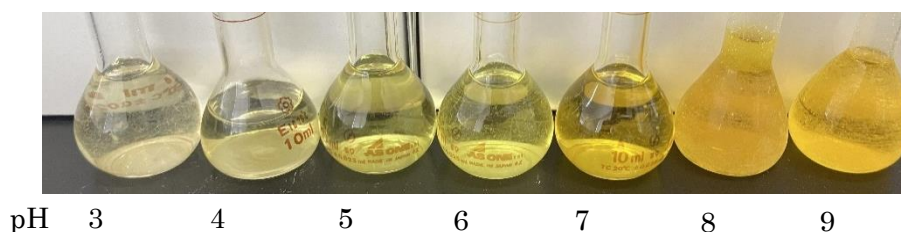


Fig5. pH Stability and colour changes of Aqueous Solution of Safleep™

## 6. Nutrition profiles

Analyzed item (/100g)	Safleep™	Method
Water (g)	3.1	Heating drying method under normal pressure
Protein (g)	0.6	Kjeldahl method, nitrogen protein conversion factor: 6.25
Fat (g)	2.8	Acid decomposition method
Ash (g)	0.8	Direct incineration method
Carbohydrate (g)	92.7	Refer note 1 Prosky's method
— Sugar (g)	92.7	
— Fiber (g)	0.1	
Energy (kcal)	398	Refer note 2
Sodium (mg)	5.6	Atomic absorption spectrophotometry
Sodium chloride equivalent (g)	0.01	Refer note 3

The nutritional information of Safleep™ (Saffron Extract-P) was analyzed according to the standard in nutrition labeling (March 30, 2015; No 139 Eishin)

Note 1: Calculation: 100-(water + protein + fat + ash)

Note 2: Energy conversion factor: Protein 4, fat 9, sugar 4, dietary fiber 2

Note 3: In terms of sodium

Test trustee: SUNATECH/ Dte of analysis: February 21, 2023

Test No: 230208659-001-01

## 7. Safety profiles

### 7.1 Acute toxicity (LD<sub>50</sub>)

Acute Toxicity test was conducted according to the Guidelines for Single-Dose Toxicity Tests for Pharmaceutical Products. Safleep™ (Saffron Extract-P) 2,000 mg/kg was orally given to fasted ICR mice (6 weeks old). After 14 days, no abnormalities and fatal event were observed at 2,000 mg/kg. No abnormalities were observed under macroscopic examination upon autopsy. Thus, LD<sub>50</sub> of Safleep™ (Saffron Extract-P) is deduced to be > 2,000 mg/kg.

### 7.2 Mutagenicity (Ames test)

Ames test was conducted to evaluate the mutagenicity of Safleep™ (Saffron Extract-P) using Salmonella typhimurium TA98, TA100, TA1535, TA1537 and E. coil WP2 at concentration 19.5-5,000 µg/plate. No mutagenicity was observed.

## 8. Recommended dosage

We recommend 200 mg/day of Safleep™ (Saffron Extract-P) based on the results of human clinical trial.

## 9. Application

	Applications	Indication	Examples
Food	Nutritional supplement, Beauty food	Sleep quality improvement Motivation maintenance	Beverages, Hard and soft capsules, tablets, Candies, Chewing gums, Gummies, Cookies, Chocolates, Wafers etc.

## 10. Packing

Safleep™

1kg , 5kg

Interior packing: Aluminium bag

Exterior packing: Cardboard box

## 11. Storage

Store in a dry, ventilated location. Keep away from high temperature and sun light, store in the closed containers.

## 12. Expression

< Food >

**Safleep™ (Saffron Extract-P)**

Maltodextrin, Saffron Extract

## PRODUCT STANDARD

PRODUCT NAME : **Safleep™** (FOOD)

(SAFFRON EXTRACT-P)

This product is a powder extracted from the stigmas of saffron (*Crocus sativus*) with aqueous ethanol. It guarantees minimum of 3.0 % of crocin.

<b><u>Appearance</u></b>	Yellow to orange powder with characteristic odor.	
<b><u>Crocin contents</u></b>	Min. 3.0 %	(HPLC)
<b><u>Loss on Drying</u></b>	Max. 10.0 %	(Analysis for Hygienic Chemists, 1 g, 105°C, 2 hr)
<b><u>Purity Test</u></b>		
<b><u>(1) Heavy Metals (as Pb)</u></b>	Max. 20 ppm	(Sodium Sulfide Colorimetric Method) (Standard Methods of Analysis in Food Safety Regulation, The Third Method, Apparatus B)
<b><u>(2) Arsenic (as As<sub>2</sub>O<sub>3</sub>)</u></b>	Max. 2 ppm	(Analysis for Hygienic Chemists)
<b><u>Standard Plate Counts</u></b>	Max. 3×10 <sup>3</sup> cfu/g	(Analysis for Hygienic Chemists)
<b><u>Moulds and Yeasts</u></b>	Max. 1×10 <sup>2</sup> cfu/g	(Analysis for Hygienic Chemists)
<b><u>Coliforms</u></b>	Negative	(Analysis for Hygienic Chemists)

<b><u>Composition</u></b>	<u>Ingredient</u>	<u>Content</u>
	Maltodextrin	70-90 %
	<u>Saffron extract</u>	<u>10-30 %</u>
	Total	100 %

**Expiry date** 3 years from date of manufacturing.

Store it at a cool, dry place.

**Storage** Keep it away from high temperature, high moisture and sunlight, and store it in a closed container.

**ORYZA OIL & FAT CHEMICAL CO., LTD.** striving for the development of the new functional food materials to promote health and general well-being.

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